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CLINICAL TRIAL REPORT

# $EC_{50}$ of Remifentanil for Inhibiting Cardiovascular Responses to Tracheal Intubation in Patients Treated by Different Doses of Oliceridine: A Randomized Controlled Trial Using Up-and-Down Sequential Allocation Methodology

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**Purpose:** The aim was to evaluate its antinociceptive potency by comparing the effect of oliceridine and sufentanil on the half maximal effective concentration ($EC_{50}$) of remifentanil in suppressing the cardiovascular response to endotracheal intubation under general anesthesia.

**Patients and methods:** A total of 120 patients scheduled for thyroid nodulectomy were randomized into four groups: (i) control group, (ii) sufentanil group, (iii) oliceridine 0.015 mg/kg group, and (iv) oliceridine 0.03 mg/kg group. The initial dosage of remifentanil for induction of general anesthesia was 3 ng/mL. The subsequent infusion dosage of remifentanil was adjusted based on the response to endotracheal intubation in the previous patient in the group, defined as a ≥ 15% change in heart rate (HR) or mean arterial pressure (MAP) before and after intubation. Adjustments were made in increments or decrements of 0.2 ng/mL. The control group received no additional medication, whereas the sufentanil group was administered a 0.15 μg/kg intravenous (IV) bolus of sufentanil. The two oliceridine groups received IV boluses of oliceridine either 0.015 mg/kg or 0.03 mg/kg respectively. Postoperative airway complications, encompassing hoarseness, sore throat, and dysphonia, were also documented.

**Results:** The $EC_{50}$ values of remifentanil was 3.728 ng/mL (95% CI: 3.536–3.943 ng/mL), 2.824 ng/mL (95% CI: 2.620–3.015 ng/mL), 3.045 ng/mL (95% CI: 2.852–3.239 ng/mL) and 2.887 ng/mL (95% CI: 2.689–3.085 ng/mL) in the control, sufentanil, oliceridine 0.015 mg/kg group and oliceridine 0.03 mg/kg group, respectively.

**Conclusion:** The effect of 0.03 mg/kg oliceridine is similar to 0.15 μg/kg sufentanil in reducing the $EC_{50}$ of remifentanil in inhibiting the cardiovascular responses induced by trachea intubation.

**Keywords:** oliceridine, $EC_{50}$, hemodynamic response to trachea intubation, the sequential method

## Introduction

Oliceridine is a novel μ-receptor agonist that produces analgesia by activating the G-protein signaling pathway downstream of the μ-opioid receptor. Oliceridine was approved for the management of moderate to severe acute pain in adults in 2020 in the US and in 2023 in China.[1] The recommended starting dose is 1.5 mg, followed by a supplemental dose of 0.75 mg after 1 hour. The total daily dose should not exceed 27 mg, and no single dose should exceed 3 mg.[2] In the mouse hot-plate test, the $ED_{50}$ values of oliceridine and morphine were 0.9 mg/kg and 4.9 mg/kg.[3] But oliceridine

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demonstrates significantly lower recruitment of β-arrestin-2 compared to morphine, may resulting in a reduced incidence of opioid-related adverse events (ORAEs).[4]

During the induction of general anesthesia, endotracheal intubation can provoke sympathetic stimulation, leading to considerable hemodynamic changes. Traditional opioids, including sufentanil, fentanyl, and morphine, produce analgesic effects via μ-opioid receptor, which helps to mitigate the intubation response. However, to date, there is no study investigating the efficacy of oliceridine in attenuating the intubation response during anesthesia induction. The Dixon's up-and-down sequential method is currently the most commonly used approach to determine the $EC_{50}$ of anesthetic drugs.[5–7] We conducted a prospective randomized controlled trial to determine the $EC_{50}$ of remifentanil required to suppress the cardiovascular response to endotracheal intubation with an additional dose of oliceridine or sufentanil. This study aims to compare the potency of two different doses of oliceridine against sufentanil in reducing the $EC_{50}$ of remifentanil required to suppress the intubation response, thereby evaluating the antinociceptive efficacy of the two doses of oliceridine relative to sufentanil.

# Methods

## Participants

This study was a prospective, double-blinded, randomized controlled trial. The protocol was approved by the Institutional Ethics Committee of Changhai Hospital (No. CHEC2024-401) and conducted in accordance with the Declaration of Helsinki. Patients scheduled for elective thyroid nodulectomy under general anesthesia between January 2025 and December 2025 were enrolled if they met the following criteria: (1) age 18–64 years; (2) BMI 18.5–30 kg/m$^2$ and weight less than 100 kg; (3) ASA physical status I–II; (4) voluntary participation with written informed consent. The exclusion criteria included: (1) anticipated difficult airway; (2) pre-existing severe cardiac, pulmonary, hepatic, renal, or neurological disorders; (3) chronic opioid use (continuous use in the past 3 months), substance abuse, or drug dependence (based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)); (4) pregnancy. All participants provided written informed consent prior to enrollment. The trial was registered in the Chinese Clinical Trial Registry (No. ChiCTR2400094931).

## Anesthesia Protocol

Upon entering the operating room, patients received 10 mL/kg lactated Ringer's solution for preinduction fluid resuscitation after establishing peripheral intravenous access. Standard monitoring, including electrocardiography (ECG), HR, non-invasive monitoring of blood pressure (BP) and pulse oxygen saturation was initiated. After 5 minutes of quiet supine rest, MAP and HR were monitored with two consecutive measurements to determine the average values as baseline blood pressure and HR. Patients were administered 6 liters per minute of oxygen via facemask for preoxygenation before anesthesia induction. Midazolam was administered intravenously at a dosage of 0.02 mg/kg and the bolus was administered over 2 minutes. Propofol was infused via a target-controlled infusion (TCI) pump to reach an effect concentration of 3 μg/mL. Remifentanil was also infused via a TCI pump and the initial effect concentration for the first patient was 3 ng/mL. As the patient began to lose consciousness, rocuronium 0.6 mg/kg was given as a 10 - second bolus. In the sufentanil group, 0.15 μg/kg of sufentanil was intravenously administered as a 10 - second bolus. In the oliceridine groups, oliceridine was administered intravenously at doses of either 0.015 mg/kg or 0.03 mg/kg as a 10 - second bolus. An equal volume of normal saline was administered to the blank control group. Endotracheal intubation was performed 3 minutes after drug administration, using video laryngoscopy, followed by mechanical ventilation. Hemodynamic monitoring was conducted at the following time points: pre-induction at 3 minutes and 1 minute before induction (BP, MAP, HR); pre-intubation at 3 minutes and 1 minute before intubation (BP, MAP, HR); and post-intubation immediately (0 min), 1 minute and 3 minutes after intubation (BP, MAP, HR). Patients were excluded if they developed severe hypotension (MAP < 50 mmHg) necessitating the use of vasoactive drugs, and the next patient will be allocated into this group instead of this patient.

## Determination of the Effective Concentration of Remifentanil Using the Dixon Sequential Method

The initial effective concentration of remifentanil was set at 3 ng/mL. According to the up-and-down sequential method, the concentration for the subsequent patient was determined based on the intubation response of the preceding patient. A positive intubation response was defined as the occurrence of either of the following at any time within the first 3 minutes after intubation: an increase in HR of ≥ 15% above the pre - intubation value, or an increase in MAP of ≥ 15% above the pre - intubation value. Meeting any one criterion was sufficient. The highest instantaneous HR and the highest instantaneous MAP observed during the 3 - minute window were compared with the respective pre - intubation averages. If either peak value reached the threshold, the case was locked as "positive" and the concentration of remifentanil for the subsequent patient was increased by 0.2 ng/mL. A negative response was defined as no change or an increase in HR or MAP of less than 15%.[8,9] In such instances, the target concentration of remifentanil was decreased by 0.2 ng/mL in the following patient of the group.

## Data Collection

The demographic data were collected including age, gender, height, weight, medical history, disease progression, illness status, treatment history, drug sensitivity history, smoking history, comorbidities, medications, and surgery type. Primary Outcome was the $EC_{50}$ of remifentanil. The secondary outcomes included the duration of anesthesia induction; airway complications, such as postoperative hoarseness, sore throat, and dysphonia; postoperative nausea and vomiting; intraoperative awareness.

## Sample Size

Based on previously reported literature, it is accepted that a sample size of 20 to 40 cases and at least 6 pairs of sequence inversions are sufficient for analyzing the assignment of up-and-down sequences.[10] Based on our previous experience and published data, a sample size of 30 cases is sufficient to capture 6 pairs of sequence inversions.[11–13] Therefore, we included 30 patients in each group for the final analysis. When a patient was excluded during the study, the next patient will be added into this group with the same allocation number.

## Randomization and Blinding

The patients were randomly allocated into four groups equally using computer-generated randomization numbers, including control group, sufentanil group, low dose oliceridine group (0.015 mg/kg) and high dose oliceridine group (0.03 mg/kg). The enrollment will be continued even if we completed the six pairs of sequence inversions.[9,10] The allocation sequences were concealed in opaque, sealed envelopes. When the patient was recruited, a nurse independent of the study checked the grouping of the patient and prepared the medication into 5 mL with saline. The syringe with transparent solution was labeled with the randomly-allocated letter from A to D. One anesthesiologist performed intubation and managed any adverse events, while a second anesthesiologist documented the case report forms. An independent anesthetic nurse prepared and administered the study drug according to the patient's weight. Participants, investigators, data management staff, and statisticians remained blinded to the group allocation throughout the study.

## Statistical methods

Using SPSS 26.0, all data were subjected to the *Shapiro–Wilk test* to determine whether they conformed to a normal distribution. Continuous data that conform to a normal distribution are expressed as mean ± standard deviation (*SD*). Continuous data that do not follow a normal distribution are expressed using the median and interquartile range. Sex, ASA grade, history of motion sickness, and incidence of adverse events were all binary variables, and they were analyzed using *Pearson's* $\chi^2$ test. Levene's test was used to assess homogeneity of variances and one-way ANOVA was used for the comparison of numerical data, followed by Tukeys HSD when variances were equal, or with Welch's ANOVA when the assumption of homogeneity was violated. The paired *Wilcoxon Signed-Rank test* was utilized to compare the circulatory status before and after endotracheal intubation. Enumeration data were expressed as cases (percentages). The

$EC_{50}$ of remifentanil and the corresponding 95% confidence interval (*CI*) were calculated using *Probit* regression analysis in SPSS 26, and analyzed by one-way *ANOVA*, pairwise comparisons between groups were performed with the *Sidak* method. Sequential diagrams and dose–response curves were plotted with GraphPad Prism 8. For all analyses, $p < 0.05$ was considered to indicate a statistically significant difference.

## Results

A total of 120 patients were randomly assigned to four groups: the control group, the sufentanil group, the 0.015 mg/kg oliceridine group, and the 0.03 mg/kg oliceridine group. The enrollment process is illustrated in Figure 1. No statistically significant differences were observed among the four groups in terms of gender, age, height, weight, as well as HR, systolic blood pressure (SBP), and DBP ($p > 0.05$, Table 1).

The sequence numbers of responses to Remifentanil infusion in the four groups of patients are shown in Figure 2. In our present study, there were 8, 6, 7 and 8 crossovers in the control, sufentanil, oliceridine 0.015 mg/kg and oliceridine 0.03 mg/kg groups respectively. The corresponding data are shown in Supplementary Table 1. The dose-response curves obtained from Probit regression analysis for both groups are shown in Figure 3. The results of the probit regression analysis indicated that the $EC_{50}$ of remifentanil for inhibiting the cardiovascular response to tracheal intubation during general anesthesia in the control group was 3.728 ng/mL (95% CI: 3.536–3.943 ng/mL). The $EC_{50}$ of remifentanil for inhibiting the cardiovascular response to tracheal intubation during general anesthesia in the sufentanil group was 2.824 ng/mL (95% CI: 2.620–3.015 ng/mL). The $EC_{50}$ of remifentanil for inhibiting the cardiovascular response to tracheal intubation during general anesthesia in the low-dose oliceridine group was 3.045 ng/mL (95% CI: 2.852–3.239 ng/mL). The $EC_{50}$ of remifentanil for inhibiting the cardiovascular response to tracheal intubation during general anesthesia in the high-dose oliceridine group was 2.887 ng/mL (95% CI: 2.689–3.085 ng/mL). The $EC_{50}$ of remifentanil in oliceridine

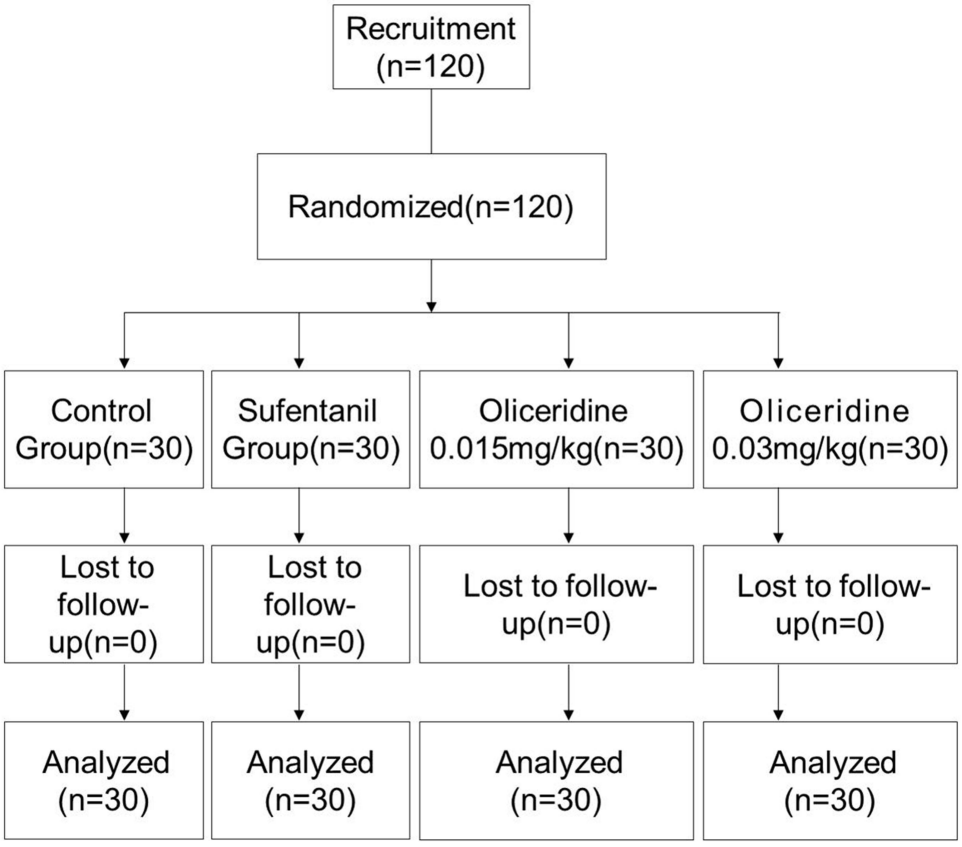


**Figure 1** The Consolidated Standards of Reporting Trials flow diagram.

**Table 1** Demographic Data

| | Control Group | Sufentani Group | Oliceridine0.015 mg/kg Group | Oliceridine 0.03 mg/kg Group | *p* value |
|---|---|---|---|---|---|
| Gender, n(%) | | | | | 0.364 |
| Male | 10(33.3) | 9(30.0) | 13(43.3) | 6(20.0) | |
| Female | 20(66.7) | 21(70.0) | 17(56.7) | 23(76.7) | |
| ASA, n(%) | | | | | 0.654 |
| I | 8(26.7) | 13(43.3) | 11(36.7) | 9(30.0) | |
| II | 22(73.3) | 17(56.7) | 19(63.3) | 21(70.0) | |
| History of motion sickness, n(%) | | | | | 0.218 |
| No | 25(83.3) | 23(76.7) | 18(60.0) | 22(73.3) | |
| Yes | 5(16.7) | 7(23.3) | 12(40.0) | 8(26.7) | |
| Age | 47.00 ± 9.93 | 45.83 ± 10.06 | 45.63 ± 10.62 | 46.73 ± 10.77 | 0.945 |
| Height | 165.03 ± 8.55 | 162.87 ± 8.81 | 167.57 ± 8.66 | 163.33 ± 7.13 | 0.124 |
| Weight | 66.97 ± 11.23 | 62.63 ± 10.38 | 67.07 ± 12.17 | 65.07 ± 8.02 | 0.327 |
| BMI | 24.47 ± 2.7 | 23.53 ± 2.81 | 23.7 ± 2.75 | 24.35 ± 2.24 | 0.438 |
| Baseline SBP, mmHg | 127.33 ± 20.45 | 133.86 ± 17.85 | 132.75 ± 16.93 | 137.41 ± 18.68 | 0.212 |
| Baseline DBP, mmHg | 78.33 ± 12.78 | 81.33 ± 7.61 | 79.76 ± 7.82 | 82.90 ± 8.84 | 0.280 |
| Baseline MBP, mmHg | 93.76 ± 16.30 | 96.83 ± 10.47 | 95.93 ± 11.20 | 98.66 ± 11.65 | 0.507 |
| Baseline HR, bpm | 74.26 ± 11.60 | 71.63 ± 9.60 | 73.96 ± 8.62 | 74.73 ± 10.51 | 0.645 |

**Notes**: Values are n (%), mean ± SD, median (IQR).
**Abbreviations**: BMI, body mass index; ASA, American Society of Anaesthesiologists.

group and sufentanil group were significantly less than that in control group ($p<0.0001$). The value of $EC_{50}$ was higher in sufentanil group than in low-dose oliceridine group ($p=0.019$). There was no significant difference in $EC_{50}$ of remifentanil between sufentanil groups and high-dose oliceridine group ($p=0.998$).

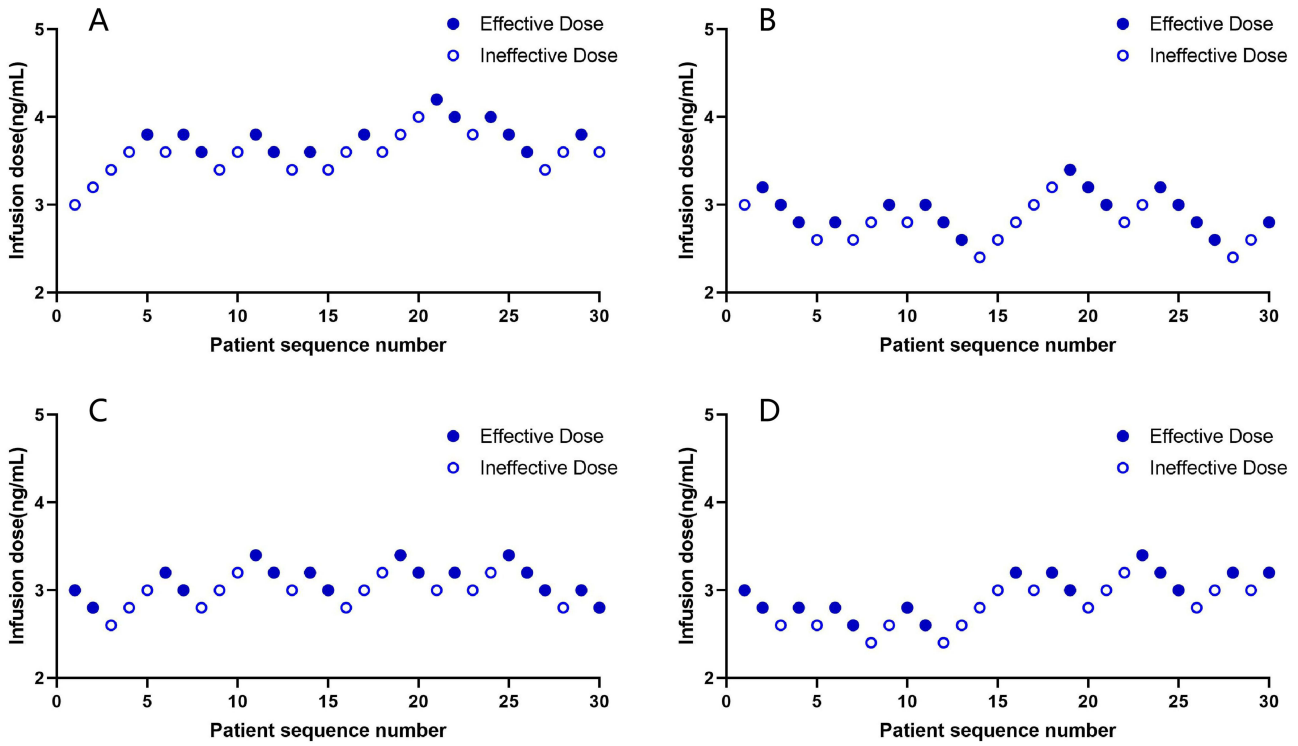


**Figure 2** The sequence number of response to remifentanil infusion in the four groups of patients. (**A**) Control Group. (**B**) Sufentanil Group. (**C**) Oliceridine 0.015 mg/kg Group. (**D**) Oliceridine 0.03 mg/kg Group.


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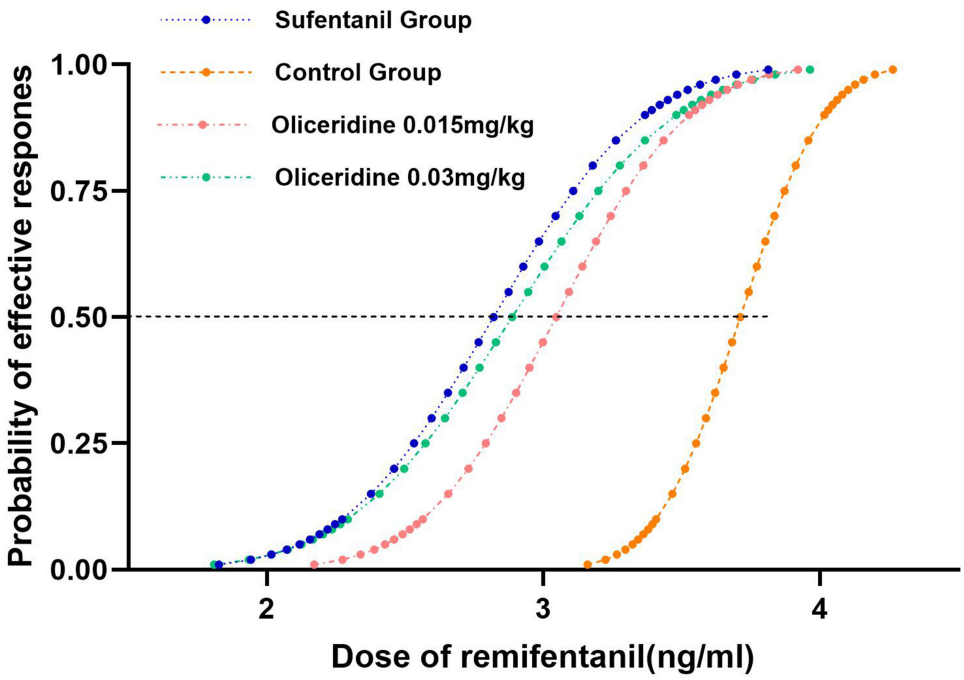


**Figure 3** Dose-effect analysis of remifentanil on probability of effective response in the four groups.

As for the secondary outcomes, the anesthesia induction time for all patients was 6.5 minutes, and none experienced intraoperative awareness. Intraoperative awareness was assessed using the modified Brice questionnaire.[14] During the period in the post-anesthesia care unit (PACU) and within 24 hours following the operation, no significant differences in the incidences of nausea, vomiting, hoarseness, sore throat, and dysphonia were observed among the four groups, as indicated in Table 2 ($p > 0.05$).

## Discussion

The present study demonstrated that the low dose (0.015 mg/kg) of oliceridine provided a weaker effect while high dose (0.03 mg/kg) of oliceridine provided a similar effect compare with 0.15 μg/kg sufentanil in sparing the effective concentration of remifentanil in inhibiting the hemodynamic responses to trachea intubation. These data may be helpful to guide the determination of the dose of oliceridine.

Oliceridine is a novel μ receptor agonist. While it activates the G-protein signaling pathway, it has a minimal effect on β-arrestin recruitment, which can significantly reduce adverse reactions mediated by the μ receptor.[15] In recent years,

**Table 2** Adverse Events in the PACU and at 24 h After Surgery

| | | Control Group | Sufentanil Group | Oliceridine 0.015 mg/kg Group | Oliceridine 0.03 mg/kg Group | *p* value |
|---|---|---|---|---|---|---|
| PACU | Nausea and vomiting n (%) | 0 (0) | 2 (6.7) | 1 (3.3) | 1 (3.3) | 0.558 |
| | Hoarseness n (%) | 3 (10.0) | 0 (0) | 3 (10.0) | 1 (3.3) | 0.251 |
| | Sore throat n (%) | 14 (46.7) | 10 (33.3) | 18 (60.0) | 12 (40.0) | 0.194 |
| | Difficulty pronouncing n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| Postoperative 24 h | Nausea and vomiting n (%) | 2 (6.7) | 3 (10.0) | 1 (3.3) | 3 (10.0) | 0.724 |
| | Hoarseness n (%) | 6 (20.0) | 3 (10.0) | 7 (23.3) | 1 (3.3) | 0.101 |
| | Sore throat n (%) | 16 (53.3) | 12 (40.0) | 16 (53.3) | 13 (43.3) | 0.636 |
| | Difficulty pronouncing n (%) | 3 (10.0) | 0 (0) | 1 (3.3) | 0 (0) | 0.102 |

**Note**: Values are n (%).
**Abbreviation**: PACU, post-anesthesia care unit.


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researches on oliceridine have progressively increased.[16] Both animal studies and international Phase III clinical trials have demonstrated that, compared to equianalgesic doses of morphine, oliceridine exhibits a lower incidence of adverse effects, such as gastrointestinal complications and respiratory depression,[1,17,18] suggesting its potential as a novel approach for surgical analgesia. Compared to morphine, patients treated with oliceridine also show a lower incidence of nausea/vomiting and dizziness,[19,20] and notably require no dose adjustment for patients with renal impairment or mild-to-moderate hepatic dysfunction.[21] A meta-analysis that included all randomized controlled trials assessing the efficacy and safety of oliceridine confirmed that, while providing analgesia comparable to morphine, oliceridine exhibits superior safety profiles.[22] Additional studies indicate that oliceridine may reduce total postoperative care costs.[23,24]

Currently, the majority of research on oliceridine concentrates on its use in managing acute pain, examining the analgesic effects of oliceridine.[20] In the mouse hot-plate test, the ratio of the $ED_{50}$ of oliceridine to that of morphine is 1:5. The analgesic potency ratio of sufentanil to morphine is 1000:1.[25] Therefore, the theoretical potency ratio of oliceridine to sufentanil is 1:200. However, there is few clinical evidence to evaluate the analgesic efficacy of oliceridine in comparison to traditional opioids. We set the sufentanil doses on the basis that 0.03 mg/kg oliceridine was estimated to be as equally efficient as 0.15 μg/kg sufentanil. In a Phase I, Single-Ascending-Dose, Open-Label Clinical Trial, when oliceridine was administered at single doses of 0.75, 1.5, or 3 mg, no serious adverse events were observed.[26] Therefore, the safe and well-tolerated dose range of oliceridine for Chinese patients with non-cancer pain is between 0.75 mg and 3.0 mg. For a patient weighing 100 kg, the maximum dose of oliceridine was 0.03 mg/kg. Therefore, we set two dose levels of oliceridine (0.015 mg/kg and 0.03 mg/kg) within the safe-dose range to investigate its analgesic effect. According to our data, the $EC_{50}$ of remifentanil in inhibiting the hemodynamic response to trachea intubation is similar in 0.03 mg/kg oliceridine group [2.887 ng/mL (95% CI: 2.689–3.085 ng/mL)] to 0.15 μg/kg sufentanil group [2.824 ng/mL (95% CI: 2.620–3.015 ng/mL)]. But the $EC_{50}$ of remifentanil in inhibiting the hemodynamic response to trachea intubation is higher in 0.015 mg/kg oliceridine group [3.045 ng/mL (95% CI: 2.852–3.239 ng/mL)] than in 0.15 μg/kg sufentanil group. Thus, the antinociceptive efficacy of 0.03 mg/kg oliceridine was similar to 0.15 μg/kg sufentanil, but that of 0.015 mg/kg oliceridine was lower. In other words, the efficacy ratio of oliceridine to sufentanil might be similar to 1:200, but lower than 1:100. These data might be useful to guide the correct dosage of oliceridine in clinical practice.

Although most of the previous studies reported fewer side effects of oliceridine than traditional μ receptor agonist, we did not observe significant differences in the side effects after surgery among the four groups, including nausea, vomiting. Other intubation-related side effects such as hoarseness, sore throat, and dysphonia were also comparable among the groups. A possible reason is that the anesthesia induction process in this study was primarily based on remifentanil, which may not fully reflect the impact of oliceridine and sufentanil on post-operative adverse effects.

Our study has some limitations that warrant attention. During the induction period, only $SpO_2$ was monitored. The intraoperative respiratory parameters and sedation depth were not fully recorded. Our baseline anesthesia relied on a continuous remifentanil infusion, whereas sufentanil or oliceridine were given as single boluses. Because remifentanil itself can induce hypotension, bradycardia, and respiratory depression, its adverse-event profile overlaps temporally with that of the study medications, potentially masking true between-group differences in safety.

## Conclusion

The effect of 0.03 mg/kg oliceridine is similar to 0.15 μg/kg sufentanil in reducing the $EC_{50}$ of remifentanil in inhibiting the cardiovascular responses induced by trachea intubation.

## Data Sharing Statement

The data that support the study findings are available from the corresponding author upon reasonable request. Requests will be jointly reviewed and fulfilled by the corresponding authors Rui Bao (Baorui_md@163.com) and Jia-feng Wang (jfwang@smmu.edu.cn).

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## Disclosure

The authors declare that they have no financial conflicts of interest to disclose.

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