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Comparison of Opioid-Free versus Opioid-Based Anesthesia on Postoperative Pain and Nausea/Vomiting in Adult Upper Airway, Sinonasal, and Cervical Surgery: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Background: Opioid-free anesthesia (OFA) may reduce opioid-related adverse effects, particularly postoperative nausea and vomiting (PONV). Evidence in adult upper airway, sinonasal, and cervical surgery—where PONV-driven Valsalva maneuver can precipitate hemorrhage—has not been synthesized at the randomized-trial level. We compared OFA with opioid-based anesthesia (OBA) for postoperative pain and PONV in this population.

Methods: Following PRISMA 2020, five databases were searched from January 2016 to March 2026 for randomized controlled trials (RCTs) comparing OFA with OBA in adults undergoing elective sinonasal, nasal, or cervical (thyroid/parathyroid) surgery. Co-primary outcomes were postoperative pain and PONV. Two reviewers independently performed screening, extraction, and Cochrane RoB 2 assessment. A narrative synthesis was conducted a priori.

Results: Five RCTs (1,369 patients) were included; dexmedetomidine anchored every OFA regimen. All showed reduced PONV with OFA: the largest trial (endoscopic sinus surgery, n=773) reported 7.0% versus 15.1% (p=0.0021) and a thyroid/parathyroid trial (n=394) 5% versus 24% (p<0.001), with absolute risk reductions of approximately 8–19 percentage points. Pain was non-inferior, with small early advantages generally below the minimum clinically important difference. OFA also reduced rescue analgesia, blood loss, and sore throat. Two trials were low risk of bias, three had some concerns. Because dexmedetomidine has independent antiemetic activity, the PONV benefit cannot be attributed solely to opioid removal; bradycardia and prolonged emergence were more frequent with OFA.

Conclusions: Dexmedetomidine-based OFA is associated with consistently reduced PONV and non-inferior pain control versus OBA, tempered by bradycardia and slower emergence. Adequately powered RCTs with active opioid-sparing comparators and explicit safety endpoints are needed.

Keywords: *opioid-free anesthesia; opioid-based anesthesia; postoperative nausea and vomiting; postoperative pain; dexmedetomidine; endoscopic sinus surgery; thyroidectomy; sinonasal surgery; systematic review.*

1. INTRODUCTION

Upper airway, sinonasal, and cervical surgery encompasses a broad spectrum of procedures performed under general

anesthesia, including Functional Endoscopic Sinus Surgery (FESS) for chronic rhinosinusitis and nasal polyposis, septoplasty, turbinoplasty, nasal polypectomy, septorhinoplasty, thyroidectomy, parathyroidectomy, and tonsillectomy.[1,2,3] These procedures share three perioperative challenges relevant to anesthetic technique: a high-risk or contested airway, susceptibility to bleeding from a vascular operative bed, and a patient population with elevated risk of postoperative nausea and vomiting (PONV). For sinonasal and upper aerodigestive procedures, vomiting-induced Valsalva maneuver can precipitate postoperative hemorrhage, compromise grafted or packed cavities, and substantially delay discharge.[4,5,6]

Opioids have traditionally been an essential component of perioperative analgesia because of their potent analgesic effects and their ability to attenuate intraoperative nociceptive responses. However, perioperative opioid use is associated with several recognized adverse effects, including respiratory depression, delayed recovery, pruritus, urinary retention, and gastrointestinal dysfunction.[10,11] Among these complications, PONV is one of the most distressing and clinically significant outcomes. Reported PONV incidence ranges from approximately 30% in the general surgical population to 70–80% in high-risk patients, particularly those receiving general anesthesia with intraoperative opioids.[7,12] In thyroid surgery specifically, PONV incidence has been reported at 60–80% with conventional opioid-based techniques.[7]

In response to growing concerns regarding opioid-related adverse effects, opioid-free anesthesia (OFA) has emerged as an alternative anesthetic strategy that eliminates intraoperative opioid administration.[13,14,15] OFA relies on multimodal non-opioid analgesia using combinations of α-2 agonists (predominantly dexmedetomidine), N-methyl-D-aspartate antagonists (ketamine or esketamine), intravenous lidocaine, magnesium sulfate, and non-steroidal anti-inflammatory drugs.[16] Several systematic reviews and meta-analyses across mixed surgical populations have concluded that OFA reduces PONV and may improve early postoperative analgesia, although both effect direction and magnitude vary across patient groups and pharmacological protocols.[17,18,30,31,32,35]

The evidence for OFA in adult upper airway, sinonasal, and cervical surgery specifically remains limited and procedurally heterogeneous. Pooled estimates from existing meta-analyses are dominated by abdominal, gynecological, thoracic, and bariatric populations, and may not generalize to a population in which surgical-field optimization, airway sensitivity, and PONV-driven hemorrhagic risk are central perioperative concerns. A focused synthesis restricted to the population of interest, and to randomized controlled trial-level evidence, is therefore needed.

The present systematic review evaluates and compares the effects of opioid-free versus opioid-based anesthesia on postoperative pain and PONV in adult patients undergoing elective upper airway, sinonasal, and cervical (thyroid/parathyroid) surgery under general anesthesia.

2. METHODS

2.1 Study Design and Protocol Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[28] Where the protocol differed from the final review (notably the a priori decision not to perform a de novo meta-analysis given anticipated heterogeneity), the deviation is reported in the relevant section.

2.2 Eligibility Criteria

Eligibility was defined using the PICOS framework.

2.2.1 Inclusion Criteria

- **Population:** Adult patients (≥18 years) undergoing elective upper airway, sinonasal, or cervical surgery under general anesthesia. Eligible procedures comprised functional endoscopic sinus surgery (FESS), septoplasty, turbinoplasty, nasal polypectomy, septorhinoplasty, rhinoplasty, thyroidectomy, parathyroidectomy, and adult tonsillectomy. Cervical (thyroid/parathyroid) procedures were included on the basis of shared perioperative concerns: airway-adjacent operative field, high baseline PONV risk, and clinical relevance of postoperative sore throat and hoarseness.
- **Intervention:** Opioid-free anesthesia (OFA), defined as a general anesthetic technique entirely eliminating intraoperative opioid administration through any route (systemic, neuraxial, or local infiltration), using multimodal non-opioid agents.
- **Comparator:** Opioid-based anesthesia (OBA), defined as a general anesthetic technique incorporating intraoperative opioid administration as a primary analgesic component.
- **Outcomes:** Co-primary outcomes were (i) postoperative pain intensity assessed by validated scales (VAS or NRS) and (ii) incidence or severity of postoperative nausea and vomiting (PONV). Secondary outcomes were rescue analgesic consumption, time to PACU discharge, hemodynamic stability, postoperative sore throat, and patient-reported quality of recovery.
- **Study design:** Randomized controlled trials only. Existing systematic reviews and meta-analyses were not eligible for inclusion in the qualitative synthesis but were used as supporting/contextual evidence in the Discussion (Table 2).
- **Time frame:** Studies published between January 2016 and March 2026.
- **Language:** English-language full-text publications.

2.2.2 Exclusion Criteria

- Pediatric-only populations (<18 years); mixed populations were eligible if adult data were separately reported.
- Studies in surgical populations outside the PICOS (e.g., abdominal, thoracic, orthopedic, gynecological, bariatric).
- Case reports, case series, conference abstracts, editorials, and animal studies.
- Studies without a concurrent OBA comparator group.
- Studies that did not report at least one primary outcome (postoperative pain or PONV).
- Opioid-sparing (rather than opioid-free) designs in which low-dose intraoperative opioids were administered.
- Studies conducted under regional or monitored anesthesia care without general anesthesia.
- Duplicate publications or studies reporting overlapping cohorts.

2.3 Search Strategy

A comprehensive electronic search was conducted in five databases: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. The search was restricted to publications from January 2016 to March 2026. The strategy combined Medical Subject Headings (MeSH) and free-text keywords with Boolean operators (AND, OR). The PubMed strategy was as follows:

("opioid-free anesthesia" OR "opioid free anaesthesia" OR "opioid-free technique" OR "non-opioid anesthesia") AND ("endoscopic nasal surgery" OR "functional endoscopic sinus surgery" OR "FESS" OR "septoplasty" OR "turbinoplasty" OR "nasal polypectomy" OR "sinonasal surgery" OR "thyroidectomy" OR "parathyroidectomy" OR "tonsillectomy" OR "upper airway surgery" OR "head and neck surgery" OR "rhinoplasty") AND ("postoperative pain" OR "postoperative nausea" OR "PONV" OR "nausea and vomiting" OR "quality of recovery")

Equivalent strategies adapted for Emtree (Embase) and CENTRAL indexing were applied. Additional terms incorporated included *"dexmedetomidine," "ketamine," "esketamine," "lidocaine infusion," "multimodal analgesia,"* and *"opioid-based anesthesia."* Reference lists of all included studies and relevant systematic reviews were hand-searched to identify additional eligible studies.

2.4 Study Selection

All retrieved citations were imported into Rayyan systematic review software and deduplicated. Two reviewers independently screened titles and abstracts against the eligibility criteria. Full texts of potentially eligible records were retrieved and independently assessed. Disagreements at any stage were resolved by discussion; a third reviewer served as arbiter when consensus was not reached. Reasons for exclusion at the full-text stage were documented.[28]

2.5 PRISMA Flow

The PRISMA 2020 flow of records is summarized below. A formal PRISMA 2020 flow diagram is provided as Figure 1 in the submitted manuscript.

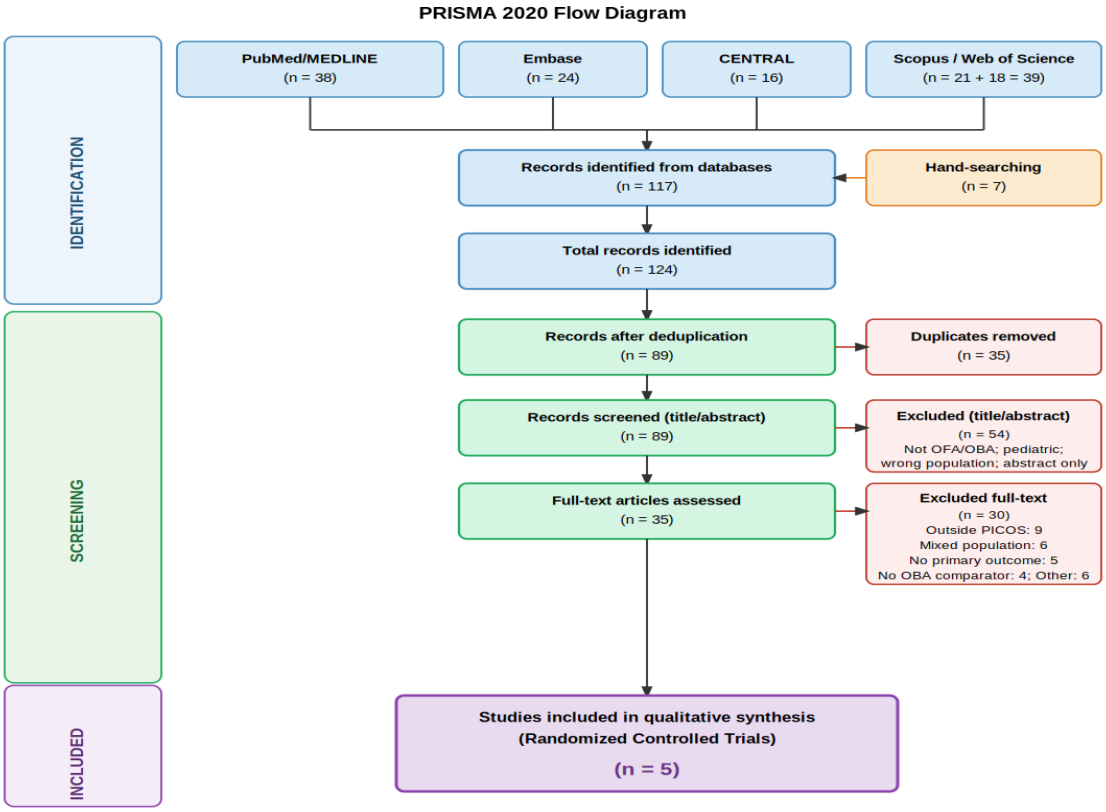

Figure 1. PRISMA 2020 Flow Diagram. Records identified from five electronic databases and hand-searching; screened, assessed, and included in the qualitative synthesis (5 RCTs). Seven supporting systematic reviews/meta-analyses cited in the Discussion are not formally included in the synthesis.

2.6 Data Extraction

Data were independently extracted by two reviewers using a pre-specified standardized form capturing: (1) author(s) and year; (2) study design and setting; (3) surgical procedure; (4) sample size and group allocation; (5) OFA protocol; (6) OBA protocol; (7) postoperative analgesic and antiemetic regimen; (8) primary and secondary outcomes; and (9) effect estimates with statistical significance.

2.7 Risk of Bias Assessment

Methodological quality of all included randomized controlled trials was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result.[29] Each domain was rated as Low risk, Some concerns, or High risk, with an overall judgment determined per Cochrane guidance. Two reviewers independently performed the assessment with disagreements resolved by discussion. Per-study judgments are reported in Table 3 and summarized narratively in Section 3.3.

2.8 Data Synthesis

Given the anticipated clinical and methodological heterogeneity across studies, a narrative (qualitative) synthesis was performed; this decision was made a priori. Findings for each primary outcome were grouped by surgical type and described. To contextualize the included RCTs, key existing systematic reviews and meta-analyses (Table 2) were summarized as supporting evidence in the Discussion. A de novo meta-analysis was not performed.

3. RESULTS

3.1 Study Selection

After systematic searching of five electronic databases supplemented by hand-searching, 124 records were identified. Following deduplication (n=35) and two-stage screening (n=84 excluded across title/abstract and full-text stages), five randomized controlled trials met the eligibility criteria and were included in the qualitative synthesis. Three RCTs were conducted in nasal/sinonasal populations (Zhou 2023, S HS 2023; one each in FESS and mixed nasal surgery)[19,33] and two in cervical (thyroid) surgery (Choi 2017, Kim 2020).[24,34] One additional RCT (Wang 2024) was conducted in thyroid and parathyroid surgery.[25] Six widely cited systematic reviews and meta-analyses spanning mixed surgical populations were identified during searches and are summarized in Table 2 as supporting evidence; they are not part of the qualitative synthesis but inform contextual interpretation in the Discussion.

3.2 Characteristics of Included Studies (Table 1)

The five included RCTs comprised a total of 1,369 randomized adult patients. Sample sizes ranged from 48 (S HS 2023)[33] to 773 (Zhou 2023).[19] Three trials were single-center (Choi 2017, Kim 2020, S HS 2023); two were multi-center (Zhou 2023 — seven sites; Wang 2024 — two sites). Four trials were double- or triple-blinded. Dexmedetomidine formed the backbone of the OFA regimen in every included study, used either alone (Choi 2017, Kim 2020) or in combination with intravenous lidocaine (S HS 2023, Zhou 2023) or with esketamine plus lidocaine (Wang 2024). The OBA comparator was remifentanil in three trials (Choi 2017, Kim 2020, Zhou 2023 [combined with sufentanil]) and sufentanil-based in two (Wang 2024, Zhou 2023); fentanyl was the comparator in S HS 2023. Postoperative regimens typically included paracetamol, an NSAID (flurbiprofen axetil or diclofenac), and ondansetron with or without dexamethasone.

Table 1. Characteristics of Included Studies (Five Randomized Controlled Trials in Adult Upper Airway, Sinonasal, and Cervical Surgery, 2016–2026).

Study (PMID/DOI)	Design / Setting	Surgery	Sample Size	OFA Protocol	OBA Protocol	Postop Medication	Primary Outcome	Key Results
Zhou et al., 2023 Eur J Anaesthesiol PMID 37377372	Multi-center double-blind RCT; 7 hospitals, China	Endoscopic sinus surgery	n=773 (OFA 388; OBA 385)	Dexmedetomidine (loading + infusion); intravenous lidocaine; propofol-sevoflurane; NO opioids	Sufentanil bolus + remifentanil infusion; propofol-sevoflurane	Flurbiprofen axetil 50 mg IV; rescue tramadol 50 mg; ondansetron 4 mg	QoR-40 at 24 h (1°); NRS pain, PONV (2°)	PONV: 7.0% vs 15.1% (p=0.0021), favoring OFA. NRS pain lower with OFA at 30 min, 1 h, 2 h, 24 h (all p<0.05). QoR-40: statistically significant difference (p=0.0014) but clinically modest.
S HS et al., 2023 Cureus DOI 10.7759/cureus.42409 PMID 37502467	Prospective triple-blind RCT; single center, India	Mixed nasal surgery: septoplasty, FESS, turbinoplasty	n=48 (OFA 24; OBA 24)	Dexmedetomidine 1 µg/kg IV bolus + 0.4 µg/kg/h; lidocaine 1.5 mg/kg + 1.5 mg/kg/h; NO opioids	Fentanyl 2 µg/kg at induction + 0.5 µg/kg/h infusion	Ondansetron PRN; rescue diclofenac or tramadol	VAS pain (1°); PONV, rescue analgesia, blood loss, hemodynamics, sedation (2°)	VAS pain: comparable between groups. PONV: reduced with OFA. Rescue analgesia: lower with OFA. Intraoperative blood loss: reduced with OFA. Hemodynamic stability: improved with OFA.
Choi et al., 2017 Korean J Anesthesiol PMID 28580080	Single-center RCT; Korea	Thyroidectomy (total/subtotal)	n=80 (OFA 40; OBA 40)	Dexmedetomidine 1 µg/kg loading over 10 min + 0.3–0.5 µg/kg/h; sevoflurane; NO opioids	Remifentanil TCI 4 ng/mL induction, 2–3 ng/mL maintenance; sevoflurane	Rescue antiemetics PRN; rescue analgesia as needed	PONV incidence 0–24 h (1°); VAS pain, sedation, hemodynamics (2°)	PONV: significantly lower with OFA in both 0–2 h and 2–24 h windows (p<0.05). Rescue antiemetic use: lower with OFA (p<0.05). VAS pain: lower with OFA at 2–24 h.

Wang et al., 2024 Anaesthesia PMID 39037325	Double-blind RCT; 2 centers, China	Thyroid and parathyroid surgery	n=394 (OFA 197; OBA 197)	Esketamine + intravenous lidocaine + dexmedetomidine + propofol TIVA; NO opioids	Sufentanil + propofol TIVA	Dexamethasone + ondansetron (both groups); paracetamol + flurbiprofen axetil	PONV incidence 0–48 h (1°); NRS pain, rescue analgesia (2°)	PONV: 5% vs 24% ($p<0.001$), favoring OFA. NRS pain: comparable at 24 h. Rescue analgesia: similar between groups.
Kim et al., 2020 Medicine (Baltimore) PMID 32702848	Single-center RCT; Korea	Thyroidectomy	n=74 (OFA 37; OBA 37)	Dexmedetomidine 1 µg/kg loading + 0.3–0.6 µg/kg/h; sevoflurane; NO opioids	Remifentanil 3–4 ng/mL TCI; sevoflurane	Rescue analgesia PRN	Postoperative sore throat (1°); NRS pain, PONV, hoarseness (2°)	POST incidence: significantly lower with OFA ($p<0.05$). NRS pain: lower with OFA at all timepoints. Hoarseness: less frequent with OFA.

Abbreviations: *FESS = Functional Endoscopic Sinus Surgery; IV = intravenous; NRS = Numeric Rating Scale; OBA = Opioid-Based Anesthesia; OFA = Opioid-Free Anesthesia; PONV = postoperative nausea and vomiting; POST = postoperative sore throat; PRN = as needed; QoR-40 = Quality of Recovery-40 questionnaire; RCT = randomized controlled trial; TCI = target-controlled infusion; TIVA = total intravenous anesthesia; VAS = Visual Analogue Scale.*

Table 2. Supporting Evidence — Existing Systematic Reviews and Meta-Analyses (cited in Discussion).

Review (PMID)	Studies / Patients	Population	Key Findings
Frauenknecht et al., 2019 Anaesthesia PMID 30802933	23 RCTs / 1,304 patients	Mixed surgical populations	OFA and OBA produced equivalent immediate postoperative analgesia and at 24 h. PONV reduced with OFA. Foundational meta-analysis on the comparator question.
Grape et al., 2019 Anaesthesia PMID 30950522	Multiple RCTs (varied)	Mixed surgical populations including ENT/thyroid	Compared dexmedetomidine vs remifentanil. Pain at 2 h: lower with dexmedetomidine (MD −0.7, p=0.004). PONV more than twofold higher with remifentanil. Shivering more frequent with remifentanil.
Salomé et al., 2021 J Clin Med PMID 34065937	33 RCTs / 2,209 patients	Mixed surgical populations	Pain at 2 h: MD −0.75 [−1.18, −0.32], not reaching minimum clinically important difference. Small reductions in 24 h morphine consumption. Authors concluded no clinically significant pain or opioid-use benefit; severe adverse effects identified.
Olausson et al., 2022 Acta Anaesthesiol Scand PMID 34724195	26 RCTs / 1,934 patients	Strict OFA (no opioids preop, induction, intraop, or emergence)	PONV: OR 0.27 for nausea ($p<0.00001$), OR 0.22 for vomiting ($p<0.00001$). Postoperative pain: no significant difference. Composite adverse events fewer with OFA (OR 0.32, $p<0.00001$).

Feenstra et al., 2023 J Clin Anesth PMID 37515877	38 RCTs	Mixed surgical populations	Pain: pooled MD −0.39 [−0.59, −0.19] at 24 h — statistically detectable but not clinically meaningful. PONV: less frequent with OFA. Bradycardia more frequent with dexmedetomidine-based OFA. Authors concluded one strategy cannot be recommended over the other.
Zhang et al., 2023 Medicine (Baltimore) PMID 37746991	14 RCTs / 1,354 patients	Mixed surgical populations	PONV: pooled RR 0.49 ($p<0.001$), favoring OFA. Time to extubation: no significant difference. Pain at 24 h: no significant difference. Time to first rescue analgesia: no significant difference.
Yu et al., 2023 Pain Physician PMID 37847917	32 RCTs / 2,509 patients	Mixed surgical populations (dexmedetomidine-based OFA)	Pain at 2 h: MD −0.53 [−1.00, −0.07], p=0.02, favoring OFA. Rescue analgesia: RR 0.70 [0.58, 0.84], favoring OFA. Extubation time prolonged with OFA. Bradycardia more frequent with OFA.

MD = mean difference; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratio.

3.3 Risk of Bias of Included Studies

RoB 2 judgments for each of the five included RCTs are presented in Table 3. Two trials (Wang 2024, Zhou 2023) were judged at **Low risk of bias** overall, supported by prospective trial registration (Wang 2024 in Frontiers in Medicine 2022; Zhou 2023 in ChiCTR2100046158), adequate randomization and allocation concealment, double-blinding, and complete outcome reporting. Three trials (Choi 2017, Kim 2020, S HS 2023) were judged with **Some concerns** overall. Concerns related primarily to the absence of pre-registered protocols (raising potential for selective reporting), single-center designs, and the inherent difficulty of blinding the administering anesthesiologist when the comparator drugs (dexmedetomidine vs remifentanil/fentanyl) have visibly different infusion characteristics. No included trial was judged at high overall risk of bias.

Table 3. Risk of Bias Assessment of Included Studies (Cochrane RoB 2 Tool).

Study	D1: Randomization	D2: Deviations from intended interventions	D3: Missing outcome data	D4: Outcome measurement	D5: Selection of reported result	Overall judgment
Zhou et al., 2023	Low	Low	Low	Low	Low (registered ChiCTR2100046158)	Low risk
S HS et al., 2023	Some concerns	Low (triple-blinded)	Low	Low	Some concerns (no published protocol)	Some concerns
Choi et al., 2017	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Wang et al., 2024	Low	Low (double-blind, syringe-matched)	Low	Low	Low (registered protocol)	Low risk
Kim et al., 2020	Some concerns	Some concerns	Low	Low (POST assessor blinded)	Some concerns	Some concerns

D = domain. RoB 2 categories: Low risk, Some concerns, High risk. Overall judgment determined per Cochrane RoB 2 algorithm.

3.4 Synthesis of Outcomes

3.4.1 Postoperative Nausea and Vomiting

Four of five included RCTs reported PONV outcomes; the fifth (Kim 2020) reported PONV as a secondary outcome with consistent direction. All five trials demonstrated a reduction in PONV with OFA. The largest single-study estimate came from Zhou 2023 in endoscopic sinus surgery (n=773), with a PONV incidence of 7.0% in the OFA group versus 15.1% in the OBA group (p=0.0021).[19] In thyroid and parathyroid surgery, Wang 2024 (n=394) reported 5% versus 24% (p<0.001),[25] and Choi 2017 (n=80) reported significantly lower PONV in both 0–2 h and 2–24 h time windows (p<0.05).[24] In mixed nasal surgery, S HS 2023 (n=48) reported PONV reduction with OFA (effect size not numerically pooled in the abstract).[33] Across studies, the absolute risk reduction ranged from approximately 8 to 19 percentage points.

3.4.2 Postoperative Pain

Pain results across the five included RCTs were directionally favorable to OFA but heterogeneous in magnitude. Zhou 2023 reported significantly lower NRS pain with OFA at 30 min, 1 h, 2 h, and 24 h after endoscopic sinus surgery (all p<0.05).[19] Choi 2017 reported lower VAS pain in the dexmedetomidine group between 2 and 24 h after thyroidectomy.[24] Kim 2020 reported lower NRS pain at all timepoints with OFA.[34] Wang 2024 reported comparable NRS pain at 24 h between groups (p>0.05).[25] S HS 2023 reported VAS pain comparable between groups.[33] The pattern is consistent with the early-phase pain advantage typically associated with replacing intraoperative remifentanil with dexmedetomidine, in the context of attenuated opioid-induced hyperalgesia (see Section 4.3).

3.4.3 Secondary Outcomes

Rescue analgesic consumption was lower with OFA in three trials (Choi 2017, Kim 2020, S HS 2023)[24,33,34] and similar between groups in two (Wang 2024, Zhou 2023).[19,25] S HS 2023 additionally reported reduced intraoperative blood loss and improved intraoperative hemodynamic stability with the dexmedetomidine–lidocaine OFA regimen for nasal surgery.[33] Kim 2020 reported a lower incidence of postoperative sore throat and reduced hoarseness with dexmedetomidine after thyroidectomy.[34] Zhou 2023 demonstrated a statistically significant but clinically modest QoR-40 advantage for OFA at 24 h (p=0.0014).[19]

4. DISCUSSION

4.1 Principal Findings

This systematic review synthesized five randomized controlled trials comparing opioid-free with opioid-based anesthesia in adult patients undergoing upper airway, sinonasal, and cervical surgery (1,369 patients in total). Three principal findings emerge. First, OFA produces a consistent and clinically meaningful reduction in postoperative nausea and vomiting in this surgical population, with absolute risk reductions of approximately 8 to 19 percentage points across the included trials and concordant directional evidence from larger meta-analyses in adjacent populations (Table 2). Second, postoperative pain control with OFA is non-inferior to OBA in the included RCTs, with several trials demonstrating small early-phase advantages that often fall short of the established minimum clinically important difference for the NRS or VAS. Third, the safety profile of dexmedetomidine-based OFA — most notably an increased risk of intraoperative bradycardia and somewhat prolonged emergence from anesthesia — requires deliberate clinical attention, particularly in light of the early termination of the POFA trial in non-cardiac major surgery.[26]

4.2 Reduction in Postoperative Nausea and Vomiting

The PONV finding is the most clinically actionable result of this review. The Zhou 2023 multicenter RCT in endoscopic sinus surgery (n=773)[19] provides the strongest

single-study evidence in the target population, demonstrating an absolute PONV reduction from 15.1% to 7.0%. The direction and magnitude of this effect is concordant with Wang 2024 in thyroid and parathyroid surgery (24% to 5%),[25] Choi 2017 in thyroidectomy,[24] and S HS 2023 in mixed nasal surgery.[33] Pooled estimates from existing meta-analyses across mixed surgical populations are equally consistent: Olausson 2022 reported odds ratios of 0.27 for nausea and 0.22 for vomiting,[17] Zhang 2023 reported a pooled risk ratio of 0.49,[31] and Frauenknecht 2019 reached the same directional conclusion.[35] The clinical relevance of this PONV reduction is amplified in upper airway and sinonasal surgery, where vomiting-induced Valsalva maneuvers can precipitate hemorrhage from the operative bed, compromise grafted or packed cavities, and delay discharge.[4,5,6]

Confounding by dexmedetomidine. An important interpretive caveat is that dexmedetomidine itself has independent antiemetic activity, separate from its role as an opioid substitute. Multiple meta-analyses and the Cochrane network meta-analysis of antiemetic interventions[9] support a class effect of α-2 agonists on PONV. Because dexmedetomidine forms the backbone of every OFA regimen included in this review, it is not possible to attribute the observed PONV reduction unambiguously to opioid avoidance per se rather than to the addition of dexmedetomidine. The clinical implication of this distinction is non-trivial: an opioid-sparing strategy that retains low-dose intraoperative remifentanil but adds dexmedetomidine could achieve much of the observed antiemetic benefit. Existing trials do not directly compare opioid-free with optimized opioid-sparing strategies in the upper airway / sinonasal population, and this represents an evidence gap (see Section 4.8). The single notable discordant trial in the broader OFA literature — Massoth 2021 in gynecological laparoscopy (PONV 68.4% vs 69.7%, p=0.86 in patients receiving dexamethasone-ondansetron prophylaxis)[27] — illustrates the boundary conditions of the OFA antiemetic effect. Where baseline PONV risk is extreme and prophylactic antiemetics are already in place, the incremental effect of opioid removal may be attenuated. This trial population, however, differs substantially from the upper airway and sinonasal cohort that is the focus of the present review, in which baseline PONV risk is moderate-to-high but typically not at the gynecological-laparoscopy ceiling.

4.3 Postoperative Pain: Non-Inferiority Rather Than Superiority

Pain outcomes in the included RCTs are directionally favorable to OFA but heterogeneous. Zhou 2023 reported lower NRS pain with OFA at four timepoints after endoscopic sinus surgery,[19] Choi 2017 reported lower VAS pain at 2–24 h after thyroidectomy,[24] and Kim 2020 reported lower NRS pain at all timepoints after thyroidectomy.[34] In contrast, Wang 2024 and S HS 2023 reported comparable pain scores between groups.[25,33] The supporting meta-analyses in Table 2 frame these findings appropriately. Salomé 2021 reported a 2-hour pain mean difference of −0.75 NRS points [−1.18, −0.32] in 33 RCTs but explicitly concluded that this difference did not reach the minimum clinically important difference.[18] Feenstra 2023, in 38 RCTs, reported a pooled 24-hour pain MD of −0.39 [−0.59, −0.19] with the same caveat that the difference is statistically detectable but unlikely to be perceived by patients as a meaningful change in pain experience.[30] Yu 2023, in 32 RCTs of dexmedetomidine-based OFA, reported a 2-hour pain MD of −0.53 [−1.00, −0.07] (p=0.02).[32] Frauenknecht 2019 concluded that opioid-free and opioid-inclusive anesthesia produced equivalent immediate postoperative analgesia and similar pain at 24 h.[35]

One mechanism that may explain the early-phase pain advantage observed when remifentanil is the comparator is opioid-

induced hyperalgesia, which is well documented in perioperative remifentanil exposure.[22] Dexmedetomidine, by contrast, provides genuine intraoperative nociception modulation through α-2 receptor-mediated sympatholysis and central analgesic effects, without contributing to hyperalgesia. The clinical implication is that OFA should be regarded as analgesically non-inferior in the upper airway and sinonasal context, with a likely small early-phase advantage when intraoperative remifentanil is the comparator.

4.4 Surgical-Field and Procedure-Specific Considerations

Endoscopic sinus surgery imposes specific intraoperative requirements: controlled hypotension to optimize the surgical field, minimal bleeding for visualization, and stable hemodynamics during application of topical vasoconstrictors.[6] S HS 2023 specifically reported reduced intraoperative blood loss with the dexmedetomidine–lidocaine OFA regimen compared with fentanyl-based anesthesia[33] — a finding consistent with the broader literature on dexmedetomidine for controlled hypotension during rhinological surgery.[6] For thyroid and parathyroid surgery, Kim 2020[34] reported a significant reduction in postoperative sore throat and hoarseness with dexmedetomidine versus remifentanil — a clinically relevant finding given the high baseline incidence of these complications after airway manipulation in cervical surgery. These procedure-specific signals — improved surgical field in nasal surgery, reduced sore throat in thyroid surgery, and reduced PONV-driven hemorrhagic risk across the population — represent advantages that are not fully captured in pooled mixed-surgery meta-analyses.

4.5 Safety, Adverse Events, and the POFA Trial Signal

Although none of the five RCTs included in this review reported serious adverse events attributable to OFA, the broader OFA literature contains an important cautionary signal. The POFA trial, a multicenter French RCT of 314 patients undergoing major or intermediate non-cardiac surgery,[26] was halted early after five cases of severe bradycardia in the OFA arm. The composite primary outcome of opioid-related adverse events at 48 h occurred in 78% of OFA patients versus 67% of OBA patients, driven by hypoxemia and bradycardia rather than the targeted opioid complications. Although PONV was reduced (24% vs 37%) and 24-hour morphine consumption fell (6 mg vs 11 mg), these benefits did not offset the safety concern within the trial's composite framework.

Two interpretive caveats are important. First, the OFA regimen was particularly intensive — combining dexmedetomidine with lidocaine, ketamine, dexamethasone, propofol, and desflurane — and is not representative of the simpler dexmedetomidine ± lidocaine regimens used in the upper airway and sinonasal RCTs reviewed here. Second, the POFA trial population was non-cardiac major and intermediate surgery, with longer dexmedetomidine exposure and higher cumulative doses than typically used in the shorter upper airway and cervical procedures of the included RCTs. Nonetheless, the bradycardia signal is corroborated by Yu 2023 (higher bradycardia incidence with dexmedetomidine-based OFA),[32] Feenstra 2023 (bradycardia more frequent with dexmedetomidine),[30] and Grape 2019 (more frequent bradycardia with dexmedetomidine vs remifentanil).[23] Prolonged PACU emergence and length of stay with dexmedetomidine-based OFA is a second consistent finding across the supporting meta-analyses, attributable to the longer pharmacokinetic profile of dexmedetomidine compared with remifentanil. This trade-off is operationally relevant for ambulatory or fast-track sinonasal surgery.

4.6 Strengths and Limitations

Strengths. This review focuses specifically on adult upper airway, sinonasal, and

cervical surgery — a population with shared perioperative concerns (airway-adjacent operative field, PONV-driven hemorrhagic risk, sore throat) that is often pooled into mixed-surgery meta-analyses. Including only randomized controlled trials in the synthesis avoids the methodological confounding of mixing primary studies with secondary syntheses. Risk of bias was formally assessed using RoB 2. Inclusion of the largest contemporary multicenter RCT in the field (Zhou 2023, n=773) and a recent two-center thyroid/parathyroid RCT (Wang 2024, n=394) provides direct, methodologically rigorous evidence in the target population.

Limitations:

Several limitations apply. First, the directly relevant evidence base remains modest — five RCTs, of which one (S HS 2023) had a small sample (n=48) and limited public reporting depth. Second, OFA pharmacological protocols are not uniform across trials (single-agent dexmedetomidine vs combinations with lidocaine and/or esketamine), and OBA comparators differ (remifentanil, sufentanil, fentanyl); these differences preclude a meaningful pooled estimate and contribute to heterogeneity in pain outcomes. Third, three of the five included RCTs were judged with some concerns of bias, primarily related to single-center design and absence of pre-registered protocols. Fourth, blinding of the administering anesthesiologist was not feasible in any included RCT given the visibly different infusion characteristics of the comparator drugs, although outcome assessors and patients were typically blinded. Fifth, dexmedetomidine itself has independent antiemetic activity, which means the observed PONV benefit cannot be unambiguously attributed to opioid removal versus dexmedetomidine addition. Sixth, the POFA trial safety signal — observed in a non-target surgical population — has not yet been comprehensively addressed in upper airway-specific trials. Finally, none of the included RCTs reported long-term outcomes such as persistent postoperative pain, opioid prescribing at discharge, or new persistent opioid use, which are increasingly recognized as relevant outcome domains for opioid-related research.

4.7 Implications for Clinical Practice

Three practical implications follow from this synthesis. First, in adult patients undergoing endoscopic sinus surgery, septoplasty, turbinoplasty, thyroidectomy, parathyroidectomy, or related upper airway and cervical procedures — particularly those with elevated baseline PONV risk per the Apfel framework[12] — opioid-free anesthesia based on dexmedetomidine, with or without lidocaine and ketamine/esketamine, is a defensible primary anesthetic strategy. The PONV benefit is consistent and clinically meaningful, and analgesic adequacy is preserved. Second, OFA protocols should be matched to procedural duration and complexity: simple regimens (dexmedetomidine ± lidocaine) appear to carry a more favorable risk-benefit profile than maximalist multi-agent regimens for shorter sinonasal and cervical surgeries. Third, the bradycardia and emergence-delay signals are real and require pre-operative case selection — patients with conduction abnormalities, severe sinus bradycardia, or those scheduled for ambulatory same-day discharge may be poor candidates for high-dose dexmedetomidine-based OFA. Adequate postoperative multimodal analgesia (NSAIDs, paracetamol, regional or superficial cervical plexus blocks where appropriate) should accompany either anesthetic strategy.

4.8 Future Research Directions

Future investigation should prioritize (1) adequately powered RCTs in adult patients undergoing FESS, septoplasty, and turbinoplasty using simplified OFA protocols (dexmedetomidine + lidocaine), with PONV and surgical-field quality as co-primary outcomes; (2) head-to-head

comparison of opioid-free versus optimized opioid-sparing anesthesia (rather than fully opioid-based comparators), to disentangle the dexmedetomidine antiemetic effect from the opioid-removal effect; (3) economic and length-of-stay analyses incorporating PONV avoidance, PACU emergence time, and unplanned readmission for hemorrhage; (4) clarification of the dose-response relationship for dexmedetomidine in shorter upper airway procedures, with explicit safety endpoints for bradycardia and conduction disturbance; and (5) inclusion of long-term outcomes such as persistent postoperative pain and discharge opioid prescribing.

5. CONCLUSION

In adult patients undergoing upper airway, sinonasal, and cervical (thyroid/parathyroid) surgery, opioid-free anesthesia based on dexmedetomidine — with or without lidocaine, ketamine, or esketamine — is associated with a consistent reduction in postoperative nausea and vomiting compared with opioid-based anesthesia. Postoperative pain control with OFA is non-inferior to opioid-based techniques and may be modestly superior in the early postoperative period when intraoperative remifentanil is the comparator (low certainty of evidence). The PONV benefit is procedurally important given the hemorrhagic risk associated with vomiting after sinonasal and cervical surgery.

These benefits are tempered by an increased risk of intraoperative bradycardia and prolonged emergence from anesthesia. The early termination of the POFA trial in non-cardiac major surgery, although not directly transferable to the upper airway / cervical population, underscores the need for thoughtful protocol selection rather than reflexive maximalism. The current evidence supports OFA as a reasonable and often preferable anesthetic strategy for high-PONV-risk patients undergoing upper airway, sinonasal, and cervical surgery, provided that simplified protocols are used, patients with conduction abnormalities are excluded, and operational tolerance for slightly prolonged emergence is acceptable. Adequately powered RCTs in pure upper airway and sinonasal populations, with active opioid-sparing comparators, aligned primary outcomes, and explicit safety endpoints, are needed to refine these recommendations.

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