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CLINICAL TRIAL REPORT

Effects of Oliceridine versus Sufentanil on Postoperative Nausea and Vomiting in Patients Undergoing Modified Radical Mastectomy: A Double-Blind Randomized Controlled Trial

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Purpose: Compare the effects of oliceridine and sufentanil on reducing postoperative nausea and vomiting (PONV) in patients undergoing modified radical mastectomy (MRM).

Patients and Methods: In this single-center, double-blind, randomized controlled trial conducted from June 2024 to March 2025, 176 female patients aged 18–75 years undergoing modified radical mastectomy were enrolled. Participants were randomly assigned (1:1) to receive either oliceridine (Group O) or sufentanil (Group S) during anesthesia induction. The primary outcome was the incidence of PONV within 48 h postsurgery. Secondary outcomes included PONV severity, Visual Analog Scale (VAS) pain scores at rest and during activities, use of rescue antiemetics and rescue analgesia, cardiovascular adverse events after induction, changes in heart rate (HR) and mean arterial pressure (MAP) around tracheal intubation, duration of anesthesia and surgery, and other drug-related adverse events after emergence.

Results: Oliceridine significantly reduced the incidence of PONV within 48 h compared with sufentanil (20.5% vs 39.8%; p = 0.005). PONV severity at 48 h was also lower in the oliceridine group (median [IQR] 0.0 [0.0–0.0] vs 0.0 [0.0–5.0]; p = 0.016), and the incidence of PONV within 24 h was reduced (13.6% vs 27.3%; p = 0.025). Analgesic efficacy, as reflected by VAS scores and the need for rescue analgesia, was comparable between groups. Hemodynamic profiles and the incidence of cardiovascular adverse events were similar, although numerically fewer hypotensive and bradycardic episodes occurred with oliceridine.

Conclusion: In patients undergoing modified radical mastectomy, oliceridine used for anesthetic induction and perioperative analgesia significantly reduced the incidence and severity of PONV compared with sufentanil, while maintaining adequate analgesia and a favorable safety profile. Oliceridine may represent a safer opioid option in breast cancer surgery, with a lower burden of opioid related adverse events (ORADEs).

Keywords: postoperative nausea and vomiting, PONV, opioid-related adverse events, ORADEs, biased ligand, visual analogue scale, VAS, opioid-free anesthesia, OFA, opioid-sparing anesthesia, OSA

Introduction

Breast cancer is the most commonly diagnosed malignancy in women worldwide and surgery remains the mainstay of curative treatment for breast cancer.[1,2] PONV is one of the most common postoperative complications in breast cancer surgery. Extensive literature demonstrates that breast cancer surgery constitutes an additional risk factor for postoperative nausea and vomiting in female surgical patients: the incidence within 24 hours postoperatively remains as high as 30%-68% among patients receiving prophylactic antiemetic therapy during surgery, while the incidence rises to 70%-80%

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among those not receiving such treatment.[3–5] Based on postoperative follow-up data from our center over the preceding year, the estimated incidence of PONV after modified radical mastectomy was approximately 40%. Gynecological surgeries involve a high-risk population for PONV, with its incidence associated with female gender, non-smoking status, and perioperative opioid use.[6]

Opioid-based analgesia is still regarded as the cornerstone of perioperative pain management.[7] Commonly used opioids, including fentanyl, sufentanil and morphine, are associated with a spectrum of opioid-related adverse events (ORADEs), such as nausea, vomiting, pruritus, sedation and respiratory depression, among which postoperative nausea and vomiting (PONV) is particularly frequent.[8] Because the risk of ORADEs is dose-dependent, clinicians often reduce intraoperative and postoperative opioid doses to mitigate adverse effects, at the expense of optimal analgesia, thereby contributing to undertreated postoperative pain.[9]

Oliceridine is a next-generation μ-opioid receptor (MOR) agonist with G-protein–signaling bias. It preferentially activates G-protein pathways while attenuating β-arrestin recruitment. G-protein signaling is primarily associated with analgesia, whereas β-arrestin pathways have been implicated in ORADEs.[10,11] Oliceridine is therefore expected to provide effective analgesia with a reduced incidence of opioid-related adverse effects. In 2020, the US Food and Drug Administration (FDA) approved oliceridine for the management of acute severe pain requiring an intravenous opioid and for whom alternative treatments are inadequate, as an alternative to conventional agents.[12]

However, whether this pharmacological bias translates into clinically meaningful reductions in PONV in the context of breast cancer surgery has not been established. In this randomized, double-blind trial, we compared the impacts of oliceridine vs sufentanil as part of the perioperative analgesic regimen for modified radical mastectomy on PONV incidence, with the aim of improving drug analgesia strategies by enhancing both their effectiveness and safety.

Materials and Methods

Study Design and Ethics

This single-center, double-blind, randomized controlled trial was conducted at Changhai Hospital, affiliated with Naval Medical University (Shanghai, China) between June 2024 and March 2025. The study enrolled women scheduled for modified radical mastectomy who met predefined eligibility criteria.

The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2400089317). The protocol was approved by the Institutional Review Board of Changhai Hospital (approval No. CHE2024-280) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Participants

Inclusion criteria included: (1) female patients aged 18–75 years; (2) body weight ≥45 kg and body mass index (BMI) ≤40 kg/m^2; (3) scheduled for modified radical mastectomy; (4) American Society of Anesthesiologists (ASA) physical status I–III.

Exclusion criteria included: (1) clinically significant systemic disease; (2) contraindications to opioid use or clinically relevant opioid intolerance; (3) conditions that may affect opioid metabolism (such as concomitant pain disorders or liver/kidney disease); (4) frequent use of any analgesics in the recent past; (5) opioid tolerance, physical dependence or substance abuse; (6) history of motion sickness.

Randomization and Blinding

Randomization was performed using a computer-generated random sequence. A random number list was created with statistical software and placed in sequentially numbered, sealed, opaque envelopes. These envelopes were stored and opened by nursing staff not otherwise involved in the study. Patients were allocated in a 1:1 ratio to the oliceridine group (Group O) or the sufentanil group (Group S) according to the randomization sequence.

All patients underwent general anesthesia. Before surgery, they were informed that they might experience nausea, vomiting or pain after emergence, or no discomfort. Patients, anesthesiologists, outcome assessors, data recorders and

statisticians were all blinded to group allocation. To maintain blinding, an independent research nurse prepared and dispensed the study drugs in identical syringes labeled only with the study identification number.

During the induction of anesthesia, drug doses for both groups were calculated based on patient body weight and diluted to a total volume of 3 mL for administration. Oliceridine was administered at a fixed dose of 3 mg (1 mg/mL), while sufentanil was prepared as a 3-mL solution at 0.4 μg/kg. Supplemental analgesic medication administered before the end of surgery was separately prepared as a 1-mL solution by the dispensing nurse: oliceridine at 1 mg (1 mg/mL), and sufentanil at 0.1 μg/kg, adjusted to a final volume of 1 mL.

Study Intervention

All patients fasted for at least 8 h preoperatively and received no premedication. Upon arrival in the operating room, a peripheral intravenous line was established. Standard monitoring included electrocardiography, non-invasive blood pressure, heart rate (HR) and pulse oximetry (SpO_2). Oxygen was administered via face mask at 2–3 L/min.

Anesthesia induction was performed according to group assignment:

Group O (oliceridine): midazolam 0.03 mg/kg, propofol 2 mg/kg, oliceridine 3 mg (3 mL) and rocuronium 0.6 mg/kg, administered intravenously.

Group S (sufentanil): midazolam 0.03 mg/kg, propofol 2 mg/kg, sufentanil 0.4 μg/kg (3 mL) and rocuronium 0.6 mg/kg, administered intravenously.

After induction, patients were manually ventilated for 3 min before tracheal intubation. Mechanical ventilation was then initiated with an oxygen flow of 2 L/min and an inspired oxygen fraction of 1.0. Tidal volume was set at 6–8 mL/kg, and the respiratory rate was adjusted to 10–15 breaths/min to maintain an end-tidal carbon dioxide partial pressure of 35–40 mmHg and SpO_2 of 97–100%.

Anesthesia was maintained with continuous infusions of propofol (4–12 mg/kg/h) and remifentanil (0.1–0.5 μg/kg/min). Additional rocuronium was administered as required. Mean arterial pressure (MAP) was maintained within ±20% of baseline. When MAP was <65 mmHg or decreased by more than 20% from baseline, a single intravenous bolus of ephedrine (6 mg) or phenylephrine (50 μg) was administered. When HR was <45 beats/min, atropine 0.5 mg was given intravenously. Other perioperative adverse events were recorded and managed according to standard clinical practice. Depth of anesthesia and vital signs were kept stable throughout surgery.

Thirty minutes before the end of surgery, patients in the Group O received oliceridine 1 mL (1 mg) and those in the Group S received sufentanil 1 mL (0.1 μg/kg) as supplemental analgesia. Propofol and remifentanil infusions were discontinued at the end of surgery. Patients were transferred to the post-anesthesia care unit (PACU) without pharmacological reversal of neuromuscular blockade. After recovery of spontaneous breathing, tracheal extubation was performed when patients were fully awake and able to lift their head. Patients were discharged from the PACU to the ward once standard discharge criteria were met.

All patients were followed up on the mornings of postoperative day 1 and day 2 by an anesthesia nurse who was blinded to group allocation.

Outcome Measurements

The primary outcome was the incidence of PONV within 48 h after surgery.

Secondary outcomes included:

- Incidence and severity of PONV within 24 h postoperatively;
- Severity of PONV within 48 h postoperatively;
- Resting and dynamic pain scores at 24 h and 48 h, assessed using a 10-cm visual analogue scale (VAS), where 0 indicates no pain and 10 indicates the worst imaginable pain (1–3, mild; 4–6, moderate; 7–10, severe);
- Number of patients requiring rescue antiemetic therapy and rescue analgesia;
- Incidence of cardiovascular adverse events after induction, including hypotension (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg) and bradycardia (HR <60 beats/min), and the use of vasoactive drugs after induction;

- Record changes in heart rate (HR) and mean arterial pressure (MAP) before and after endotracheal intubation;
- Duration of anesthesia and duration of surgery;
- Incidence of other drug-related adverse events after emergence, including respiratory depression/hypoxemia, somnolence and pruritus;

Sample Size Calculation

Sample size was calculated using PASS 15.0 software. Based on postoperative follow-up data from our center over the preceding year, the estimated incidence of PONV after modified radical mastectomy was approximately 40%. Pilot data suggested that the use of oliceridine at induction could reduce the incidence of PONV to about 20%. Assuming a reduction from 40% to 20%, with a two-sided α of 0.05 and 80% power, and allowing for a 10% dropout rate, we calculated that 88 patients per group (176 in total) were required.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0. Categorical variables are presented as numbers (percentages) and were compared using the χ^2-test. Continuous variables with a normal distribution are expressed as mean (standard deviation, SD) and were compared using the independent-samples *t* test. Non-normally distributed continuous variables are expressed as median (interquartile range, IQR) and were compared using non-parametric tests (eg. Wilcoxon rank-sum test). Fisher's exact test was used when appropriate. A two-sided p value <0.05 was considered statistically significant.

For repeated measurements of HR, MAP and SpO_2 at T0 (before induction), T1 (before intubation) and T2 (after intubation), within-group changes were assessed using the Wilcoxon signed-rank test, and between-group comparisons of baseline values, absolute changes and percentage changes were performed using the Wilcoxon rank-sum test.

Results

Patient Characteristics

Of 190 patients screened, 4 were excluded due to a change in surgical switch to local anesthesia, 6 did not meet the inclusion criteria and 4 declined participation. The remaining 176 patients were randomized, with 88 assigned to each group, and all completed the trial (Figure 1). Protocol adherence was complete (100% compliance), and no serious adverse events occurred in either group.

Baseline demographic and clinical characteristics were well balanced between groups, with no statistically significant differences (p > 0.05) (Table 1).

Efficacy Outcomes

The incidence of PONV within 48 h postoperatively was significantly lower in the oliceridine group than in the sufentanil group (20.5% vs 39.8%; p = 0.005; odds ratio (OR) 0.389, 95% confidence interval (CI) 0.199–0.762; Table 2). PONV severity scores at 48 h were also reduced in the oliceridine group (median [IQR] 0.0 [0.0–0.0] vs 0.0 [0.0–5.0]; p = 0.016). Within the first 24 h after surgery, the incidence of PONV was significantly lower with oliceridine (13.6% vs 27.3%; p = 0.025).

At 24 h, resting VAS scores were 0.0 [0.0–3.0] in the oliceridine group vs 0.0 [0.0–0.0] in the sufentanil group (p = 0.027), and dynamic VAS scores were 0.0 [0.0–3.2] vs 0.0 [0.0–3.0] (p = 0.008). At 48 h, most patients in both groups reported mild pain (VAS <4), and there were no clinically meaningful differences in resting or dynamic VAS scores or in the number of patients requiring rescue analgesia (Table 3). Overall, both regimens provided adequate analgesia for modified radical mastectomy.

SpO_2 values at T0, T1 and T2 did not differ significantly between groups, and within-group and between-group changes over time were not statistically significant (Figure 2).

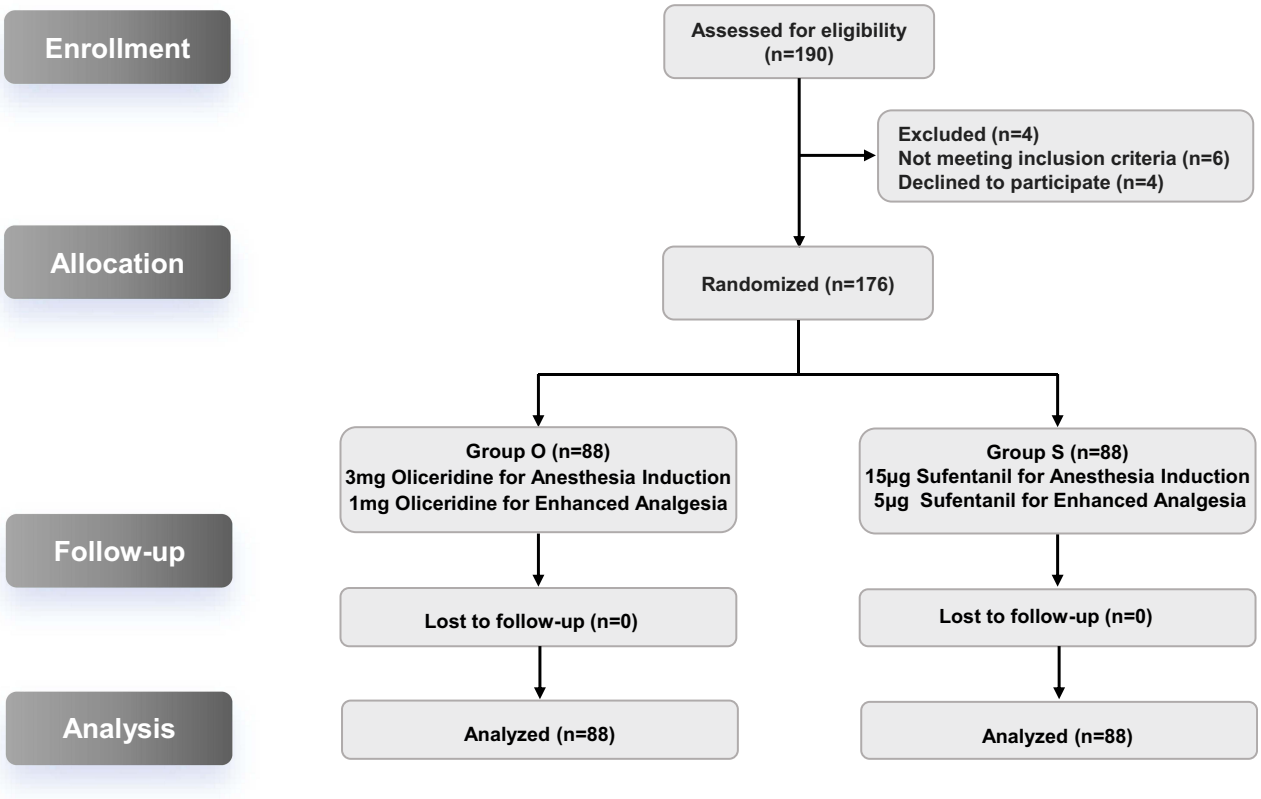

Figure 1 Study Flow Diagram.

HR and MAP at T0, T1 and T2 are shown in Figures 3 and 4. Both groups exhibited the expected hemodynamic responses to induction and intubation. HR and MAP in the oliceridine group tended to remain closer to baseline values, suggesting stable hemodynamic control.

Table 1 Baseline Characteristics

	Total (N=*176*)	Group O (N=*88*)	Group S (N=*88*)	P-value
Sex: Female	176 (100.0)	88 (100.0)	88 (100.0)	NA
Age	53.4 (11.4)	52.8 (11.1)	53.9 (11.6)	0.504
Height, cm	159.5 (5.2)	159.1 (5.3)	159.8 (5.0)	0.398
Weight, kg	59.9 (8.1)	59.8 (8.5)	60.1 (7.6)	0.802
BMI, kg/m^2	23.6 (3.0)	23.6 (3.0)	23.6 (3.1)	0.998
Hypertension	22 (12.5)	8 (9.1)	14 (15.9)	0.172
Diabetes Mellitus	7 (4.0)	2 (2.3)	5 (5.7)	0.444
Coronary Artery Disease	5 (2.8)	4 (4.5)	1 (1.1)	0.368
Oncologic History	12 (6.8)	4 (4.5)	8 (9.1)	0.232
Surgical History	17 (9.7)	8 (9.1)	9 (10.2)	0.799

(*Continued*)

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Table 1 (Continued).

	Total (N=*176*)	Group O (N=*88*)	Group S (N=*88*)	P-value
ASA				1.000
I	82 (46.6)	41 (46.6)	41 (46.6)	
II	94 (53.4)	47 (53.4)	47 (53.4)	

Notes: Date are presented as mean (SD), median (interquartile range, IQR) or frequency (%). Statistical tests for P-value calculation: independent samples *t*-test, Chi-square test or Fisher's exact test with categorical correction.
Abbreviations: Group O, Oliceridine group; Group S, Sufentanil group; ASA, American Society of Anesthesiologists.

Table 2 Primary Endpoint

	Total (N=176)	Group O (N=88)	Group S (N=88)	Risk Difference (95% CI) *	Odds Ratio (95% CI) †	P-value
Incidence of PONV within 48 hours after surgery						0.005
No	123 (69.9)	70 (79.6)	53 (60.2)			
Yes	53 (30.1)	18 (20.5)	35 (39.8)			
Incidence of PONV within 48 hours after surgery, % (95% CI)	30.1 (23.4 to 37.5)	20.5 (12.6 to 30.4)	39.8 (29.5 to 50.8)	−19.3 (−32.9 to −5.8)	0.389 (0.199 to 0.762)	

Notes: *Risk difference, % (group O – group S); †group O vs group S (group S as the reference). Statistical tests for P-value calculation. Incidence: 95% confidence intervals were calculated using the Clopper–Pearson method. Risk difference: 95% confidence intervals were calculated using the Farrington–Manning method.
Abbreviations: Group O, Oliceridine group; Group S, Sufentanil group; PONV, Postoperative Nausea and Vomiting.

Table 3 Secondary Endpoint

	Total (N=*176*)	Group O (N=*88*)	Group S (N=*88*)	P-value
Duration of anesthesia, h	2.0 (0.7)	2.0 (0.6)	2.0 (0.7)	0.737
Duration of surgery, h	1.7 (0.6)	1.6 (0.6)	1.7 (0.7)	0.655
Use of antiemetics, n (%)	39 (22.2)	12 (13.6)	27 (30.7)	0.007
Use of rescue analgesics, n (%)	32 (18.2)	20 (22.7)	12 (13.6)	0.118
PONV score at 24 h postoperatively	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.0 (0.0–5.0)	0.156
PONV within 24 h, n (%)				0.025
No	140 (79.5)	76 (86.4)	64 (72.7)	
Yes	36 (20.5)	12 (13.6)	24 (27.3)	
PONV score at 48 h postoperatively	0.0 (0.0–5.0)	0.0 (0.0–0.0)	0.0 (0.0–5.0)	0.016
Resting VAS score at 24 h	0.0 (0.0–2.2)	0.0 (0.0–3.0)	0.0 (0.0–0.0)	0.027
Dynamic VAS score at 24 h	0.0 (0.0–3.0)	0.0 (0.0–3.2)	0.0 (0.0–3.0)	0.008
Resting VAS score at 48 h	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.489
Dynamic VAS score at 48 h	0.0 (0.0–3.2)	3.0 (0.0–4.0)	0.0 (0.0–3.0)	0.244

Notes: Date are presented as number (percentage), mean (SD), median (interquartile range, IQR) or frequency (%). Statistical tests for P-value calculation: independent samples *t*-test, Chi-square test or Fisher's exact test with categorical correction.
Abbreviations: Group O, oliceridine group; Group S, sufentanil group; VAS, Visual Analogue Scale.

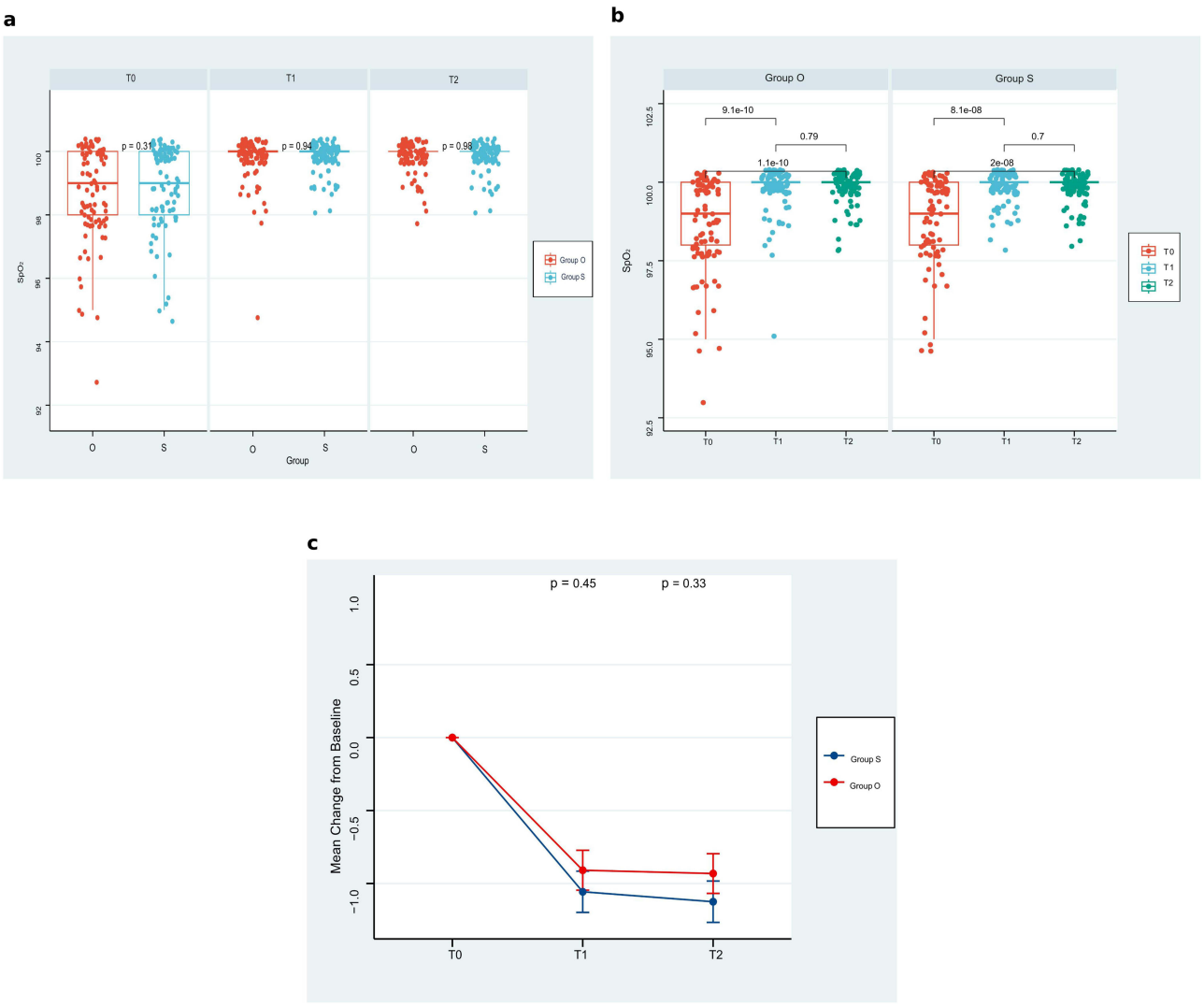

Figure 2 SpO_2 at T0 (before induction), T1 (before intubation) and T2 (after intubation). (**a**) Comparison between groups at each recorded time point; (**b**) Comparison within groups at each recorded time point; (**c**) Mean Change from Baseline between groups.

Safety Outcomes

The incidence of cardiovascular adverse events during induction did not differ significantly between groups, but numerically fewer events occurred with oliceridine. Hypotension was observed in 22.7% of patients in the oliceridine group vs 29.5% in the sufentanil group (p = 0.302), bradycardia in 2.3% vs 4.5% (p = 0.682), and coughing during induction in 0% vs 2.3% (p = 0.497) (Table 4).

The incidence of other drug-related adverse events after emergence, including hypoxemia, respiratory depression and somnolence, was low and comparable between groups (Table 5).

Discussion

In this randomized, double-blind trial in women undergoing modified radical mastectomy, oliceridine used for anesthetic induction and peri-induction analgesia significantly reduced the incidence of PONV within 48 h compared with sufentanil. The odds of PONV were reduced by approximately 60% with oliceridine (OR 0.323–0.389, depending on the time point), highlighting a clinically meaningful advantage. Meanwhile, it maintained comparable analgesic efficacy and a more favorable safety profile, lowering down the adverse events peri-operatively, including hypotension, bradycardia and coughing, which is consistent with the previous studies.[13]

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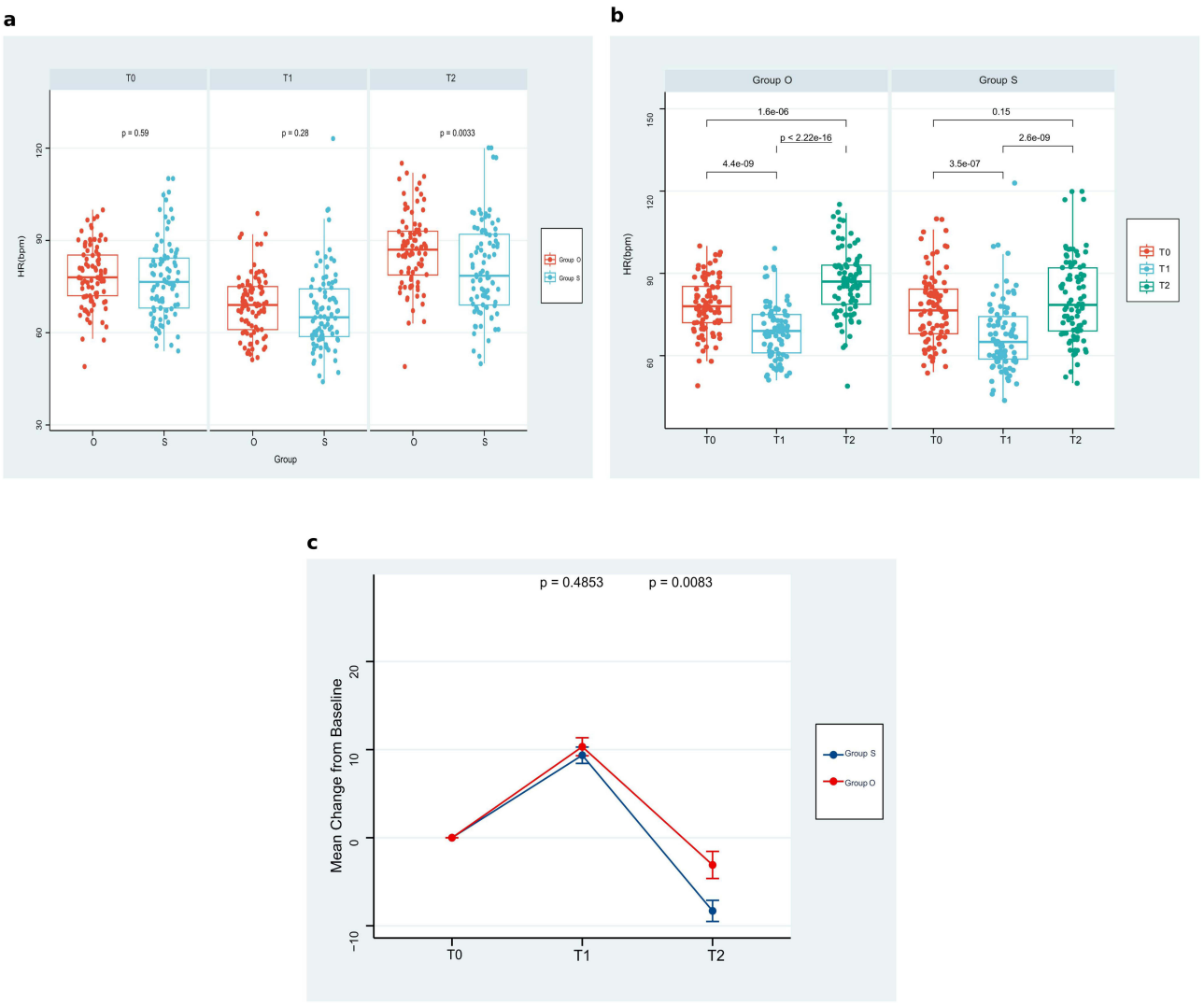

Figure 3 HR at T0 (before induction), T1 (before intubation) and T2 (after intubation). (**a**) Comparison between groups at each recorded time point; (**b**) Comparison within groups at each recorded time point; (**c**) Mean Change from Baseline between groups.
Abbreviation: HR, Heart Rate.

The dosing strategy in our study was informed by pharmacological data.[14] We used 3 mg oliceridine at induction (a dose within the recommended intravenous range) and 1 mg as supplemental analgesia at the end of surgery. These doses were compared with 0.4 μg/kg sufentanil at induction and 0.1 μg/kg as supplemental analgesia at the end of surgery, which was consistent with our routine anesthetic practice. Hemodynamic responses to intubation (HR and MAP) remained close to baseline in the oliceridine group, suggesting that this regimen provided sufficient antinociception for intubation while avoiding excessive cardiovascular depression. The numerically lower rates of hypotension and bradycardia further support the hemodynamic safety of oliceridine in this setting, although these differences did not reach statistical significance and require confirmation in larger trials.

Regarding postoperative analgesic efficacy, although resting and dynamic VAS pain scores at 24 h were statistically different between the oliceridine and sufentanil groups ($p = 0.027$ and $p = 0.008$, respectively), with slightly higher scores in the former, the median scores of both groups were 0.0 with overall extremely low pain levels, suggesting satisfactory analgesia provided by both agents. The more concentrated and stable VAS scores in the sufentanil group corresponded to its higher analgesic potency and longer duration of action, whereas the greater interindividual variability in the oliceridine group was associated with its short-acting, rapidly metabolized pharmacokinetic profile and demand for careful titration. At 48 h, most patients in both groups had mild pain (VAS < 4), and no clinically meaningful differences

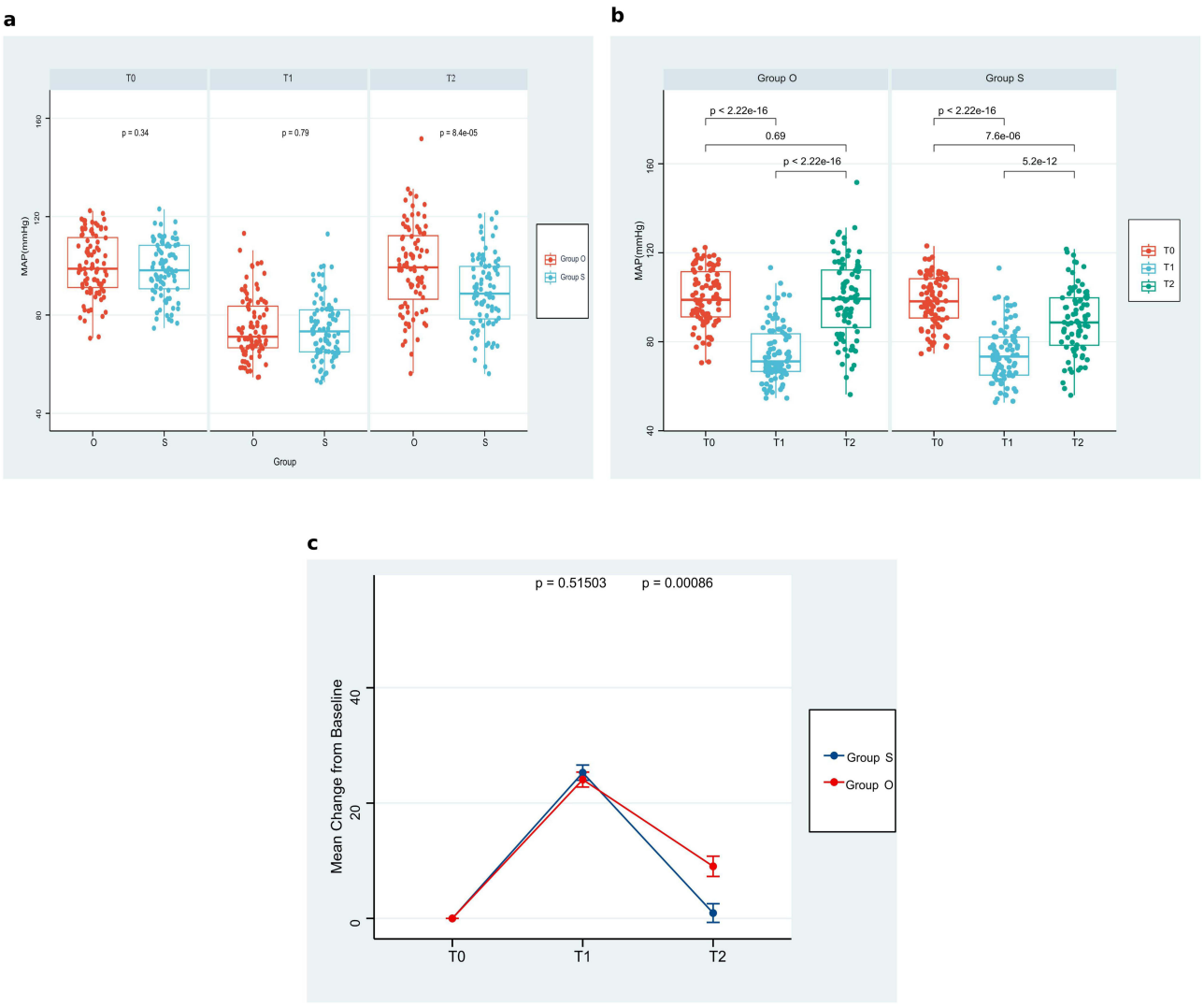

Figure 4 MAP at T0 (before induction), T1 (before intubation) and T2 (after intubation). (**a**) Comparison between groups at each recorded time point; (**b**) Comparison within groups at each recorded time point; (**c**) Mean Change from Baseline between groups.
Abbreviation: MAP, Mean Arterial Pressure.

were observed in resting or dynamic VAS scores or rescue analgesia use, indicating comparable and satisfactory analgesic effects in the medium-to-long term. Collectively, oliceridine yields slightly weaker early analgesic potency than sufentanil but still achieves clinically sufficient analgesia, with similar analgesic efficacy between the two drugs in the later postoperative period.

Table 4 Adverse Events During Induction

	Total (N=*176*)	**Group O (N=*88*)**	**Group S (N=*88*)**	**P-value**
Hypotension, n (%)	46 (26.1)	20 (22.7)	26 (29.5)	0.303
Bradycardia, n (%)	6 (3.4)	2 (2.3)	4 (4.5)	0.682
Coughing, n (%)	2 (1.1)	0 (0.0)	2 (2.3)	0.497
Allergic reaction, n (%)	1 (0.6)	0 (0.0)	1 (1.1)	1.000

Notes: Data are presented as number (percentage). Statistical tests for P-value calculation: independent samples *t*-test, Chi-square test or Fisher's exact test with categorical correction.
Abbreviations: Group O, oliceridine group; Group S, sufentanil group.

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Table 5 Adverse Events in the PACU

	Total (N=*176*)	Group O (N=*88*)	Group S (N=*88*)	P-value
Hypoxemia, n (%)	1 (0.6)	1 (1.1)	0 (0.0)	1.000
Respiratory depression, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Somnolence, n (%)	1 (0.6)	0 (0.0)	1 (1.1)	1.000

Notes: Data are presented as number (percentage). Statistical tests for P-value calculation: independent samples *t*-test, Chi-square test or Fisher's exact test with categorical correction.
Abbreviations: Group O, oliceridine group; Group S, sufentanil group.

PONV is the most frequent ORADES, which delays oral intake, impairs wound healing, prolongs hospital stay and increases healthcare costs.[15,16] As a next-generation G-protein–biased μ-opioid receptor agonist, oliceridine offers a novel pharmacological strategy for addressing the challenge of PONV. In contrast to sufentanil, which produces a relatively balanced activation of both downstream μ-receptor pathways, oliceridine preferentially engages the G-protein pathway that mediates analgesia, while markedly attenuating β-arrestin recruitment, which is implicated in ORADEs.[17] This "functional selectivity" enables oliceridine to provide equipotent analgesia while reducing gastrointestinal adverse effects at their mechanistic origin. In the present study, patients receiving oliceridine not only exhibited a lower incidence of PONV, but also required significantly fewer rescue antiemetics within 48 hours (13.6% vs 30.7%), indicating that its benefit lies in proactive prevention of PONV rather than merely facilitating postoperative rescue treatment.[18,19] Notably, the between-group difference in PONV incidence at 48 hours (20.5% vs 39.8%) was more pronounced than at 24 hours (13.6% vs 27.3%), a finding that appears closely related to postoperative dietary resumption. By 48 hours after surgery, most patients have returned to normal oral intake, and the reactivation of gastrointestinal function may amplify the inhibitory effects of conventional opioids on gut motility.[20,21] In contrast, the weak activation of the β-arrestin pathway by oliceridine substantially mitigates its impact on gastrointestinal smooth muscle, allowing it to maintain a relatively low risk of PONV even after diet has been resumed. This advantage is particularly relevant in the context of enhanced recovery after surgery (ERAS), in which early nutritional intake is a cornerstone of postoperative recovery.[22] By lowering the risk of PONV, oliceridine provides a safer window for early feeding and thereby supports ERAS-aligned perioperative care.[23,24]

Current PONV management relies predominantly on a "risk stratification plus multimodal prophylaxis" paradigm, which includes opioid-sparing strategies, combination antiemetic therapy, and optimization of anesthetic techniques.[25,26] However, approaches such as opioid-free anesthesia (OFA) are constrained by limited applicability and inconsistent analgesic efficacy. In more invasive procedures, such as radical mastectomy, complete avoidance of opioids may result in inadequate intraoperative analgesia and exacerbation of acute postoperative pain.[27] The use of oliceridine circumvents this trade-off: it preserves robust analgesia while improving the safety profile through pharmacological refinement, thereby achieving a more clinically realistic "analgesia–safety" balance. Moreover, the fourth consensus guidelines for the management of PONV emphasize that reducing opioid exposure is a key modifiable determinant of PONV risk.[28] Oliceridine does not reduce risk by lowering opioid dose, but rather by improving opioid "quality" through selective signaling pathway engagement. This paradigm of "precision analgesia" offers a new prophylactic option for high-risk populations—such as women, patients with a history of PONV, and those undergoing prolonged surgery—and can be integrated with existing antiemetic regimens to further enhance the overall effectiveness of PONV prevention.[29,30]

A survey of practicing physicians has revealed that opioids remain an indispensable analgesic for perioperative pain management.[31] The fourth consensus guidelines for the management of PONV identify perioperative opioid use as a major modifiable risk factor and recommend minimizing total opioid exposure whenever feasible.[28] Against this backdrop, our findings support a more nuanced approach: rather than eliminating opioids altogether, selecting agents with favorable signaling profiles may allow clinicians to retain the analgesic benefits of opioids while mitigating ORADEs. Mechanistically, G-protein signaling at the MOR is primarily responsible for analgesia, whereas β-arrestin recruitment has been linked to respiratory depression, constipation and PONV.[10,11] Oliceridine, as a G-protein–biased MOR agonist, was designed to exploit this divergence. Our trial provides clinical evidence in support of this concept: under conditions

of comparable analgesia, oliceridine was associated with a substantially lower incidence of PONV than sufentanil. Besides, oliceridine may also offer advantages in specific patient populations. Because of delayed clearance, patients with severe hepatic impairment may benefit from reduced initial doses and less frequent subsequent dosing.[32]

In the context of breast cancer surgery, where recovery is typically rapid and early mobilization and oral intake are critical, minimizing PONV and other ORADEs is particularly important. Routine use of patient-controlled analgesia (PCA) with conventional opioids can delay gastrointestinal recovery, increase PONV risk, raise costs and, in some cases, contribute to persistent opioid use or dependence.[33,34] Based on the fourth consensus guidelines for the management of PONV, we prefer a strategy that maintains adequate perioperative analgesia while reducing the overall dose of opioid to decrease the related adverse events.

Our study has limitations. First, this was a single-center trial including only female patients undergoing a single type of surgery, which may limit generalizability to other procedures and populations. Second, the timing of oral intake was not standardized after endotracheal intubation during surgery, which makes it difficult to rule out bias in research results caused by postoperative oral feeding. Future multicenter trials across diverse surgical populations to evaluate long-term outcomes such as persistent postoperative pains and other ORADES, are warranted to further define the optimal dosing and strategy.

Conclusion

Oliceridine can be used as an alternative to sufentanil for anesthetic induction and peri induction analgesia in women undergoing modified radical mastectomy, with potentially a decreased risk of PONV and excellent cardiovascular safety.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author Rui Bao (email: baorui_md@163.com), upon reasonable request.

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Disclosure

All authors declare no financial or non-financial conflicts of interest that could influence the study outcomes, including the verifiable absence of economic associations with pharmaceutical entities.

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