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Beyond Opioid Elimination: Does Opioid-Free Anesthesia Improve Outcomes Compared With Multimodal Opioid-Sparing Anesthesia in Adult Laparoscopic Abdominal Surgery? A Critical Narrative Review

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ABSTRACT

Background: Opioid-free anesthesia (OFA) is increasingly promoted to reduce opioid-related adverse effects after laparoscopic surgery. Its clinical value, however, depends on the comparator: superiority over conventional opioid-based anesthesia does not establish superiority over a contemporary multimodal opioid-sparing strategy (OSA). Further, replacing opioids with alpha-2 agonists and other co-analgesics may exchange one adverse-effect profile for another.

Objective: To critically evaluate whether complete intraoperative opioid avoidance offers incremental benefit over optimized OSA in adults undergoing laparoscopic abdominal surgery, emphasizing analgesic effectiveness, postoperative nausea and vomiting (PONV), quality of recovery, and hemodynamic safety.

Evidence synthesis: We undertook a focused narrative synthesis based on a structured PubMed search (January 2015 to November 2026), with verification of primary randomized trials, systematic reviews, and procedure-specific guidance against the original publications. We distinguished direct OFA–OSA comparisons from trials with conventional opioid-inclusive comparators and broader mixed-surgery meta-analyses. No pooled estimates or formal risk-of-bias grading were produced.

Key observations: Four particularly relevant laparoscopic trials compared OFA with a multimodal opioid-inclusive strategy. In laparoscopic colectomy (160 randomized; 155 analyzed), 48-hour oral morphine equivalents were 9 versus 14 mg (P=0.861), with more bradycardia during OFA. Following bariatric surgery (172 randomized), 24-hour morphine use was 16 versus 15 mg (P=0.183), although PONV was less frequent with OFA (37% versus 59%). In sleeve gastrectomy, a transient first-hour opioid-sparing effect did not persist to 24

hours, while ephedrine and fluid requirements increased. A cholecystectomy trial reported similar overall pain, but its published 95% confidence interval crossed the prespecified noninferiority margin, and was inconsistent with the reported variance, so noninferiority cannot be confirmed. Wider meta-analyses favor OFA for PONV more consistently than for sustained analgesia, but most comparisons do not isolate the effect of eliminating opioids from an otherwise equivalent multimodal pathway.

Conclusion: OFA is feasible in selected laparoscopic operations, but the evidence does not establish its routine superiority over well-designed OSA for postoperative pain, cumulative opioid use, or global recovery. Favoring patient- and procedure-specific multimodal analgesia, with opioids available as selective rescue and explicit attention to adverse effects of alternative agents, is more evidence-concordant than a universal opioid-free mandate.

KEYWORDS

opioid-free anesthesia; opioid-sparing anesthesia; multimodal analgesia; laparoscopic surgery; dexmedetomidine; postoperative nausea and vomiting; enhanced recovery; narrative review.

MAIN ARTICLE

1. INTRODUCTION: THE CLINICALLY RELEVANT COMPARISON

Opioids have traditionally provided the rapidly titratable antinociceptive component of balanced general anesthesia. Their perioperative disadvantages are familiar: postoperative nausea and vomiting (PONV), sedation, respiratory depression, pruritus, delayed gastrointestinal recovery, and possible contributions to opioid-related hyperalgesia or persistent postoperative use. Avoiding unnecessary exposure is therefore a legitimate goal of enhanced recovery after surgery (ERAS). Yet opioid reduction and opioid elimination are not interchangeable concepts, and the mere absence of opioids during surgery is not itself a patient-centered outcome [1–5].

Laparoscopic abdominal surgery provides a particularly informative setting for this debate. Port-site pain, visceral manipulation, pneumoperitoneum, and referred shoulder pain generate different nociceptive components; their relative importance varies between laparoscopic cholecystectomy, sleeve gastrectomy, gastric bypass, and colorectal resection. A successful protocol must address those mechanisms, not simply substitute one infusion for another. Contemporary procedure-specific recommendations prioritize nonopioid basic analgesia, local anesthetic techniques, dexamethasone, and rescue opioids when clinically necessary [3,4]. These measures may make a low-opioid pathway highly effective before complete avoidance is even considered.

Published systematic reviews commonly compare opioid-free anesthesia (OFA) with broadly defined opioid-based anesthesia (OBA). That comparison is easier to study but clinically less decisive. A conventional OBA protocol may lack scheduled acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), local infiltration, or regional blocks; a sophisticated OFA protocol often adds several of these simultaneously. Better outcomes can then reflect multimodal care rather than opioid absence. The pertinent clinical question is narrower: *when both groups receive an adequate multimodal foundation, does removing the remaining intraoperative opioid improve outcomes that matter to patients?* [1,2,6].

This review critically examines the direct randomized evidence in adult laparoscopic abdominal surgery and uses the wider evidence to contextualize analgesia, PONV, recovery, and harm. Its central contention is not that OFA is ineffective; rather, any incremental benefit must be demonstrated against a sufficiently effective comparator, with the physiological cost of nonopioid substitutions included in the balance.

2. SCOPE, EVIDENCE IDENTIFICATION, AND INTERPRETIVE FRAMEWORK

This is a focused critical narrative review, guided by the principles proposed for narrative reviews in anesthesia and pain medicine [6]. PubMed/MEDLINE was searched on 3 November 2026 for records published since January 2015 using the strategy ("opioid-free"[tiab] OR "opioid free"[tiab] OR "non-opioid"[tiab]) AND (anesthesia[tiab] OR anaesthesia[tiab]) AND (laparoscop*[tiab] OR cholecystectomy[tiab] OR bariatric[tiab] OR "sleeve gastrectomy"[tiab] OR "gastric bypass"[tiab] OR colectomy[tiab] OR colorectal[tiab]), limited to randomized controlled trials, systematic reviews, and meta-analyses; this search retrieved 60 records. Studies were selected purposively for their relevance to the OFA-versus-OSA question rather than through exhaustive dual screening, and an AI-assisted literature discovery tool (Consensus) was used as a supplementary source. Pivotal studies, bibliographic details, and key quantitative outcomes were checked against PubMed records and full-text publications whenever accessible, and contemporary procedure-specific recommendations were consulted. We prioritized adult laparoscopic abdominal procedures and examined landmark nonlaparoscopic trials only when they addressed a mechanism or safety signal relevant to those procedures.

The studies are interpreted in three explicitly differentiated categories. **Category A** comprises direct or near-direct comparisons of OFA with an opioid-inclusive *multimodal* regimen, where co-analgesia is available in both arms. **Category B** comprises OFA versus conventional or

otherwise incompletely described opioid-inclusive anesthesia, where the comparator cannot confidently be classified as optimized OSA. **Category C** comprises mixed-procedure reviews, network meta-analyses, guidelines, and trials outside the precise population, used for context rather than direct effect attribution. The distinction is qualitative and does not purport to be an independently conducted formal eligibility assessment.

A narrative approach is appropriate because drug combinations, perioperative pathways, trial endpoints, and definitions of OFA differ substantially. Nevertheless, its flexibility introduces selection bias. We did not conduct a reproducible exhaustive search of all databases, independent dual screening, standardized extraction by two reviewers, a RoB 2 assessment, or GRADE analysis. The tables therefore summarize selected verified studies, not a complete registry of eligible trials or a new meta-analysis. The numerical estimates that follow are from the cited original reports and must not be mistaken for pooled estimates generated for this article.

3. A BETTER CONCEPTUAL MODEL: OPIOID AVOIDANCE, OPIOID SPARING, AND ANALGESIC SUBSTITUTION

3.1. Definitions that should govern interpretation

For the present discussion, **intraoperative OFA** means no systemic opioid during induction or maintenance of anesthesia. The use of postoperative morphine or oxycodone for rescue does not negate this definition. **OSA** describes deliberate minimization of intraoperative opioid administration through a documented multimodal program, with small titrated doses retained when necessary. **OBA** describes an opioid-containing anesthetic but, without additional detail, says nothing about how much multimodal analgesia it incorporates [1,2]. The term *opioid-free care pathway* is different again: it can encompass postoperative prescribing, ward protocols, and rescue thresholds, and should not be treated as an isolated anesthesia intervention (Table 1).

An important methodological implication follows. Opioid consumption must be measured separately during surgery, in the postanesthesia care unit (PACU), over the first 24–48 hours, and after discharge. Replacing 0.5 mg of intraoperative remifentanil with dexmedetomidine does not necessarily decrease postoperative opioid use, and postoperative opioid consumption is only one component of overall exposure. A trial can appropriately call its intervention intraoperative OFA even if some participants require rescue opioids; that rescue, however, should be reported transparently as a treatment deviation or protocol-permitted response.

3.2. Why multimodal analgesia may explain much of the observed benefit

The mechanistic appeal of OFA rests on combining drugs with complementary actions: acetaminophen and NSAIDs or COX-2 inhibitors for inflammatory pain; ketamine/esketamine for NMDA-mediated modulation and potential opioid sparing; local infiltration, intraperitoneal local anesthetic, or fascial-plane blocks for afferent interruption; and alpha-2 agonists for sympatholysis and sedation. Intravenous lidocaine, magnesium, esmolol, and other agents appear in selected protocols, but their efficacy and safety are procedure- and dose-dependent. None is a universally benign substitute for an opioid [1–4].

These mechanisms are available to OSA as well. Thus, when one arm receives ketamine, lidocaine, dexmedetomidine, and a block while the other receives fentanyl without equivalent adjuncts, the experiment primarily compares *packages of care*. In contrast, holding the multimodal background constant and replacing a titrated opioid with a nonopioid agent more closely estimates the incremental value of opioid elimination. Even that comparison may be confounded by non-equivalent sedative depth, sympathetic suppression, or postoperative rescue algorithms.

3.3. The outcome hierarchy should be patient-centered

Pain intensity, pain on movement, rescue opioid requirements, PONV, early function, patient-reported recovery, and cardiorespiratory safety should be considered jointly. An apparent reduction in first-hour opioid use may have little value if pain equalizes at 24 hours, additional vasopressors are required, or PACU discharge is prolonged. Conversely, a substantial reduction in PONV can be meaningful despite unchanged morphine consumption, especially in a patient at high baseline emetic risk. This is why a claim of 'superior' anesthesia based on a single favorable secondary endpoint is usually too strong [3–5].

4. DIRECT RANDOMIZED COMPARISONS WITH MULTIMODAL OPIOID-SPARING ANESTHESIA

4.1. Laparoscopic colectomy: the clearest test of the incremental hypothesis

The trial by Collange et al. directly addressed OFA versus OSA during multimodal antinociception for laparoscopic colectomy [7]. Of 160 randomized patients, 155 were analyzed in a modified intention-to-treat population. The primary endpoint, cumulative oral morphine equivalents at 48 hours, was **9 mg (interquartile range [IQR] 0–30) with OFA versus 14 mg (IQR 0–30) with OSA (P=0.861)**. Pain and the reported major exploratory

outcomes did not meaningfully distinguish the approaches. Bradycardia was approximately three times more frequent in the OFA arm.

The trial has high clinical relevance because the comparator was deliberately opioid sparing rather than an inadequately treated conventional control. The background was nonetheless not perfectly identical: the OFA arm additionally received continuous ketamine and a magnesium dose, whereas the OSA arm received sufentanil boluses with lidocaine infusion, so the comparison is near-direct rather than a pure substitution. Its finding is not proof that the two strategies are equivalent—the absence of a statistically significant difference cannot establish equivalence without a prespecified equivalence framework and adequate precision. Rather, it indicates that **a measurable superiority of OFA on postoperative opioid use was not demonstrated** in this setting. The higher bradycardia incidence underscores the need to count adverse consequences of the substitute regimen when evaluating a purported reduction in opioid harm.

4.2. Gastric bypass: less PONV without less morphine

Clanet et al. conducted a randomized, double-blind study in **172 adults** with class III obesity undergoing bariatric surgery, comparing a dexmedetomidine-based OFA strategy with remifentanil and morphine transition within a common multimodal framework [8]. Both groups received several nonopioid elements, including ketamine, lidocaine, magnesium, acetaminophen, diclofenac, and dexamethasone. The primary endpoint—morphine consumption in the first 24 postoperative hours—was **16 mg (IQR 13–26) in OFA versus 15 mg (IQR 10–24) in the opioid-containing arm (P=0.183)**. QoR-40 was similar on postoperative days 1 and 30.

Importantly, the analgesic result was not uniformly favorable to OFA: at 4 hours, median visual analog pain scores were 4 versus 3 (P=0.015), whereas later scores converged. In contrast, PONV from PACU admission through 24 hours occurred in **37% versus 59% (P=0.005)**, and antiemetic treatment was less frequent (37% versus 57%, P=0.015). The relative value of this trade-off depends on whether the clinical aim is opioid minimization, emesis prevention, or global recovery. The study shows that avoiding opioids may yield a tolerability advantage even when its hypothesized reduction in postoperative morphine does not materialize. It does not establish an improvement in all components of recovery, and its secondary comparisons were exploratory [8].

4.3. Sleeve gastrectomy: a short-lived benefit with greater hemodynamic support

In a small randomized study of **59 analyzed patients** undergoing laparoscopic sleeve gastrectomy, Mieszczański et al. contrasted intraoperative OFA with a remifentanil-containing multimodal regimen [9]. The OFA group used less oxycodone in the first postoperative hour (**4.60 versus 7.72 mg; P=0.008**), and the PONV impact score was more favorable at that time. However, neither 24-hour oxycodone consumption nor serial pain scores differed significantly over the longer observation window.

The cost of the intervention was clinically relevant: mean ephedrine requirements were **23.67 versus 15.69 mg (P=0.039)**, accompanied by greater intravenous fluid administration (**1160 versus 925.86 mL; P=0.007**). Two participants assigned to OFA required fentanyl rescue intraoperatively for hemodynamic responses. This illustrates that eliminating opioids on paper may be difficult in everyday practice and that a protocol's practical feasibility differs from strict pharmacologic purity. The trial is too small to provide definitive safety estimates, but its direction of effect parallels signals in other dexmedetomidine-based approaches.

4.4. Laparoscopic cholecystectomy: a promising design with an important statistical qualification

Xiong et al. randomized **86 adults** undergoing laparoscopic cholecystectomy; **81** completed the study (41 OFA, 40 OSA) [10]. Both arms received an erector spinae plane block and several nonopioid agents, including esketamine and dexmedetomidine, making the comparator unusually informative. The reported 36-hour pain area-under-the-curve values were **7.3 ± 1.4 with OFA versus 6.9 ± 1.3 with OSA (P=0.201)**, and bowel function returned at **13.8 ± 2.4 versus 15.5 ± 2.3 hours (P=0.002)**. Quality-of-recovery scores and overall rescue analgesic use were similar.

The study authors declared noninferiority of OFA, citing a prespecified margin of 1.0 and a noninferiority significance level (α) of 0.025. However, the published difference (OFA minus OSA) was **0.384, with a 95% confidence interval from −0.296 to 1.064**. With α=0.025, noninferiority requires the upper limit of the two-sided 95% confidence interval to lie below the margin; the reported upper limit exceeds 1.0, so the published interval does not support the authors' conclusion. The report is, moreover, internally inconsistent: the published means and standard deviations (7.3 ± 1.4 versus 6.9 ± 1.3; n=41 and 40) imply a standard error of approximately 0.30 and a 95% confidence interval of roughly −0.21 to 0.98, which would lie within the margin and is concordant with the reported P=0.201, whereas the published interval implies a standard error of approximately 0.34. Whichever figure is erroneous, noninferiority

cannot be confirmed from the published data; this is an interpretive concern, not evidence that OFA is inferior. The defensible finding is that group mean pain was similar, while modestly faster bowel recovery was reported. A statistically nonsignificant superiority test (P=0.201) cannot substitute for a correctly evaluated noninferiority analysis [10].

4.5. What the direct evidence actually says

Across these four especially relevant studies, a consistent *sustained* reduction in postoperative opioid requirements has not emerged when a meaningful multimodal comparator is used [7–10] (Table 2). One trial demonstrated a clinically relevant PONV advantage despite unchanged morphine use [8], and another suggested faster bowel recovery, but the endpoints and periods were not uniform [10]. Hemodynamic effects were variable, with concerning bradycardia or greater vasopressor/fluid requirements in some studies [7,9]. Because many trials were small, procedure-specific, and not designed to exclude clinically important differences, these findings do not establish equivalence either. Rather, the **burden of proof for routine OFA superiority remains unmet**.

5. ADDITIONAL RANDOMIZED EVIDENCE: WHY THE COMPARISON STRATEGY MATTERS

Several trials broaden the picture without cleanly isolating OFA from OSA. Perez et al. studied opioid-free versus fentanyl-containing anesthesia in laparoscopic bariatric surgery (181 patients in the reported analysis) [11]. Twenty-four-hour oral morphine equivalents were approximately **55 versus 52 mg (P=0.49)**, with no convincing improvement in pain or hospitalization. The degree of comparator optimization is less clear than in Collange or Clanet; the trial therefore supports the absence of a large obvious advantage in that context but is not definitive for the OFA-versus-OSA question.

In a two-centre, nonblinded randomized trial of 110 analyzed patients, Olausson et al. compared an opioid-free care pathway, combining intraoperative OFA with first-line postoperative transcutaneous electrical nerve stimulation (TENS), against opioid-based standard care in bariatric surgery [12]. Postoperative pain changes during PACU stay were essentially indistinguishable (mean difference **0.04; 95% CI −1.00 to 1.08; P=0.97**), while reported PACU and in-hospital opioid consumption fell substantially with the opioid-free pathway (PACU mean difference −45 mg morphine equivalents); patient-reported recovery did not clearly improve. Crucially, the intervention was a *care pathway*, not only a substitution during anesthetic maintenance. Because postoperative TENS, perioperative prescribing, and

rescue practice can themselves determine measured opioid consumption, these results should not be attributed solely to intraoperative opioid avoidance. This study demonstrates feasibility of protocolized opioid minimization; it cannot answer the narrower pharmacologic question alone.

Mogianos et al. enrolled **154 adults** considered at low risk of acute postoperative pain and compared a dexmedetomidine–esketamine–lidocaine OFA strategy with standard opioid-based care during laparoscopic surgery [13]. In this patient- and assessor-blinded noninferiority trial, the authors concluded that OFA was noninferior for the primary endpoint: mean worst PACU pain was 4.8 **versus 4.6 (P=0.67)**; PACU rescue opioid use was lower with OFA (**3.4 versus 5.1 mg; P=0.039**), but 24-hour recovery and PONV were not improved. The proportion reporting at-rest pain NRS ≥4 at 24 hours was greater with OFA (76% versus 60%; P=0.042), but this was one of several secondary comparisons and should be interpreted cautiously. Again, short-term opioid sparing did not translate consistently into superior longer-term recovery.

Other randomized laparoscopic studies—including trials by Yu et al., Vishnuraj et al., and Accurso et al.—show that OFA can produce acceptable analgesia and sometimes favorable immediate outcomes [14–16]. Yet several also differ in regional blocks, local anesthetic techniques, or background co-analgesics; their findings are useful as demonstrations of *protocol feasibility*, not automatic evidence that eliminating opioids adds independent benefit over an equivalent OSA strategy.

6. REASSESSING THE OUTCOMES THAT MATTER

6.1. Pain and postoperative opioid use: different endpoints, different clocks

An intraoperative opioid-free label does not predict a patient's postoperative morphine requirement. Analgesia is influenced by surgery type, pre-existing pain, tissue trauma, regional block duration, inflammatory agents, and rescue protocols. The strongest head-to-head data show little evidence of sustained reduction in 24–48-hour opioid use [7–10]. The early advantage in the sleeve-gastrectomy trial disappeared by 24 hours; the bariatric trial by Clanet reported a higher pain score at 4 hours in the OFA arm despite similar total morphine [8,9]. Conversely, multicenter pathway studies that fundamentally change prescribing may reduce recorded postoperative doses without improving global pain or recovery [12].

Future comparisons should report intraoperative opioid exposure separately from cumulative postoperative oral morphine equivalents (OME) at 0–2, 0–24, and 0–48 hours, standardizing conversion factors and distinguishing oral from parenteral morphine equivalents. They should

simultaneously report movement-evoked pain, the proportion of patients with moderate-to-severe pain, and rescue-treatment failure. A lower medication total that is achieved by restricting availability is not necessarily an analgesic benefit. Interpretation should also include the absolute clinical importance of any dose reduction, not merely statistical significance.

6.2. PONV: the most plausible and recurrent benefit, but not a universal one

Because opioid exposure is an established emetogenic factor, the reduction in PONV observed in some OFA studies is biologically credible. The Clanet trial provides an unusually persuasive direct example, showing fewer PONV episodes despite no improvement in morphine consumption [8]. The POFA trial and broader syntheses also repeatedly show less PONV with OFA [17–22]. Yet emesis is multifactorial: sex, prior PONV, motion sickness, smoking status, volatile anesthetic use, prophylactic antiemetics, and postoperative opioid administration all influence risk [5]. Nonopioid adjuncts can also change anesthetic requirements and rescue treatment, creating additional causal pathways.

A practical implication is that the PONV question should be analyzed separately from analgesic effectiveness. A high-risk patient may plausibly value an OFA regimen if the expected antiemetic benefit exceeds its cardiovascular and sedative burden; another patient receiving propofol anesthesia, multiple antiemetics, and minimal opioids may gain little further benefit. The evidence supports multimodal PONV prevention, not routine reliance on OFA as a substitute for risk-based antiemetic prophylaxis [5].

6.3. Quality of recovery: statistical improvements are not automatically meaningful

Quality-of-recovery instruments capture physical comfort, independence, emotional state, and pain-related dimensions. Results have been mixed. Clanet et al. found no clear QoR-40 advantage on days 1 or 30; Xiong et al. similarly found comparable QoR-40; and the multicenter bariatric pathway study reported no clear global patient-reported recovery improvement despite lower opioid administration [8,10,12]. Some pooled analyses report small improvements, but high between-study heterogeneity limits interpretability [18].

If a statistically significant scale difference is only one or two points, the reader must ask whether it exceeds a validated clinically important threshold, whether the scale was measured at an appropriate time, and whether the patient actually returned to normal function sooner. Extubation time, PACU length of stay, and hospital discharge are particularly susceptible to surgical protocols and institutional practice. Opioid avoidance should not be assumed to accelerate recovery unless such an effect is actually demonstrated.

6.4. Hemodynamic stability and the hazard of analgesic substitution

Eliminating opioids frequently entails increasing dexmedetomidine or other nonopioid adjuncts. Alpha-2 agonism can attenuate stress responses but also causes bradycardia and hypotension; treatment may require anticholinergics, vasopressors, or additional fluids. In the direct laparoscopic evidence, Collange et al. observed more bradycardia with OFA, while Mieszczański et al. reported greater ephedrine and crystalloid use [7,9]. These are not cosmetic endpoints: hemodynamic instability, delayed emergence, and resource use can offset a reduction in PONV or early opioid doses.

The multicenter **POFA** trial, although not confined to laparoscopic abdominal surgery, is a major safety warning [17]. It compared dexmedetomidine-based OFA with remifentanil-based balanced anesthesia in 312 analyzed patients and was stopped early following **five severe bradycardia events** in the OFA group. The primary outcome, a composite of postoperative opioid-related adverse events (hypoxemia, ileus, or cognitive dysfunction within 48 hours), occurred in **78% versus 67%** (relative risk 1.16; 95% CI 1.01–1.33), and hypoxemia occurred in **72% versus 61%** (relative risk 1.19; 95% CI 1.02–1.40). For balance, the dexmedetomidine arm received less postoperative morphine over 48 hours (median 6 versus 11 mg) and had less PONV (24% versus 37%; relative risk 0.64; 95% CI 0.45–0.90). Patients in the dexmedetomidine arm also had delayed extubation and longer PACU stays. Thus, despite lower opioid exposure, the opioid-free arm experienced more of the very adverse events that opioid avoidance is intended to prevent. These results do not prove that every OFA protocol is unsafe, but they challenge the assumption that avoiding opioids intrinsically reduces perioperative adverse events. Safety is regimen-specific, dose-specific, and population-specific.

Other substitutions require individual scrutiny. Systemic lidocaine carries toxicity concerns if dosing, infusion timing, and concurrent local anesthetic exposure are poorly controlled. Ketamine may be problematic in selected patients because of psychoperceptual or cardiovascular effects. Fluid loading to manage sympatholysis may be counterproductive in patients with cardiac or renal vulnerability. The proper comparison is therefore not 'opioid toxicity versus no toxicity' but **the net burden of opioid-related harm versus the adverse effects and complexity of the alternative regimen** [1,2,17].

6.5. Bowel function, length of stay, and longer-term outcomes

Earlier bowel recovery in Xiong et al. suggests a possible procedure-specific effect, but an interval of approximately 1.7 hours after cholecystectomy should not be generalized to

meaningful reductions in postoperative ileus after colorectal resection [10]. Hospital stay is strongly influenced by operative technique, discharge criteria, oral intake, bed availability, and postoperative care pathways. In the direct bariatric trial by Clanet, median length of stay was one day in both arms [8]. Evidence that intraoperative OFA prevents chronic postsurgical pain, long-term opioid dependence, pulmonary complications, or readmission remains insufficient [1,2,13,23]. Claims of long-term benefit should not be extrapolated from short-term reductions in drug administration.

7. WHAT SYSTEMATIC REVIEWS REVEAL—AND WHAT THEY CANNOT PROVE

The large literature on OFA is not a single coherent treatment effect (Table 3). An earlier meta-analysis by Frauenknecht et al. (23 trials, 1,304 patients) found equivalent pain scores at 2 hours with or without intraoperative opioids but less PONV in opioid-free groups (risk ratio 0.77; 95% CI 0.61–0.97); its comparators, however, were placebo or no intraoperative opioid rather than structured multimodal OFA [22]. A subsequent synthesis by Olausson et al. suggested that opioid-free general anesthesia could improve selected postoperative outcomes, but the broad surgical inclusion and heterogeneous comparators limit direct application to optimized OSA [24]. Cheng et al. pooled **12 randomized trials comprising 983 laparoscopic patients** and reported less early pain and PONV with multimodal OFA versus conventional opioid anesthesia [18]. However, reported heterogeneity for early pain was substantial (**I^2=92%**) and for quality-of-recovery scores even greater (**I^2=94.2%**). The comparators were broadly labeled opioid-containing anesthesia, not uniformly verified OSA. An average benefit in this network cannot by itself identify an incremental benefit over a contemporary well-standardized multimodal program.

A laparoscopic meta-analysis by Bersot et al. included **16 randomized trials (1,322 patients)** and reported less PONV (risk ratio **0.60**, 95% CI **0.48–0.75**) and lower 24-hour morphine equivalents (mean difference **−6.4 mg**, 95% CI **−9.1 to −3.7**), while pain scores at 24 hours were similar [19]. These figures are informative but the control was OBA, not consistently matched OSA; the numerical opioid reduction should not be transferred to a direct OFA–OSA decision. Meanwhile, Tripodi et al.'s network meta-analysis of **42 trials (4,666 patients)** across noncardiac procedures found no statistically significant 24-hour pain advantage for any OFA drug combination compared with OBA, with substantial protocol heterogeneity and frequent risk-of-bias concerns [20].

The most informative recent synthesis for the role of regional analgesia is the 2026 network meta-analysis by de Carvalho et al., encompassing **885 randomized trials and approximately 74,880 patients** across diverse operations [21]. Approaches incorporating regional anesthesia generally achieved better postoperative pain control, and where regional anesthesia was used, differences between opioid-free and opioid-inclusive strategies were small. Regional anesthesia combined with an opioid-free strategy nevertheless ranked highest for minimizing postoperative opioid consumption, and opioid-free approaches were associated with less PONV. Nevertheless, its immense breadth is a limitation for extrapolation to any individual abdominal procedure, and some rankings had low certainty. A high network ranking is not equivalent to proof of clinically meaningful benefit for a specific drug substitution.

These syntheses appear to disagree mainly when their questions are treated as identical. They are not. A broad OFA-versus-OBA synthesis may detect benefits of enhanced nonopioid multimodal care or improved antiemetic performance; a direct OFA-versus-OSA trial estimates the smaller incremental effect of *removing the residual opioid*. Both findings can be simultaneously true. This phenomenon is a **comparator-quality problem**, not necessarily a contradiction in clinical pharmacology.

8. FIVE METHODOLOGICAL PITFALLS THAT HAVE DISTORTED THE DEBATE

8.1. Comparator contamination and unequal co-interventions

Trials should specify whether both arms receive equivalent baseline acetaminophen, NSAIDs/COX-2 inhibitors, dexamethasone, local infiltration, regional techniques, and postoperative rescue. Comparators described merely as 'opioid-based' may be less than standard multimodal care. Conversely, an OSA group receiving multiple agents may be sufficiently effective that additional OFA drugs offer limited incremental benefit. The use of total nonopioid medication counts is not a valid substitute for reporting actual doses, onset, duration, and patient-specific contraindications.

8.2. Treatment label versus treatment actually delivered

The sleeve-gastrectomy study documented intraoperative fentanyl rescue in two patients assigned to OFA [9]. This does not invalidate randomization, but it shows why protocols should report adherence, crossover, and rescue separately while retaining appropriate intention-to-treat analyses. The true clinical comparison is assignment to an OFA-oriented strategy versus

assignment to OSA, not an idealized claim that every OFA patient remains opioid-free in all circumstances.

8.3. Misinterpretation of null findings and noninferiority

A nonsignificant superiority test does not prove equivalence, and a claimed noninferiority finding must satisfy its confidence-bound decision rule. The Xiong report, whose published upper 95% confidence limit (1.064) exceeds the 1.0 margin and is inconsistent with its own reported standard deviations, illustrates this problem [10]. Small randomized trials may be unable to detect important harm or modest outcome differences. Authors should avoid describing 'no statistically significant difference' as proof of 'equal effectiveness' unless the corresponding equivalence or noninferiority design is explicit and adequately supported.

8.4. Outcome timing and multiplicity

A first-hour reduction in opioid use may be clinically useful but is not interchangeable with 24-hour or 48-hour analgesic burden. PONV, pain, and hemodynamic outcomes can also show different time courses. Many OFA studies contain multiple exploratory comparisons without adjustment for multiplicity; isolated favorable P values need replication. Reviews should state whether a reported outcome was primary or secondary, whether it was prespecified, and whether the effect is clinically substantial.

8.5. Confounding by regional anesthesia and the entire perioperative pathway

Regional anesthesia may be the strongest determinant of pain control in some procedures [21], while antiemetic prophylaxis and discharge policies affect recovery independently of intraoperative opioid exposure. Trials comparing an opioid-free *pathway* with conventional care conflate anesthesia, rescue prescribing, ward nursing, and postoperative treatment availability [12]. To identify the additive effect of OFA, future pragmatic randomized studies should keep a minimum multimodal background constant, separate regional-analgesia strata, and prospectively define clinically important endpoints.

9. TRANSLATING EVIDENCE INTO PERIOPERATIVE PRACTICE

The evidence does not warrant either indiscriminate opioid administration or compulsory opioid elimination. For **laparoscopic cholecystectomy**, PROSPECT recommends acetaminophen plus an NSAID or COX-2 inhibitor when appropriate, perioperative dexamethasone, port-site infiltration or intraperitoneal local anesthetic, and opioid rescue if necessary; ESP or TAP blocks are generally second-line for selected higher-risk circumstances

[3]. Of note, the same procedure-specific recommendations do not routinely recommend intravenous dexmedetomidine, ketamine, or lidocaine despite possible analgesic effects, because the adverse-effect trade-off matters. These recommendations should not be replaced by a generic OFA recipe.

For **bariatric surgery**, careful opioid minimization is attractive because obstructive sleep apnea, sedation, and respiratory vulnerability complicate recovery. ERAS recommendations support multimodal opioid-sparing anesthesia and appropriate monitoring [4]. Nevertheless, bariatric trials have shown both PONV advantages and neutral analgesic outcomes under OFA [8,9,11,12]. For **laparoscopic colorectal surgery**, where postoperative ileus, mobilization, and recovery are especially important, the colectomy RCT offers a reason not to assume a large incremental benefit of routine OFA over a strong multimodal OSA pathway [7].

An evidence-informed decision process is therefore best framed around the patient's expected opioid-related risk, the procedure's nociceptive burden, the adequacy of basic multimodal analgesia, the availability and expertise for regional techniques, and the cardiovascular effects of proposed substitutes. An OFA-oriented plan is defensible when a credible patient-specific benefit is anticipated, its drugs can be safely administered, and postoperative rescue remains available. OSA is a robust default when a small titrated opioid can provide controllable antinociception without compromising a strong multimodal strategy.

There is also an implementation issue. Complex OFA combinations can require infusion pumps, additional monitoring, careful drug preparation, specialist expertise, and resources to manage adverse effects. An inexpensive but well-executed program of acetaminophen, a suitable NSAID, local infiltration, dexamethasone, and selective opioid rescue may be more reproducible than an elaborate infusion-based OFA regimen in settings with limited resources. That is an argument about feasibility and safe stewardship, not a claim that resource-limited settings cannot provide OFA.

10. RESEARCH AGENDA: TRIALS THAT WOULD SETTLE THE INCREMENTAL QUESTION

The next decisive trials should compare **optimized OSA** against OFA while keeping the rest of care as identical as possible. Ideally, patients would be randomized within one laparoscopic procedure or prespecified procedure strata, with transparent protocols specifying drug doses, regional block allocation, antiemetics, anesthetic depth, and the same postoperative rescue algorithm. Primary outcomes should be chosen from patient-centered effects such as 24–48-

hour pain on movement with an appropriately powered noninferiority hypothesis, cumulative OME with a prespecified minimally important difference, or a clinically meaningful composite of opioid-related and nonopioid-agent adverse effects.

Investigators should systematically record intraoperative drug exposure, hypotension/bradycardia requiring treatment, time to extubation and PACU readiness, patient-reported recovery, PONV, functional milestones, and rescue failure. Follow-up beyond discharge should assess persistent opioid use or chronic pain rather than infer them from immediate postoperative doses. Statistical plans should specify how crossovers and rescue opioids are handled, analyze outcomes by intention to treat, and report confidence intervals rather than relying on P values alone (Table 4). Multicenter pragmatic trials are particularly needed in older adults, patients with cardiovascular comorbidity, and chronic opioid users, who are often underrepresented in existing studies [1,2,17,20].

11. STRENGTHS AND LIMITATIONS OF THE PRESENT REVIEW

This review's principal strength is its explicit separation of direct OFA–OSA evidence from OFA–OBA literature, supported by a critical reading of randomized outcomes and the 2025–2026 synthesis landscape. It also evaluates drug substitution, the time-dependent nature of outcomes, and clinically important safety signals. The noninferiority reporting issue noted in Xiong et al. and the rescue-opioid crossover reported by Mieszczański et al. highlight details that can be lost when study conclusions are repeated uncritically.

The limitations are equally important. This is a selective narrative synthesis; it is not a systematic study census, and studies may have been missed. We did not retrieve or audit every protocol, adjudicate trial-level RoB 2 domains, or recalculate effect estimates from individual participant data. Some endpoint descriptions are based on abstracts rather than complete individual trial datasets, and formal bibliographic verification does not eliminate errors in the published records. No original patient-level data, new pooled statistics, PRISMA selection count, or GRADE certainty estimates are claimed. These limitations constrain the strength of any comparative causal conclusion.

12. CONCLUSION

In adult laparoscopic abdominal surgery, the value of opioid-free anesthesia depends less on the absence of opioids itself than on the strength of the comparator and the total perioperative pathway. Direct randomized comparisons with multimodal OSA have not demonstrated consistent superiority of OFA for sustained postoperative analgesia, opioid consumption, or

quality of recovery, although selected protocols may reduce PONV or accelerate specific recovery measures. Dexmedetomidine-related bradycardia, hemodynamic support, and delayed emergence must be weighed against such benefits. Until adequately powered procedure-specific trials establish incremental advantages, the most defensible standard is individualized, evidence-based multimodal opioid stewardship: reduce unnecessary opioids, use regional and nonopioid analgesia intelligently, and retain titrated opioids as appropriate rescue rather than treating complete avoidance as an end in itself.

TABLES :

Table 1. Distinct clinical constructs often grouped under the same label

Strategy	Practical definition	What the label does *not* tell the reader
Intraoperative OFA	No intraoperative systemic opioid is planned or delivered, barring documented rescue/deviation	Postoperative rescue can still involve opioids; co-analgesic regimens may vary widely
Multimodal OSA	A planned reduction of opioid dose within documented systemic and/or regional multimodal analgesia	The actual opioid exposure cannot be inferred without drug doses and time windows
Conventional OBA	An opioid-containing anesthetic, sometimes with nonopioid adjuncts	It is not necessarily a high-opioid regimen, and is not automatically equivalent to optimized OSA
Opioid-free *care pathway*	A perioperative package that may also alter PACU, ward, and discharge prescribing	Effects cannot be attributed to intraoperative opioid elimination alone

Table 2. Selected randomized trials that inform the specific OFA-versus-OSA question

Study	Procedure, participants	Comparator quality	Key outcomes (OFA vs comparator)	Critical interpretation
Collange et al., 2024 [7]	Laparoscopic colectomy; 160 randomized, 155 analyzed	Near-direct OSA: shared multimodal base; OFA arm also received ketamine infusion and magnesium	48-h OME 9 [0–30] vs 14 [0–30] mg; P=0.861; bradycardia approximately threefold more frequent with OFA	No demonstrated 48-h opioid advantage; higher bradycardia risk
Clanet et al., 2024 [8]	Gastric bypass; n=172	**Near-direct OSA:** shared multimodal adjuncts	24-h morphine 16 [13–26] vs 15 [10–24] mg; P=0.183; PONV	Better PONV, without less morphine or better global QoR

Study	Procedure, participants	Comparator quality	Key outcomes (OFA vs comparator)	Critical interpretation
			37% vs 59%; P=0.005	
Mieszczański et al., 2023 [9]	Sleeve gastrectomy; n=59 analyzed	**Direct/near-direct OSA:** remifentanil plus MMA	1-h oxycodone 4.60 vs 7.72 mg; P=0.008; 24-h total not different; ephedrine 23.67 vs 15.69 mg; P=0.039	Early-only signal; greater vasopressor/fluid support; fentanyl rescue in 2 OFA cases
Xiong et al., 2025 [10]	Cholecystectomy; 86 randomized, 81 completed	**Direct OSA:** shared esketamine, dexmedetomidine, ESP block	36-h pain AUC 7.3 ± 1.4 vs 6.9 ± 1.3; recovery of bowel function 13.8 vs 15.5 h	The reported upper 95% CI for pain difference (1.064) exceeds the noninferiority margin (1.0); also inconsistent with reported SDs, so noninferiority is unconfirmed
Perez et al., 2025 [11]	Bariatric laparoscopy; 181 in report	**OBA/unclear OSA:** fentanyl-containing comparator	24-h oral morphine equivalents about 55 vs 52 mg; P=0.49	Important corroboration, but weaker isolation of OSA comparator
Olausson et al., 2025 [12]	Bariatric laparoscopy; two-centre nonblinded RCT; n=110	**Whole-pathway comparator:** opioid-free care (OFA + postoperative TENS) vs standard care	PACU pain change MD 0.04 (95% CI −1.00 to 1.08); marked reduction in administered opioids	Postoperative TENS and prescribing are part of the intervention: cannot attribute dose effect to intraoperative OFA alone
Mogianos et al., 2026 [13]	Low predicted pain-risk laparoscopic adults; n=154	**Standard care**, not optimized OSA established	PACU pain 4.8 vs 4.6; P=0.67; rescue opioid 3.4 vs 5.1 mg; P=0.039	Noninferior for PACU pain; less early rescue, but no recovery or PONV benefit

Abbreviations: AUC, area under the curve; ESP, erector spinae plane; IQR, interquartile range; MD, mean difference; MMA, multimodal analgesia; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia; OME, oral morphine equivalents; OSA, opioid-sparing anesthesia; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; QoR, quality of recovery. Values reported are those published by the original studies, not results of new extraction or statistical pooling.

Table 3. Existing syntheses and why they do not resolve OFA versus optimized OSA

Synthesis	Coverage	Main reported pattern	Limitation for the present question
Cheng et al., 2025 [18]	12 RCTs, 983 laparoscopic patients	Less early pain/PONV; very high I^2 for early pain and QoR	OFA vs broadly conventional opioid anesthesia; not consistently optimized OSA
Bersot et al., 2026 [19]	16 RCTs, 1,322 laparoscopic patients	PONV RR 0.60 (0.48–0.75); OME −6.4 mg; 24-h pain similar	Study controls broadly OBA and may differ in co-interventions
Tripodi et al., 2025 [20]	42 RCTs, 4,666 noncardiac surgical patients	No OFA combination clearly superior for pain at 24 h	Mixed procedures and heterogeneous OFA drug combinations
de Carvalho et al., 2026 [21]	885 RCTs, ~74,880 patients, mixed surgery	Regional anesthesia most influential for pain; OFA/OI difference small when regional techniques included	Network effects and ranking are not direct procedure-specific OFA–OSA estimates

Table 4. Reporting items needed for interpretable future OFA–OSA trials

Domain	Minimum useful reporting
Exposure fidelity	Induction/maintenance opioids (drug and total dose); rescue/crossover; actual delivered adjuncts
Comparator quality	Identical basic analgesia, local/regional technique, antiemetics and postoperative rescue rules where feasible
Outcomes over time	Pain at rest/movement; 0–2, 0–24 and 0–48 h postoperative OME; PONV and antiemetic rescue
Safety	Bradycardia/hypotension definitions, atropine/vasopressors, fluids, hypoxemia, delayed emergence, sedation and toxicity
Recovery	Validated QoR score with clinical-importance threshold, bowel function where relevant, time to PACU readiness, discharge
Analysis	Prespecified superiority/noninferiority hypothesis; suitable margin; intention-to-treat; CIs and multiplicity control

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