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Research Article

Comparison of Opioid-Free versus Opioid-Based Total Intravenous Anesthesia in Elderly Patients Undergoing Short-Duration Surgery: A Randomized Controlled Trial

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ABSTRACT

Background: Older adults undergoing short-duration surgery are vulnerable to opioid-related complications. It is uncertain whether an opioid-free total intravenous anesthesia (OFA) can reduce these events. We aimed to determine if OFA reduces the incidence of major postoperative adverse events compared with standard opioid-based total intravenous anesthesia (OBA).

Materials and Methods: This single-center, randomized clinical trial was conducted in China. From May to August 2025, 400 patients aged 60 years or older undergoing elective, short-duration surgery were randomized 1:1 to receive either OFA (propofol, esketamine, dexmedetomidine, lidocaine; n=200) or OBA (propofol, sufentanil, remifentanil; n=200). The primary outcome was a composite of postoperative hypoxemia, delirium, or nausea and vomiting (PONV) within 48 hours.

Results: Among 400 randomized patients (mean [SD] age, 69.5 [7.0] years; 125 [31.3%] women), all completed the trial and were included in the intention-to-treat analysis. The primary composite outcome occurred in 50 patients (25.0%) in the OFA group and 87 patients (43.5%) in the OBA group (adjusted odds ratio, 0.40; 95% CI, 0.25 to 0.62; P < .001). Of the components, the OFA group had a lower incidence of hypoxemia (15.0% vs 32.0%) and PONV (8.0% vs 16.0%). Intraoperative hemodynamic stability was greater in the OFA group.

Conclusion: In this trial of older adults undergoing short-duration surgery, OFA significantly reduced the incidence of a composite of postoperative adverse events compared with OBA. These findings support the use of OFA as a strategy to enhance perioperative safety in this patient population.

Highlights

- In older adults undergoing short-duration surgery, an opioid-free total intravenous anesthesia (OFA) regimen significantly reduced a composite of major postoperative adverse events compared to standard total intravenous opioid-based anesthesia (OBA).
- The OFA was associated with substantially greater intraoperative hemodynamic stability, characterized by less hypotension and a lower need for vasopressor support.
- The study provides robust, randomized evidence supporting OFA as a preferred strategy to enhance perioperative safety in this large and vulnerable patient population.

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1. Introduction

As the population ages globally, an increasing proportion of elective surgical patients are older adults [1, 2]. Although clinical attention has traditionally focused on the risks associated with major, lengthy surgeries, a substantial and often under recognized burden of morbidity also follows short-duration elective surgeries [3]. Older adults are at increased risk of postoperative complications because of reduced physiologic reserve and comorbidities [4]. Among these, opioid-related adverse events- including postoperative hypoxemia, postoperative nausea and vomiting (PONV), and postoperative delirium (POD)- are particularly common in this population and can disproportionately delay recovery from procedures that would otherwise be expected to have a rapid course [5, 6]. These concerns underscore the need to re-evaluate standard anesthetic practices in older patients, even for short-duration surgeries.

Conventional general anesthesia, which typically combines inhaled anesthetics with intravenous opioids, is limited by the adverse effects of both drug classes. Inhaled agents may contribute to hemodynamic instability and postoperative cognitive dysfunction, whereas opioids are strongly associated with respiratory depression, PONV, and POD, particularly in older adults [7, 8]. These concerns have led to interest in opioid-free total intravenous anesthesia (OFA) as a potentially feasible alternative. This approach is based on the two components: first, an opioid-free multimodal regimen using non-opioid adjuncts- such as dexmedetomidine, lidocaine, and esketamine- to provide analgesia while avoiding opioid-related harms [9]. Esketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is particularly valuable for its ability to attenuate central sensitization and provide analgesia with cardiovascular stability [10, 11]. Second, the use of total intravenous anesthesia (TIVA) avoids the risks of volatile agents and allows for more stable hemodynamics and rapid emergence [12, 13]. By combining these two concepts, OFA has the potential to provide adequate anesthesia while simultaneously mitigating the risks of both opioids and inhaled agents, although its clinical benefits in the older surgical population require rigorous validation in randomized controlled trials.

Previous trials of opioid-free or opioid-based strategies have been heterogeneous in patient populations, anesthetic regimens, and outcomes, with few focusing specifically on short-duration procedures in the elderly [14]. High-quality randomized data are lacking to establish whether OFA can meaningfully reduce opioid-related complications while maintaining anesthetic adequacy in this population. We therefore conducted a single-center, single-blind, randomized controlled trial to compare OFA with OBA in older adults undergoing short-duration surgery. The primary outcome was a composite of opioid-related adverse events- postoperative hypoxemia, PONV, and POD—within 48 hours postoperatively. We hypothesized that OFA would reduce the risk of the primary composite outcome compared with OBA.

2. Method

2.1. Study Design

This was an investigator-initiated, prospective, single center, parallel-group randomized controlled trial (RCT) conducted in the Affiliated Hospital of Jiaxing University in China (Link ChiCTR2500102550; May 20, 2025). The trial protocol is available in (Supplement 1). The study was approved by the Ethics Committee of the Affiliated Hospital of Jiaxing University (April 30, 2025). Written informed consent was obtained from all participating patients before inclusion in the study. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline [15].

2.2. Participants

Eligible participants were patients aged 60 years or older, scheduled to undergo elective, non-major surgery with an anticipated duration of less than 90 minutes (e.g., urologic procedures such as lithotripsy, transurethral resection of bladder tumors [TURBT], or transurethral resection of the prostate [TURP], and vascular procedures such as great saphenous vein stripping). All patients were required to be classified as American Society of Anesthesiologists (ASA) physical status I to III and planned for general anesthesia with a laryngeal mask airway. Only patients able to provide written informed consent were eligible for enrollment.

Exclusion criteria were as follows: contraindications to the use of a laryngeal mask airway or a predicted difficult airway; severe cardiovascular disease (e.g., unstable angina, New York Heart Association class III-IV heart failure); severe hepatic or renal dysfunction (e.g., Child-Pugh class C, or an estimated glomerular filtration rate < 30 mL/min); and uncontrolled diabetes (defined as HbA1c > 9%). To avoid confounding the assessment of our primary outcome, patients with significant pre-existing cognitive impairment (mini-mental state examination score < 18), a history of major psychiatric disorders, or chronic opioid use or dependency were also excluded. Further exclusion criteria included known allergies to any of the study medications, participation in another interventional trial within 30 days, or refusal to provide consent.

2.3. Blinding and Randomization

Participants were randomly assigned in a 1:1 ratio to the OFA or OBA group. A statistician not involved in the study generated the allocation sequence using SPSS software (version 26.0) with a block size of 4 or 6. The sequence was stratified by the type of surgery (non-urological vs urological). To ensure allocation concealment, the assignments were placed in sequentially numbered, sealed, opaque envelopes for each stratum.

On the day of surgery, after a participant provided consent, an independent research assistant selected the next appropriate envelope. An unblinded anesthesiologist then opened it to reveal the treatment allocation. All other individuals, including the participants, outcome assessors, and data analysts, remained blinded to the group assignment

throughout the trial. To minimize potential bias, the unblinded anesthesiologists were not involved in any postoperative data collection or outcome assessment.

2.4. Outcome

The primary outcome was a composite of major opioid-related adverse events occurring within the first 48 hours after surgery. The components of the primary outcome were: i) postoperative hypoxemia, defined as a pulse oximetry saturation < 95% while breathing room air, requiring supplemental oxygen; ii) POD, assessed as positive using the 3-Minute Disorientation Assessment Method (3D-CAM) [16]; and iii) PONV, defined as any episode of nausea, retching, or vomiting.

The secondary outcomes were measures of intraoperative hemodynamic stability and postoperative recovery. Hemodynamic stability was assessed by the area under the curve for mean arterial pressure (MAP AUC) relative to baseline during the first 15 minutes of anesthesia induction and the requirement for intraoperative vasopressors. Postoperative recovery outcomes included the time to laryngeal mask airway removal, the length of stay in the post-anesthesia care unit (PACU), and the length of hospital stay, the severity of PONV, which was assessed using a 4-point ordinal scale. The grades were defined as follows: 0 (none), no nausea or vomiting reported; 1 (mild), subjective nausea without vomiting and not requiring rescue antiemetic therapy; 2 (moderate), vomiting of 1 to 2 episodes or persistent nausea requiring rescue antiemetic therapy; and 3 (severe), vomiting of more than 2 episodes or nausea and vomiting that were refractory to rescue antiemetic therapy [17]. And postoperative pain intensity assessed using the Numerical Rating Scale (NRS) at rest and during movement. Safety outcomes included the incidence of injection pain during induction, as well as other adverse events such as significant bradycardia or tachycardia, dizziness, headache, and emergence agitation.

To ensure data quality and minimize missing data, a trained research coordinator, who was blinded to the treatment allocation and not involved in patient care, prospectively collected all outcome data using a standardized electronic case report form from randomization until hospital discharge.

2.5. Intervention

All patients followed standard fasting guidelines (no solid food for 6 hours and no clear liquids for 2 hours preoperatively). Upon arrival in the operating room, standard monitoring was applied, including electrocardiography, pulse oximetry, and non-invasive blood pressure. Analgesic depth was specifically monitored using the Surgical Pleth Index (SPI).

In OFA group, induction was performed with intravenous lidocaine (1 $mg \cdot kg^{-1}$), esketamine (0.2-0.4 $mg \cdot kg^{-1}$), and propofol (1.5-2.0 $mg \cdot kg^{-1}$). In OBA group, induction was performed with intravenous sufentanil (0.2-0.4 $\mu g \cdot kg^{-1}$) and propofol (1.5-2.0 $mg \cdot kg^{-1}$). For both groups, rocuronium (0.6-1.0 $mg \cdot kg^{-1}$) was used to facilitate laryngeal mask airway (LMA) insertion.

Following LMA placement, mechanical ventilation was initiated with tidal volumes set at 6-8 mL/kg of ideal body weight and the respiratory rate was adjusted to maintain an end-tidal carbon dioxide ($EtCO_2$) between 35 and 45 mmHg. Anesthesia was maintained with a continuous infusion of propofol (2-10 $mg \cdot kg^{-1} \cdot h^{-1}$) in both groups. In the OFA group, analgesia was maintained with continuous infusions of esketamine (0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) and dexmedetomidine (0.3-1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$). In the OBA group, analgesia was maintained with a continuous infusion of remifentanil (0.1-0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The propofol infusion was adjusted based on clinical signs, while the primary analgesic infusions were adjusted to maintain an SPI value between 20 and 50. Intraoperative hypotension (defined as MAP < 65 mmHg or a decrease >20% from baseline for more than 1 minute) was treated with boluses of phenylephrine. Bradycardia (heart rate < 50 beats/min) was treated with atropine.

At the end of surgery, residual neuromuscular blockade was antagonized with intravenous sugammadex, with the dose determined by train-of-four (TOF) monitoring. The LMA was removed in the operating room once standard criteria for emergence were met, including regular spontaneous respiration, adequate tidal volumes, and response to verbal commands. Upon arrival at the post-anesthesia care unit (PACU), all patients routinely received intravenous ketorolac 30 mg for analgesia and ondansetron 4 mg for prophylaxis against PONV. Patients were subsequently transferred from the PACU to the ward once they met standard discharge criteria.

2.6. Sample Size

The sample size for this trial was determined based on the primary composite outcome. Based on published literature, the incidence of opioid-related adverse events in this patient population is approximately 20% for postoperative hypoxemia, 15% for PONV, and 5% for POD [18-20]. Accordingly, we estimated the incidence of primary composite outcome to be approximately 40% in the OBA group. We considered a relative risk reduction of 40% (i.e., a reduction in the primary outcome incidence from 40% to 24%) to be a clinically meaningful treatment effect. To detect this difference with 80% power at a two-sided alpha level of 0.05, a sample size of 130 patients per group was required. To account for potential dropouts and to ensure adequate power for prespecified subgroup analyses, we increased the target sample size to 400 participants (200 per group).

2.7. Statistical Analysis

All analyses will be conducted according to the intention-to-treat (ITT) principle, in which all randomized participants are analyzed in the group to which they were originally assigned, regardless of protocol adherence or the treatment ultimately received. Baseline demographic and clinical characteristics will be summarized to assess the balance achieved between the two groups by randomization. Continuous variables will be presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs), while categorical variables will be presented as frequencies and percentages. Between-group comparisons will be

performed using the independent samples t-test, the Mann-Whitney U test, or the χ^2 test (or Fisher's exact test, as appropriate).

The primary outcome was a composite binary endpoint, defined as the occurrence of at least 1 prespecified opioid-related adverse event within 48 hours after surgery. The primary hypothesis was tested using a multivariable logistic regression model to estimate the adjusted odds ratio (aOR) and 95% CI for the OFA group compared with the OBA group. The model was adjusted for six baseline covariates: age, sex, The body-mass index (BMI), ASA physical status, Charlson Comorbidity Index, and educational level. To account for potential nonlinear relationships with the outcome, age and BMI were modeled using restricted cubic splines. To quantify the clinical effect size, a supplementary analysis was conducted. We used a modified Poisson regression model with a robust error variance to directly estimate the adjusted relative risk (aRR) after adjusting for the same covariates. The absolute risk reduction (ARR) and the number needed to treat (NNT), with their corresponding 95% CIs, were then calculated from the aRR. Missing data for the primary outcome were handled using multiple imputation.

A comprehensive assessment of efficacy was conducted through the analysis of a series of secondary outcomes. For the key hemodynamic outcome- the area under the curve for the MAP AUC during the first 15 minutes after anesthesia induction- an analysis of covariance (ANCOVA) model was used, with the baseline MAP value included as a continuous covariate to improve statistical precision. For all other secondary outcomes, continuous variables were compared using the independent samples t-test or the Mann-Whitney U test; ordinal outcomes were analyzed with the Mann-Whitney U test; and binary outcomes, including the individual components of the primary composite endpoint, were compared using the χ^2 test or Fisher's exact test. Safety outcomes, including the incidence of adverse events such as bradycardia, tachycardia, headache, dizziness, and emergence agitation, were also compared between groups using the χ^2 test or Fisher's exact test.

Additionally, two exploratory analyses were conducted. To identify potential predictors of the primary composite endpoint, we performed separate univariable logistic regression analyses for each baseline and clinical characteristic, reporting unadjusted odds ratios and 95% CIs. Second, to assess the dose-response relationship between cumulative propofol exposure and time to extubation, we fitted a linear regression model with RCS to accommodate potential nonlinearity.

We performed a series of subgroup analyses for the primary outcome to explore potential heterogeneity of the treatment effect (i.e., effect modification) across patient characteristics. The primary subgroup analysis was based on the type of surgery (urological vs non-urological). We also explored subgroup effects based on age (< 75 vs ≥ 75 years) and Charlson comorbidity index (< 5 vs ≥ 5). These analyses were performed by including an interaction term between the treatment assignment and the subgrouping variable in the primary univariable logistic regression model. We primarily focused on the P value for the interaction to assess for statistically significant effect modification and presented the aORs and 95% CIs for each subgroup in a forest plot. To test the robustness of the primary findings under different analytical assumptions, we conducted a series of sensitivity analyses. First, to assess the impact of protocol adherence, we performed a per-protocol analysis and compared its results with the primary ITT analysis. Second, to evaluate the overall impact of covariate adjustment, we fitted a univariable model containing only the treatment assignment and compared its effect estimate (crude odds ratio) with that from our primary multivariable model (aOR).

3. Results

3.1. Patients

From May 20, 2025, to August 15, 2025, a total of 485 patients were screened for eligibility in this single-center trial. Of these, 85 patients were excluded, primarily because they did not provide informed consent (n = 47) or refused to participate (n = 30). The remaining 400 eligible patients were randomized in a 1:1 ratio to receive either OFA (n = 200) or OBA (n = 200). All randomized patients completed the study, with no participants lost to follow-up. Consequently, all 400 patients (200 in each group) were included in the ITT analysis. Seven patients were excluded from the PP analysis owing to surgery duration exceeding 90 minutes (6 in the OFA group and 1 in the OBA group). Accordingly, the PP analysis comprised 194 patients in the OFA group and 199 in the OBA group. The participant flow is shown in (Figure 1).

3.2. Baseline and Clinical Characteristics

A total of 400 randomized patients were included in the intention-to-treat analysis (OFA, n=200; OBA, n=200). Baseline demographic were generally similar between groups (Table 1). The duration of surgery was similar between the two groups (median [IQR], 32 [17] min for the OBA group vs 33 [22] min for the OFA group). As per the study protocol, patients in the OBA group received sufentanil and remifentanil, while patients in the OFA group received esketamine, dexmedetomidine, and lidocaine. Propofol administration was significantly higher in the OFA group compared to the OBA group (median [IQR], 404 [160] mg vs 351 [118] mg; P < .001). The percentage of time that the SPI was maintained within the target range was high and comparable in both groups.

Table. 1. 1 Baseline and peri-operative data of patients[a].

Variable	No. (%)	
	OFA (n=200)	OBA (n=200)
Age,y, Mean ± SD,y	70 ± 7	69 ± 7
BMI, Mean ± SD[b]	23.5 ± 3.6	24.3 ± 3.0
APFEl score, Mean ± SD[c]	1.18 ± 0.92	1.22 ± 0.98

ASA physical status		
II	181 (90.5%)	179 (89.5%)
III	19 (9.5%)	21(10.5%)
Type of surgery		
urological surgery	149 (74.5%)	148 (74.0%)
Vascular surgery	51 (25.5%)	52 (26.0%)
Gender		
Male	133 (66.5%)	142(71.0%)
Female	67 (33.5%)	58 (29.0%)
Educational level,y		
≤6	116 (58.0%)	118 (59.0%)
6-9	67 (33.5%)	65 (32.5%)
>9	17 (8.5%)	17 (8.5%)
Drinking alcohol	39 (19.5%)	41 (20.5%)
smoking	53 (26.5%)	50(25.0%)
Comorbidities		
Hypertension	102 (51.0%)	109 (54.5%)
Diabetes	34 (17.0%)	31 (15.5%)
Atrial fibrillation	7 (3.5%)	8 (4.0%)
Coronary heart disease	12 (6.0%)	6 (3.0%)
Prior stroke	9 (4.5%)	14 (7.0%)
Medication on admission		
β-Adrenergic receptor blocker	6 (3.0%)	7 (3.5%)
Calcium Channel Blockers	55 (27.5%)	50 (25.0%)
Lipid-lowering drug	15 (7.5%)	18 (9.0%)
Antiplatelet	27 (13.5%)	24 (12.0%)
ACEIs/ARBs	54 (27.0%)	47 (23.5%)
Diuretics	11 (5.5%)	14 (7.0%)
Charlson comorbidity index_group		
< 5	139 (69.5%)	148 (74.0%)
≥ 5	61 (30.5%)	52 (26.0%)
History of nausea and vomiting	14 (7.0%)	21 (10.5%)
Duration of surgery, median (IQR), min[d]	33 ± 22	32 ± 17
Dose of propofol, median (IQR), mg	404 ± 160	351 ± 118
Dose of esketamin, median (IQR), mg	31 ± 14	NA
Dose of dexmethomidine, median (IQR), μg	18 ± 12	NA
Dose of lidocaine, median (IQR), μg	63 ± 10	NA
Dose of sufentanil, median (IQR), mg	NA	14.4 ± 3.3
Dose of remifentanil, median (IQR), mg	NA	0.28 ± 0.18
% of Time with SPI value 20-50, median (IQR), %[e]	89.23 ± 2.70	90.83 ± 2.83

ACEIs: Angiotensin-Converting Enzyme Inhibitors; APFEL: Apfel Simplified Risk Score for Postoperative Nausea and Vomiting; ARBs: angiotensin receptor blockers; ASA: American Society of Anesthesiologists; BMI: Body Mass Index; OBA: Opioid-Based Anesthesia; OFA: Opioid-Free Anesthesia; SD: Standard Deviation.

[a]Values are reported as No. (%) unless otherwise indicated.

[b]The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

[c]APFEL score (range, 0-4), with higher scores indicating greater risk of postoperative nausea and vomiting; 1 point each for female sex, nonsmoking status, history of nausea/vomiting or motion sickness, and use of postoperative opioid

[d]Duration of surgery was defined as the time from skin incision to skin closure.

3.3. Primary Outcome

The primary composite outcome occurred in 50 of 200 patients (25.0%) in the OFA group and in 87 of 200 patients (43.5%) in the OBA group (Table 2). After adjusting for prespecified baseline covariates, the use of OFA was associated with significantly lower odds of the primary outcome compared with OBA (adjusted odds ratio, 0.40; 95% CI, 0.25 to 0.62; P < .001). This corresponded to an NNT of 5 (95% CI, 3-8) to prevent one additional primary outcome event.

In prespecified analyses to assess the assumptions of our primary model, we evaluated the relationship between continuous baseline covariates

and the primary outcome using restricted cubic splines. We found no evidence of a significant association for age (P for overall association = .338; P for nonlinearity = .512). For BMI, we observed a borderline significant nonlinear (J-shaped) relationship (P for nonlinearity = .051). Detailed results and graphical representations are provided in the Supplement (eFigure 1 and eFigure 2 in Supplement 2).

Among the components of the primary outcome, the incidence of postoperative hypoxemia was significantly lower in the OFA group than in the OBA group (15.0% vs 32.0%; crude OR, 0.37; 95% CI, 0.23 to 0.61; P < .001), with an NNT of 6 (95% CI, 4 to 12). The incidence of PONV was also significantly lower in the OFA group (8.0% vs 16.0%; crude OR, 0.46; 95% CI, 0.24 to 0.86; P = .014), with an NNT of 13 (95% CI, 7 to 59). There was no significant difference between the groups in the incidence of POD (2.5% vs 2.5%; P > .99).

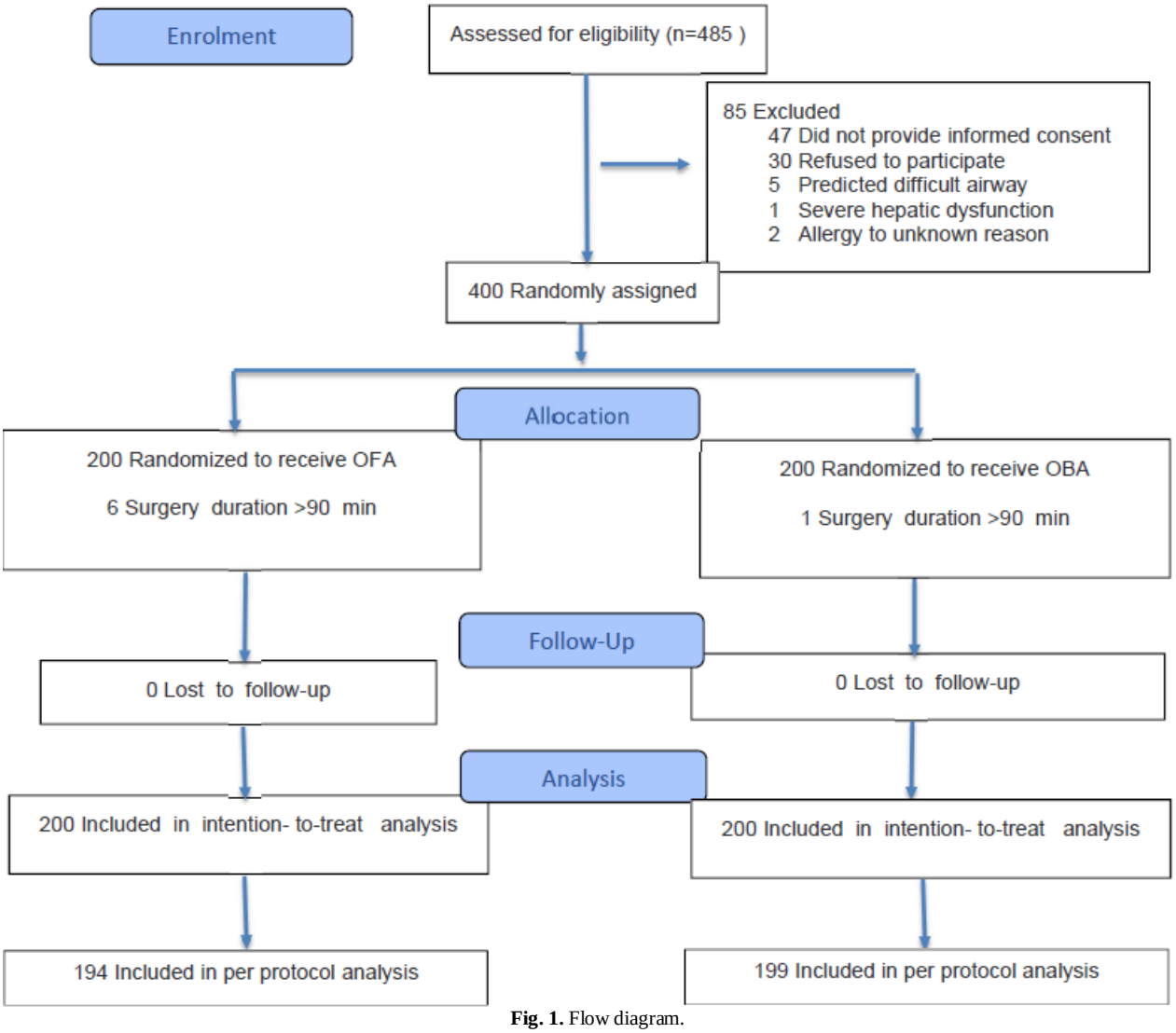

Fig. 1. Flow diagram.

Table. 2. Primary outcome and its components.

Variable	No. (%) OFA (n=200)	OBA(n=200)	Odds Ratio (95% CI)	p value[a]	Adjusted Odds Ratio (95% CI)[b]	Adjusted p value	NNT[c]
Primary composite outcome	50(25%)	87 (43.5%)	0.43 (0.28 - 0.66)	<0.001	0.40 (0.25- 0.62)	<0.001	5 (3-8)
Components of the primary outcome·							
Postoperative[d]	30 (15.0%)	64 (32.0%)	0.37 (0.23 - 0.61)	<0.001	NA	NA	6 (4-12)

hypoxemia							
POD[e]	5 (2.5%)	5 (2.5%)	1.00 (0.28 - 3.51)	>0.99	NA	NA	
PONV[f]	16 (8.0%)	32 (16.0%)	0.46 (0.24 - 0.86)	0.014	NA	NA	13 (7-59)

Values are number (proportion).

CI: Confidence Interval; POD; Postoperative Delirium; PONV: Postoperative nausea and vomiting.

[a]All tests were 2-sided. P value of less than .05 was considered significant.

[b]The adjusted odds ratio and its 95% CI were calculated using a multivariable logistic regression model. The model was adjusted for the following prespecified baseline covariates: age, gender, body mass index, ASA physical status, Charlson comorbidity index, educational level, age and body mass index.

[c]Derived from absolute risk difference and given only for incidence of primary composite outcome, postoperative hypoxemia and PONV.

[d]Postoperative hypoxemia was defined as a pulse oximetry saturation <95% requiring supplemental oxygen.

[e]POD was assessed using the 3-Minute Disorientation Assessment Method (3D-CAM).

[f]PONV included any episode of nausea (an urge to vomit), retching, or vomiting.

3.4. Secondary and Safety Outcome

Secondary and safety outcomes are shown in (Table 3). Patients in the OFA group demonstrated significantly greater hemodynamic stability compared with the OBA group. Changes in MAP after induction are shown in (Figure 2). The mean AUC of the difference in mean arterial pressure from baseline was smaller in the OFA group (mean, -179.0 vs -466.2 mmHg·s; P < .001), and the requirement for intraoperative vasopressors was significantly lower (10.0% vs 35.0%; P < .001). Extubation time was longer in the OFA group (mean, 9.5 vs 7.2 minutes; P<.001). PACU length of stay and postoperative pain scores did not differ between groups. The severity of postoperative nausea and vomiting was lower in the OFA group (P < .001).

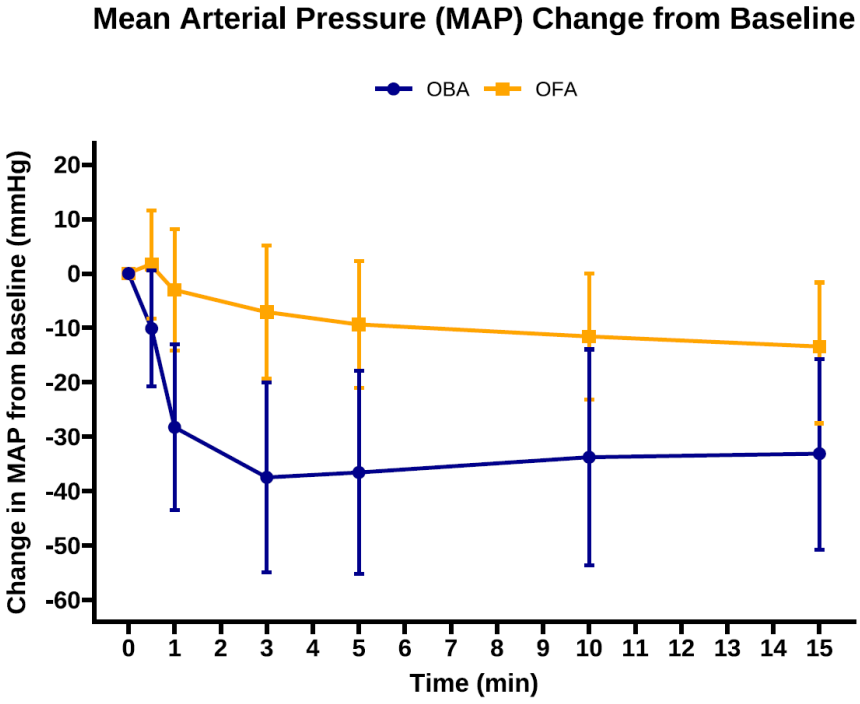

Fig. 2.

Table. 3. Secondary and safety outcomes.

	No. (%)		
Variable[a]	**OFA (n=200)**	**OBA(n=200)**	**p value[b]**
AUC of MAP difference from baseline, mmHg · s[c]	-179.04 (-201.20 to -156.88)	-466.17 (-488.33 to -444.01)	<0.001
Requirement for intraoperative vasopressors[d]	20 (10.0%)	70 (36.0%)	<0.001
Degree of nausea and vomiting[e]			<0.001
0	184 (92.0%)	168 (84.0%)	
1	10 (5.0%)	17 (8.5%)	
2	3 (1.5%)	12 (6.0%)	

3	3 (1.5%)	3 (1.5%)	
Length.of.PACU.stay.min	38.4 (15.05)	37.8 (15.81)	0.73
Extubation.duration.min	9.5 (2.15)	7.2 (2.09)	<0.001
The.NRS.score.at.rest[f]	0.6 (0.68)	0.6 (0.79)	0.595
The.NRS.score.at.exercise	1.7 (1.37)	1.9 (1.36)	0.269
Safety Outcomes[g]			
Emergence agitation	8 (4.0%)	11 (5.5%)	0.48
Headache and dizziness	18 (9.0%)	9 (4.5%)	0.073
Injection pain	2 (1.0%)	24 (12.0%)	<0.001
Bradyarrhythmia	20 (10.0%)	6 (3.0%)	0.005
Tachycardia	5 (2.5%)	8 (4.0%)	0.40

AUC: Area Under the Curve; MAP: Mean Arterial Pressure; NRS: Numerical Rating Scale; PACU: Post-Anesthesia Care Unit.

[a]Data are presented as mean (SD), median [IQR], or n (%).

[b]Between-group comparisons were performed using independent-samples t tests or Wilcoxon rank-sum tests for continuous variables and χ^2 tests or Fisher exact tests for categorical variables, except for the ANCOVA-derived P value for MAP AUC.

[c]The AUC of the MAP difference from baseline was calculated for the first 15 minutes after anesthesia induction. A more negative value indicates greater hemodynamic instability. The comparison was performed using an Analysis of Covariance (ANCOVA) model, adjusting for the baseline MAP value.

[d]Requirement for intraoperative vasopressors was defined as the need for norepinephrine bolus (5 μg) administration if mean arterial pressure (MAP) decreased by more than 20% from baseline or fell below 65 mmHg for at least 1 minute.

[e]Nausea and vomiting were graded on a 4-point ordinal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

[f]NRS, numerical rating scale (0-10, higher scores indicating greater pain).

[g]Emergence agitation was assessed during recovery. Headache/dizziness were patient-reported in the PACU. Injection pain, bradyarrhythmia, and tachycardia were defined as intraoperative adverse events documented by the anesthesiologist.

For safety outcomes, the incidence of bradyarrhythmia was significantly higher in the OFA group (10.0% vs 3.0%; P = .005), while injection pain was reported significantly less often (1.0% vs 12.0%; P < .001). There were no significant differences between the groups in the incidence of emergence agitation, headache and dizziness, or tachycardia.

3.5. Subgroup Analysis

eFigure 4 (Supplement 2) shows the results of the subgroup analyses for the effect of OFA on the primary composite outcome. No significant interactions were observed across prespecified subgroups including type of surgery (P for interaction=.93), age (P for interaction=.15), and Charlson comorbidity index (P for interaction=.91). These findings indicate that the beneficial effect of OFA was consistent across subgroups, despite numerical variation in the adjusted odds ratios. The protective effect of OFA remained statistically significant and clinically relevant in each subgroup, including patients undergoing urological or vascular surgery and those younger or older than 75 years.

3.6. Exploratory Analysis

As prespecified, we conducted exploratory analyses to examine potential risk factors for the primary outcome and to evaluate the dose-response relationship between propofol exposure and extubation time (eAppendix 2 in Supplement 2). Univariable analyses indicated that female sex, a history of nausea or vomiting, and higher APFEL scores were associated with increased odds of the composite outcome, whereas age, BMI, hypertension, and smoking were not significantly associated (eTable 2 in Supplement 2). Restricted cubic spline analysis suggested a non-linear association between cumulative propofol dose and extubation time, with higher doses progressively associated with longer extubation times (eFigure 3 in Supplement 2). These findings are exploratory and should be interpreted with caution.

3.7. Sensitivity Analysis

The primary finding was robust across a series of sensitivity analyses. The treatment effect of OFA was consistent in the PP analysis, when comparing models with different covariate adjustments, and under best-case and worst-case scenarios for the 3 participants with missing data. Detailed results of all sensitivity analyses are provided in the Supplement (eAppendix 3 in Supplement 2).

4. Discussion

In this randomized controlled trial involving older adults undergoing short-duration surgery, OFA significantly reduced the incidence of a composite of major postoperative adverse events compared with a standard OBA group. This benefit was primarily associated with a lower incidence of postoperative hypoxemia and PONV and was accompanied by greater intraoperative hemodynamic stability. These findings provide pragmatic evidence that OFA is a viable alternative to OBA for improving perioperative safety in this vulnerable population.

The observed reduction in hypoxemia and PONV is mechanistically consistent with the complete avoidance of intraoperative opioids, which are established risk factors for respiratory depression and PONV [21, 22]. Our findings are consistent with those of several meta-analyses that have shown the benefits of multimodal OFA strategies in various surgical settings [23, 24]. However, many of these previous studies focused on major abdominal or orthopedic surgery [25-31]. Our trial contributes specific evidence for the context of shorter, less invasive

procedures in older adults, a population that remains susceptible to opioid-related adverse events. The superior hemodynamic profile in the OFA group is likely attributable to the sympathomimetic properties of esketamine counteracting propofol-induced vasodilation. This finding corroborates smaller observational studies and provides robust RCT evidence for a key physiological advantage of this OFA combination.

The safety profiles of the OFA and OBA groups differed. The higher incidence of bradycardia is a known pharmacodynamic effect of dexmedetomidine, a core component of our OFA protocol [32, 33]. Similarly, the slightly longer extubation time may be explained by the longer context-sensitive half-time of dexmedetomidine or by the higher cumulative dose of propofol required in the OFA group. Importantly, this minor delay in extubation did not translate into a longer PACU stay, and postoperative pain control was equivalent between the groups.

From a broader perspective, our findings suggest that even brief intraoperative opioid exposure is associated with a significant increase in adverse events in this population. This trial provides a rationale for considering opioid-free strategies as a primary approach to enhance perioperative safety, rather than reserving them for select high-risk individuals. The results support a practice paradigm that prioritizes opioid elimination, where feasible, for older adults undergoing surgery.

Our study has several limitations. First, as a single-center trial, our findings may not be fully generalizable to other institutions with different clinical practices or patient populations. Secondly, while outcome assessors were blinded, the attending anesthesiologists were not, which could produce performance bias. We sought to mitigate this by standardizing the anesthetic protocol and separating the roles of intervention delivery from outcome assessment. Thirdly, our composite primary outcome was driven primarily by differences in hypoxemia and PONV; the study was not powered to detect a difference in the less frequent outcome of POD. Finally, a limitation of our study is the routine administration of ondansetron to all patients in the PACU for PONV prophylaxis. While ethically necessary and reflective of standard clinical practice, this intervention may have attenuated the observed difference in PONV incidence between the two groups. The true effect of the OFA group on preventing PONV in the absence of prophylactic antiemetics may therefore be even larger than what we reported.

5. Conclusion

In summary, our study demonstrates that OFA, using a dexmedetomidine-esketamine-based multimodal regimen, is a feasible and beneficial alternative to conventional OBA for older patients undergoing short surgeries. OFA markedly reduced the incidence of common opioid-related complications (notably hypoxemia and PONV) and provided more stable hemodynamics, without increasing pain or delaying overall recovery. These results suggest that even for short-duration surgeries, anesthetic strategies in the elderly should prioritize minimization of opioids to enhance safety and postoperative quality of recovery. While some caution is warranted regarding dexmedetomidine's side effects (bradycardia and mild sedation prolongation), these are manageable with appropriate dosing and monitoring. Our findings contribute to a growing evidence base supporting OFA as a method to improve perioperative outcomes in vulnerable populations.

Conflicts of Interest

None.

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Role of the Funder/Sponsor

The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Ethical Approval

The study was approved by the Ethics Committee of The Affiliated Hospital of Jiaxing University (2025-KY-346).

Data Sharing Statement

The data that support the findings of this study are not openly available. Deidentified individual participant data may be made available to qualified researchers for non-commercial purposes upon reasonable request to the corresponding author, pending the submission of a research proposal and execution of a data sharing agreement.

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Data Sharing Statement

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Trial Registration

Chinese Clinical Trial Registry Identifier: ChiCTR2500102550.

References

[1] Hiten Naik, Tyler M Murray, Mayesha Khan, et al. "Population-Based Trends in Complexity of Hospital Inpatients." *JAMA Intern Med*, vol. 184, no. 2, pp. 183-192, 2024. View at: Publisher Site | PubMed

[2] Ellen Leigard, Daniel Hertzberg, David Konrad, et al. "Increasing perioperative age and comorbidity: a 16-year cohort study at two University hospital sites in Sweden." *Int J Surg*, vol. 110, no. 7, pp. 4124-4131, 2024. View at: Publisher Site | PubMed

[3] Carolyn D Seib, Holly Rochefort, Kathryn Chomsky-Higgins, et al. "Association of Patient Frailty With Increased Morbidity After Common Ambulatory General Surgery Operations." *JAMA Surg*, vol. 153, no. 2, pp. 160-168, 2018. View at: Publisher Site | PubMed

[4] Ashish K Khanna, Vida Motamedi, Bethany Bouldin, et al. "Automated Electronic Frailty Index-Identified Frailty Status and Associated Postsurgical Adverse Events." *JAMA Netw Open*, vol. 6, no. 11, pp. e2341915, 2023. View at: Publisher Site | PubMed

[5] Antje M Barreveld, Robert J McCarthy, Nabil Elkassabany, et al. "Opioid Stewardship Program and Postoperative Adverse Events: A Difference-in-differences Cohort Study." *Anesthesiology*, vol. 132, no. 6, pp. 1558-1568, 2020. View at: Publisher Site | PubMed

[6] N Levy, J Quinlan, K El-Boghdadly, et al. "An international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients." *Anaesthesia*, vol. 76, no. 4, pp. 520-536, 2021. View at: Publisher Site | PubMed

[7] Marijke Hyke Algera, Jasper Kamp, Rutger van der Schrier, et al. "Opioid-induced respiratory depression in humans: a review of pharmacokinetic-pharmacodynamic modelling of reversal." *Br J Anaesth*, vol. 122, no. 6, pp. e168-e179, 2019. View at: Publisher Site | PubMed

[8] Sean Cuninghame, Angela Jerath, Kevin Gorsky, et al. "Effect of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults: a systematic review and meta-analysis." *Br J Anaesth*, vol. 131, no. 2, pp. 314-327, 2023. View at: Publisher Site | PubMed

[9] Michele Carron, Enrico Tamburini, Federico Linassi, et al. "Efficacy of nonopioid analgesics and adjuvants in multimodal analgesia for reducing postoperative opioid consumption and complications in obesity: a systematic review and network meta-analysis." *Br J Anaesth*, vol. 133, no. 6, pp. 1234-1249, 2024. View at: Publisher Site | PubMed

[10] Marieke Niesters, Christian Martini, Albert Dahan "Ketamine for chronic pain: risks and benefits." *Br J Clin Pharmacol*, vol. 77, no. 2, pp. 357-367, 2014. View at: Publisher Site | PubMed

[11] Marjorie R Levinstein, Reece C Budinich, Jordi Bonaventura, et al. "Redefining Ketamine Pharmacology for Antidepressant Action: Synergistic NMDA and Opioid Receptor Interactions." *Am J Psychiatry*, vol. 182, no. 3, pp. 247-258, 2025. View at: Publisher Site | PubMed

[12] Jasper M Kampman, Jeroen Hermanides, Markus W Hollmann, et al. "Mortality and morbidity after total intravenous anaesthesia versus inhalational anaesthesia: a systematic review and meta-analysis." *EClinicalMedicine*, vol. 72, pp. 102636, 2024. View at: Publisher Site | PubMed

[13] David Miller, Sharon R Lewis, Michael W Pritchard, et al. "Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery." *Cochrane Database Syst Rev*, vol. 8, no. 8, pp. CD012317, 2018. View at: Publisher Site | PubMed

[14] Minke L Feenstra, Simone Jansen, Wietse J Eshuis, et al. "Opioid-free anesthesia: A systematic review and meta-analysis." *J Clin Anesth*, vol. 90, pp. 111215, 2023. View at: Publisher Site | PubMed

[15] Sally Hopewell, An-Wen Chan, Gary S Collins, et al. "CONSORT 2025 statement: updated guideline for reporting randomized trials." *Nat Med*, vol. 31, no. 6, pp. 1776-1783, 2025. View at: Publisher Site | PubMed

[16] Jordan Oberhaus, Wei Wang, Angela M Mickle, et al. "Evaluation of the 3-Minute Diagnostic Confusion Assessment Method for Identification of Postoperative Delirium in Older Patients." *JAMA Netw Open*, vol. 4, no. 12, pp. e2137267, 2021. View at: Publisher Site | PubMed

[17] P S Myles, R Wengritzky "Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review." *Br J Anaesth*, vol. 108, no. 3, pp. 423-429, 2012. View at: Publisher Site | PubMed

[18] Zheng Zhang, Chengwei Li, Lin Xu, et al. "Effect of opioid-free anesthesia on postoperative nausea and vomiting after gynecological surgery: a systematic review and meta-analysis." *Front Pharmacol*, vol. 14, pp. 1330250, 2024. View at: Publisher Site | PubMed

[19] Dan Wang, Yu-Qin Long, Yan Sun, et al. "Opioid-free total intravenous anesthesia for thyroid and parathyroid surgery: Protocol for a randomized, double-blind, controlled trial." *Front Med (Lausanne)*, vol. 9, pp. 939098, 2022. View at: Publisher Site | PubMed

[20] Carlos A B da Silveira, Ana C D Rasador, Heitor J S Medeiros, et al. "Opioid-free anesthesia for minimally invasive abdominal surgery: a systematic review, meta-analysis, and trial sequential analysis." *Can J Anaesth*, vol. 71, no. 11, pp. 1466-1485, 2024. View at: Publisher Site | PubMed

[21] Justin H Wong, Yujin Na, Fereydoun D Parsa "Evolving Toward Non-narcotic Perioperative Enhanced Recovery After Surgery and Opioid-Free Analgesia in the Management of Postoperative Pain." *Cureus*, vol. 16, no. 12, pp. e76605, 2024. View at: Publisher Site | PubMed

[22] Anthony G Doufas, Mariana L Laporta, C Noelle Driver, et al. "Incidence of postoperative opioid-induced respiratory depression episodes in patients on room air or supplemental oxygen: a post-hoc analysis of the PRODIGY trial." *BMC Anesthesiol*, vol. 23, no. 1, pp. 332, 2023. View at: Publisher Site | PubMed

[23] Raghu S Thota, Seshadri Ramkiran, Rakesh Garg, et al. "Opioid free onco-anesthesia: Is it time to convict opioids? A systematic review of literature." *J Anaesthesiol Clin Pharmacol*, vol. 35, no. 4, pp. 441-452, 2019. View at: Publisher Site | PubMed

[24] Michela Rauseo, Lucia Mirabella, Angelo Antonio Carrideo, et al. "Opioid-sparing Anesthesia in Cardiac Surgery: A Meta-analysis." *J Cardiothorac Vasc Anesth*, vol. 27, pp. S1053-0770, 2025. View at: Publisher Site | PubMed

[25] Melanie Hamilton, Stephanie Mathieson, Masoud Jamshidi, et al. "Effectiveness of Interventions to Reduce Opioid Use After

Orthopaedic Surgery: A Systematic Review of Randomised Controlled Trials." *Drugs*, vol. 85, no. 3, pp. 385-396, 2025. View at: Publisher Site | PubMed

[26] Jessica M Selle, Danielle M Strozza, Megan E Branda, et al. "A bundle of opioid-sparing strategies to eliminate routine opioid prescribing in a urogynecology practice." *Am J Obstet Gynecol*, vol. 231, no. 2, pp. 278.e1-278.e17, 2024. View at: Publisher Site | PubMed

[27] Xiang Yan, Chen Liang, Jia Jiang, et al. "Effects of balanced opioid-free anesthesia on post-operative nausea and vomiting in patients undergoing video-assisted thoracic surgery: a randomized trial." *BMC Anesthesiol*, vol. 25, no. 1, pp. 62, 2025. View at: Publisher Site | PubMed

[28] Dan Wang, Yan Sun, Ya-Juan Zhu, et al. "Comparison of opioid-free and opioid-inclusive propofol anaesthesia for thyroid and parathyroid surgery: a randomised controlled trial." *Anaesthesia*, vol. 79, no. 10, pp. 1072-1080, 2024. View at: Publisher Site | PubMed

[29] Helene Beloeil, Matthias Garot, Gilles Lebuffe, et al. "Balanced Opioid-free Anesthesia with Dexmedetomidine versus Balanced Anesthesia with Remifentanil for Major or Intermediate Noncardiac Surgery." *Anesthesiology*, vol. 134, no. 4, pp. 541-551, 2021. View at: Publisher Site | PubMed

[30] Clement Chassery, Vincent Atthar, Philippe Marty, et al. "Opioid-free versus opioid-sparing anaesthesia in ambulatory total hip arthroplasty: a randomised controlled trial." *Br J Anaesth*, vol. 132, no. 2, pp. 352-358, 2024. View at: Publisher Site | PubMed

[31] Pei Wang, Xia Zhou, Shijie Wang, et al. "Opioid-free anesthesia improves postoperative recovery quality of small and medium-sized surgery: a prospective, randomized controlled study." *Minerva Anestesiol*, vol. 90, no. 9, pp. 759-768, 2024. View at: Publisher Site | PubMed

[32] Shubham Chamadia, Juan C Pedemonte, Lauren E Hobbs, et al. "A Pharmacokinetic and Pharmacodynamic Study of Oral Dexmedetomidine." *Anesthesiology*, vol. 133, no. 6, pp. 1223-1233, 2020. View at: Publisher Site | PubMed

[33] Migena Demiri, Tiago Antunes, Dominique Fletcher, et al. "Perioperative adverse events attributed to α2-adrenoceptor agonists in patients not at risk of cardiovascular events: systematic review and meta-analysis." *Br J Anaesth*, vol. 123, no. 6, pp. 795-807, 2019. View at: Publisher Site | PubMed