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ORIGINAL ARTICLE

Oliceridine Reduces the EC50 of Remifentanil Required to Attenuate Tracheal Intubation Responses During Anesthesia Induction

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Abstract

OBJECTIVE: This study aimed to determine whether preemptive oliceridine reduces the half maximal effective concentration (EC_{50}) of remifentanil required to attenuate hemodynamic responses to tracheal intubation during propofol target-controlled infusion anesthesia.

METHOD: In this prospective randomized trial, 50 patients received either 1.5 mg intravenous oliceridine or an equivalent volume of saline (placebo) before anesthesia induction. All patients underwent induction with target-controlled infusion of propofol at an effect-site concentration of 3.0 μg/mL, in combination with remifentanil. The remifentanil concentration for each subsequent patient was determined using Dixon's up-and-down sequential allocation method, based on the preceding patient's hemodynamic response. The primary outcome was the remifentanil EC_{50} required to prevent a tracheal intubation response, defined as a ≥20% increase in heart rate or blood pressure from baseline or the presence of tearing, muscle tremor, or coughing/choking, with EC_{50} estimated using probit analysis.

RESULTS: The remifentanil EC_{50} was significantly lower in the oliceridine group (2.52 ng/mL; 95% CI: 2.19–2.80) than in the control group (3.52 ng/mL; 95% CI: 3.27–3.81), corresponding to an approximate 29% reduction in the target effect-site concentration required to blunt the intubation response. This difference was accompanied by significantly lower induction doses of both remifentanil and propofol ($p < 0.01$). Additionally, patients who received oliceridine demonstrated lower pain scores immediately after extubation ($p < 0.05$).

CONCLUSION: Preemptive oliceridine significantly reduced the remifentanil EC_{50} for suppressing tracheal intubation responses, demonstrating an opioid-sparing effect in this setting. This effect-site reduction may support hemodynamic stability and help limit remifentanil exposure during anesthesia induction.

Abbreviations:

EC_{50}	- Half-maximal effective concentration
TCI	- Target-controlled infusion
CI	- Confidence interval
TI	- Tracheal intubation
ASA	- American Society of Anesthesiologists
$ETCO_2$	- End-expiratory carbon dioxide partial pressure
BIS	- Bispectral index
MAP	- Mean arterial pressure
HR	- Heart rate
PACU	- Post-anesthesia care unit
PONV	- Postoperative nausea and vomiting
BMI	- Body mass index
NRS	- Numerical rating scale
NRS-R	- Numerical rating scale at rest

INTRODUCTION

Tracheal intubation (TI) evokes marked hemodynamic responses, including hypertension and tachycardia, driven by sympathetic nervous system activation. Opioids, including fentanyl, sufentanil, alfentanil, and remifentanil, are widely administered to attenuate these cardiovascular responses, with findings indicating a dose-dependent association between opioid concentration and suppression of hemodynamic fluctuations. Among these, remifentanil is particularly effective in blunting sympathetic activation triggered by TI and surgical stimulation. Its distinctive pharmacokinetic and pharmacodynamic characteristics, specifically rapid onset and short duration of action, render it well suited for continuous intravenous infusion (Pan *et al.* 2022). Target-controlled infusion (TCI) systems, which deliver anesthetic agents via computer-assisted dosing, have demonstrated superior efficacy compared with conventional weight-based infusions in maintaining cardiovascular stability (Yeganeh *et al.* 2010). Substantial evidence indicates that remifentanil facilitates optimal intubation conditions during general anesthesia induction by rapidly achieving steady plasma concentrations and minimizing cardiovascular reactivity. Compared with sufentanil, remifentanil has been associated with a lower incidence of post-intubation hypotension. However, higher remifentanil doses may increase the likelihood of bradycardia after induction and contribute to postoperative hyperalgesia, effects that have been linked to β-arrestin–mediated signaling (Shin *et al.* 2010; Colvin *et al.* 2019). Propofol also exhibits a synergistic relationship with remifentanil, decreasing the required remifentanil concentration to suppress responses to laryngoscopy, tracheal intubation, and intra-abdominal stimulation. Consequently, the combination of propofol and remifentanil is commonly adopted as a TCI regimen for anesthesia induction (Mertens *et al.* 2003).

Oliceridine, a novel G protein–biased μ-opioid receptor agonist, demonstrates a rapid onset, sustained activity, and approximately twice the potency of morphine, while being associated with a reduced incidence of opioid-related adverse events such as nausea and respiratory depression (Daksla *et al.* 2023). Its mechanism involves selective engagement of G protein signaling while minimizing the recruitment of β-arrestin proteins. This not only underlies its favorable side-effect profile but may also reduce the potential for opioid-induced hyperalgesia. Clinical studies have shown that oliceridine exhibits a favorable safety and tolerability profile in the management of acute moderate-to-severe pain, with fewer gastrointestinal and respiratory side effects (Jin *et al.* 2022; Duan *et al.* 2025). Furthermore, a recent randomized controlled trial demonstrated that oliceridine provides an opioid-sparing effect when used in combination with other opioids, reducing the required dose of concomitant analgesics (Tian *et al.* 2025). Notably, recent investigations have further defined its effective dose (ED_{50}) for attenuating hemodynamic responses to specific procedural stimuli, such as gastroscopy insertion and laryngeal mask airway placement during anesthesia induction (Yang *et al.* 2025).

Most clinical studies of oliceridine have focused on postoperative analgesia, with limited data on its intraoperative use to blunt intense noxious stimuli such as tracheal intubation. To our knowledge, no trial has quantified the effect of preemptive oliceridine on the remifentanil EC_{50} required to suppress intubation induced hemodynamic responses under propofol target controlled infusion. Given its G protein–biased μ receptor agonism and favorable safety profile, we hypothesized that preemptive oliceridine would attenuate TI induced cardiovascular stress while reducing the remifentanil concentration needed during induction.

METHODS

Ethical approval and participants

This study was approved by the institutional ethics committee (reference number: 2024CDFSFLYYEC-056). Written informed consent was obtained from all participants before enrollment. Eligible participants were ASA physical status I or II, aged 18–70 years, and scheduled for elective surgery under general anesthesia with tracheal intubation and an anticipated duration of 1–2 hours (e.g., short duration laparoscopic or brief otorhinolaryngologic procedures). The distribution of surgical types was similar between groups.

Exclusion criteria included: (i) known allergy to the investigational drug; (ii) contraindications to general anesthesia; (iii) history of clinically significant cardiac, pulmonary, or renal disease; (iv) anticipated difficult airway, defined as Mallampati class III or IV, or any condition potentially complicating laryngoscopy and intubation, such as cervical spine abnormalities, dental malformations, micrognathia, limited mouth opening (< 3 finger-widths), diagnosed sleep apnea syndrome, habitual snoring, active upper respiratory tract infection, subglottic stenosis, enlarged thyroid or tonsils,

mediastinal mass, or pharyngeal tumor; (v) recent surgical procedures or participation in another investigational drug trial within the preceding week; and (vi) communication impairments, including dyslexia, dysgraphia, dyspraxia, or visual and hearing deficits; (vii) patients receiving chronic opioid therapy or medications known to markedly alter hemodynamic responses (e.g., long-term β-blockers). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The trial was prospectively registered with the Chinese Clinical Trial Registry (ChiCTR2400091591).

Randomization and allocation concealment

Participants were randomly allocated using a computer generated sequence to receive either 1.5 mg intravenous oliceridine before anesthesia induction (Group O) or an equal volume of saline (Group C). Both participants and attending clinical staff were blinded to group assignments.

To maintain allocation concealment, an independent research nurse not involved in the study prepared the study medications. Both Oliceridine and saline solutions were identical in volume and appearance. Hemodynamic responses to tracheal intubation were evaluated by an investigator who was blinded to group allocation. The anesthesiologist performing the intubation and all patients remained unaware of treatment assignments throughout the study.

Study procedures

Participants fasted for at least 6 hours before surgery and did not receive any premedication. Upon arrival in the operating room, an 18-gauge intravenous cannula was inserted into a forearm vein. Standard intraoperative monitoring included noninvasive and invasive arterial blood pressure, heart rate (lead II), pulse oximetry, electrocardiography, body temperature, end expiratory carbon dioxide ($ETCO_2$), and bispectral index (BIS) (N15 Anesthesia Monitor, Mindray, China).

Following preoxygenation with a tight-fitting face mask, participants received either 1.5 mg oliceridine (diluted to 5 mL with normal saline) or 5 mL of saline intravenously. Five minutes later, anesthesia induction was initiated with propofol (AstraZeneca Investment [China] Co., Ltd.) and remifentanil (AC4070221, Yichang Humanwell Pharmaceutical Co., Ltd.) administered via a TCI system (Beijing Oriental Chengyitong Technology Co., Ltd.). Propofol was administered using the Marsh pharmacokinetic model at a target effect-site concentration of 3.0 μg/mL to maintain a BIS value between 40 and 50. Simultaneously, remifentanil infusion was initiated using the Minto model at a predetermined target concentration as described below (Minto *et al.* 1997).

After loss of consciousness, manual ventilation was supported, and 0.6 mg/kg rocuronium was administered intravenously to facilitate tracheal intubation. Intubation was performed 90 seconds after rocuronium administration using video laryngoscopy, and each intubation was required to be completed within 30 seconds by the same experienced anesthesiologist. All airway devices, including endotracheal tubes and video laryngoscopes, were obtained from the same manufacturer. Female participants received a 7.0-mm reinforced endotracheal tube, and male participants received a 7.5-mm tube.

Participants were excluded if MAP decreased to a level requiring vasoactive intervention (systolic blood pressure < 80 mmHg) or if heart rate (HR) fell below 50 beats per minute, necessitating atropine administration. In such cases, the same remifentanil concentration was applied to the next patient. Anesthesia was maintained with propofol, remifentanil, and sevoflurane. The remifentanil infusion rate in both groups was titrated according to changes in MAP and HR, with a recommended range of 0.1 to 0.3 μg/kg/min. The infusion rate was increased by 0.1 μg/kg/min if MAP or HR increased by 10% or more from baseline and decreased by the same increment if MAP or HR decreased by 10% or more. Sevoflurane administration was discontinued 30 minutes before the end of surgery, and propofol and remifentanil infusions were adjusted accordingly. Propofol was discontinued 10 minutes before the end of surgery, and remifentanil was discontinued immediately after the procedure. Following surgery, patients were transferred to the Post-Anesthesia Care Unit (PACU). After the monitoring equipment was established and spontaneous breathing had resumed, all patients received neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg) for antagonism of residual neuromuscular blockade. Tracheal extubation was performed once the patients regained consciousness and resumed spontaneous breathing. Postoperative rescue analgesia consisted of 50 mg intravenous tramadol for patients reporting severe pain (verbal rating score 4–10) or exhibiting signs of discomfort, such as agitation, grimacing, or groaning.

Dixon's up-and-down method and sample size

The target propofol concentration was selected based on standard clinical practice, with an effect-site concentration maintained at 3.0 μg/mL. For each patient, the remifentanil effect site concentration was determined using Dixon's up and down sequential allocation method, based on the hemodynamic response of the preceding patient (Dixon, 1991). The initial remifentanil concentration was set at 3.0 ng/mL, corresponding to the reported EC_{50} of 3.57 ng/mL for tracheal intubation under propofol TCI at 3.0 μg/mL (Ziqiang *et al.* 2024). When a positive hemodynamic response was observed in the preceding patient, the remifentanil concentration was increased by 0.3 ng/mL for the next patient. Conversely, if the response was negative, the concentration was decreased by the same increment.

The response to tracheal intubation was classified as either positive or negative. A positive response was defined as any of the following occurring within 3 minutes of intubation: a ≥20% increase in HR or MAP relative to the baseline mean, or the presence of tearing, muscle tremor, or coughing/choking during intubation. This predefined composite endpoint, incorporating both objective hemodynamic criteria and standardized clinical signs of nociceptive stimulation, was selected to reflect routine practice while ensuring reproducible assessment across patients. A negative response indicated the absence of these signs and smooth completion of intubation. Assessment of the tracheal intubation response integrated objective hemodynamic parameters with subjective clinical signs. All intubation procedures were performed by a fixed senior anesthesiologist, and the determination of positive subjective signs (tearing, muscle tremor, coughing/choking) was preceded by unified training and calibration. For all patients, endpoint assessment was independently performed by two observers blinded to group allocation. In case of disagreement, a third researcher was consulted for arbitration, and the consensus classification was used in the analysis. This procedure was implemented to reduce inter-observer variability when applying the composite endpoint.

Recruitment continued until seven crossover points (transitions between positive and negative responses) were obtained, which is considered sufficient for stable EC_{50} estimation in Dixon designs. Although the sample size in Dixon's method is primarily determined by this stopping rule, the total number of patients required to reach this endpoint typically ranges between 20 and 40 in anesthetic studies, which is considered sufficient to provide a stable estimate of the target dose in most realistic scenarios (Pace & Stylianou, 2007).

Data collection

To comprehensively evaluate the intervention and perioperative responses, data collection encompassed multiple domains: hemodynamic parameters recorded at eight predefined time points (T1 before induction to T8 after extubation); baseline patient characteristics, including demographics, American Society of Anesthesiologists physical status, and surgical type; anesthesia-related details such as dosages of induction and maintenance agents (propofol, remifentanil, sevoflurane), durations of anesthesia induction and maintenance, time to tracheal extubation (from discontinuation of anesthetics), and consumption of rescue vasoactive drugs; the response to tracheal intubation for each patient, classified as positive or negative according to the criteria defined in Section 2.4; and postoperative recovery data collected in the Post-Anesthesia Care Unit and up to 24 hours postoperatively, including pain assessed using a verbal rating scale at specified intervals, the number of patients requiring rescue analgesia and the incidence of adverse events.

Statistical analyses

All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data are expressed as mean ± standard deviation ($x \pm S$) and compared using independent-sample t-tests; non-normally distributed continuous data are expressed as median [interquartile range] and compared using non-parametric tests (Mann-Whitney U test). Categorical variables are presented as counts (n, %) and analyzed using Fisher's exact test. The EC_{50} and EC_{95} values, along with their 95% confidence intervals, were estimated using probit regression analysis. Differences in the dose-response relationship between groups were assessed by testing the significance of the 'group' effect in a pooled probit regression model. A two-tailed p-value < 0.05 was considered statistically significant; secondary hemodynamic and postoperative outcomes were treated as exploratory without adjustment for multiple comparisons.

Tab. 1. Preoperative baseline characteristics of patients in Group O and Group C

	Group O	Group C	*p* value
Sex(male/female)	8/14	9/19	0.773†
Ages(years)	45.05±9.65	45.11±11.46	0.984*
Height (cm)	161.5(157.00,165.50)	158(155.00,165.75)	0.209#
Weight(kg)	61.54±9.16	61.58±9.27	0.989*
BMI(kg/m^2)	23.30±2.81	23.85±2.77	0.494*
Types of surgery			
Laparoscopic Surgery	16	15	0.242†
Otorhinolaryngology	6	13	

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage), as appropriate. Abbreviation: BMI, body mass index. Statistical tests: † Fisher's exact test; * independent sample t test; # Mann–Whitney U test.

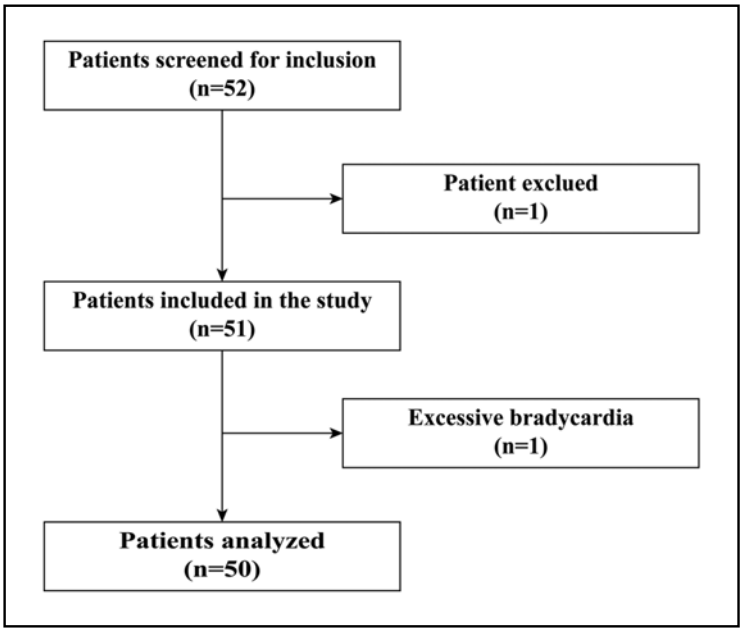

Fig. 1. Flowchart of participant enrollment, allocation, follow up, and analysis.

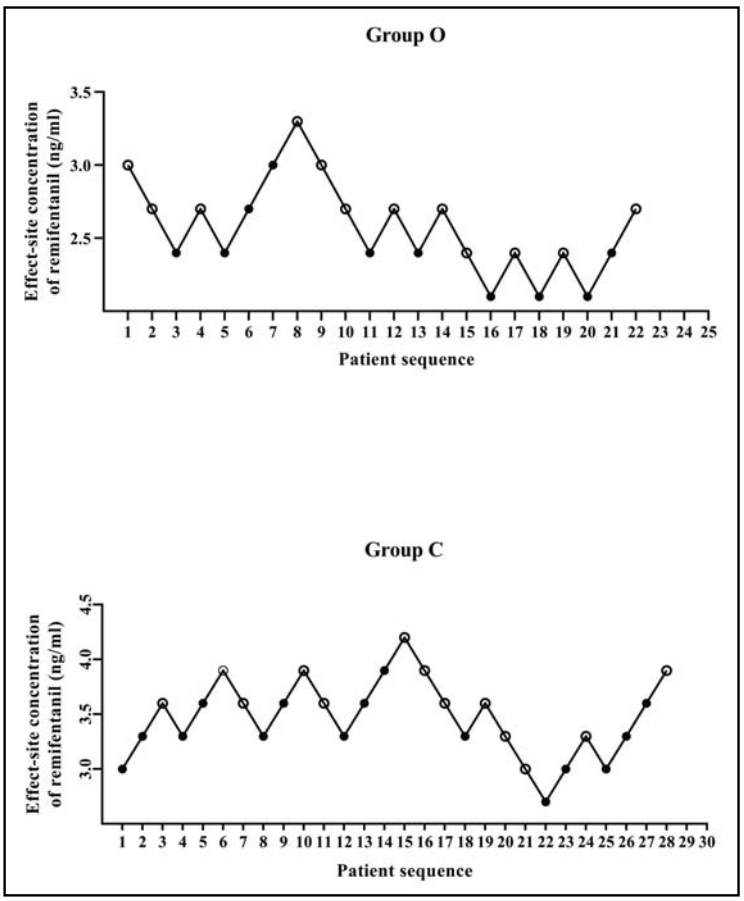

Fig. 2. Individual responses to tracheal intubation assessed using Dixon's up and down sequential method. Each point represents one patient in chronological order. Open circles indicate positive responses (increase in heart rate or blood pressure ≥ 20% from baseline or clinical signs), prompting an increase in the remifentanil effect site concentration for the subsequent patient; filled circles indicate negative responses, prompting a decrease in concentration.

RESULTS

Basic information

Based on Dixon's sequential design criteria, enrollment concluded after seven crossover points between negative and positive responses had been obtained. A total of 52 patients were screened, and all met the inclusion criteria. One patient was excluded due to the development of hypertension after admission, and another was excluded following the onset of bradycardia after intubation, for which atropine was administered. The remaining 50 patients completed the trial in accordance with the study protocol and were included in the final analysis. Among these, 28 patients were allocated to Group C and 22 to Group O. The participant flow is illustrated in Figure 1. No statistically significant differences were observed in the baseline characteristics of patients between the two groups ($p > 0.05$) (Table 1).

EC_{50} and EC_{95} of remifentanil

Figure 2 presents individual response data for endotracheal intubation obtained using the up-and-down sequential method. In Group C, the remifentanil EC_{50} and EC_{95} under propofol TCI at 3.0 μg/mL were 3.52 ng/mL (95% CI: 3.27–3.81) and 4.23 ng/mL (95% CI: 3.90–5.33), respectively, whereas in Group O they were 2.52 ng/mL (95% CI: 2.19–2.80) and 3.22 ng/mL (95% CI: 2.90–4.24). This corresponds to an approximate 29% reduction in EC_{50} (from 3.52 to 2.52 ng/mL) and 24% reduction in EC_{95} (from 4.23 to 3.22 ng/mL). A pooled probit regression analysis was performed to test the difference between groups, with the tracheal intubation response as the dependent variable and remifentanil concentration and group assignment as covariates. This analysis revealed a statistically significant effect of group, indicating that the dose–response curve for Group O was shifted to the left compared with Group C (B = -4.02, p =0.004). These findings show that preemptive administration of oliceridine reduced the remifentanil EC_{50} required to blunt the hemodynamic response to tracheal intubation in this patient population. Figure 3 presents the dose–response relationship between remifentanil concentration and the probability of suppressing the intubation response.

Comparison of intraoperative and postoperative outcomes between groups

Hemodynamic responses at eight predefined time points are presented in Figure 4. Heart

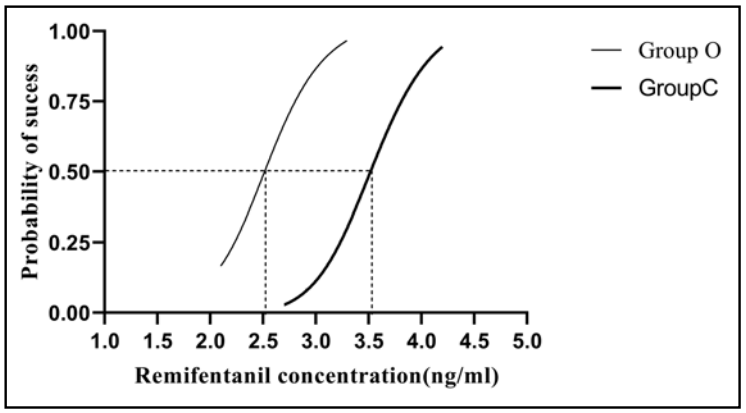

Fig. 3. Dose–response relationship of remifentanil for suppressing cardiovascular responses to tracheal intubation. Curves are fitted using probit regression and show a leftward shift for Group O compared with Group C, with estimated EC_{50} values of 2.52 ng/mL in Group O and 3.52 ng/mL in Group C.

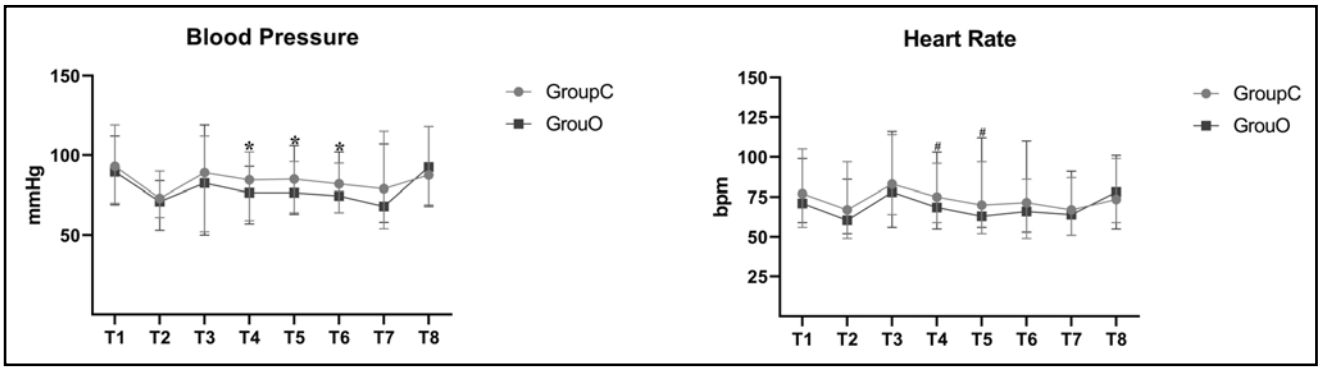

Fig. 4. Mean arterial pressure (MAP) and heart rate (HR) at eight time points in Group O and Group C (T1: before induction; T2: after induction before intubation; T3: immediately after intubation; T4: 1 min after intubation; T5: 5 min after intubation; T6: at surgical incision; T7: at the end of surgery; T8: after extubation). HR was lower in Group O than in Group C at T4 and T5, and MAP was lower in Group O at T4, T5, and T6; no significant between group differences were observed at the other time points (T1–T3, T7, T8).

rate (HR) in Group O was significantly lower than in Group C at T4 (1 min after intubation) and T5 (5 min after intubation) (p = 0.034 and 0.033, respectively). Mean arterial pressure (MAP) in Group O was also lower at T4, T5, and T6 (surgical incision) (p = 0.019, 0.012, and 0.005, respectively), while no significant between-group differences in MAP or HR were observed at the other time points (T1, T2, T3, T7, T8; $p > 0.05$).

During anesthesia induction, the required doses of propofol and remifentanil in Group O were significantly lower than those in Group C ($p < 0.05$), and the induction time was also significantly shorter ($p < 0.05$). No significant differences were observed between the two groups in the induction dose of rocuronium bromide, the duration of intraoperative anesthesia maintenance, or the maintenance doses of propofol, remifentanil, and sevoflurane ($p > 0.05$) (Table 2).

Similarly, no statistically significant differences were identified between the two groups in anesthesia recovery time, resting pain scores on postoperative day 1, or the number of patients requiring rescue analgesia ($p > 0.05$) (Table 3). However, pain scores recorded immediately after extubation were significantly lower in Group O than in Group C ($p < 0.05$). The most frequent adverse event was postoperative nausea and vomiting, whereas other complications—including hypotension, bradycardia, cough, chest wall rigidity, and postoperative delirium—were not observed in any patient.

DISCUSSION

This prospective, randomized, double-blind, sequential allocation study examined the effect of preemptive oliceridine on the dose–response relationship of remifentanil during propofol-based TCI anesthesia induction. The principal finding was that intravenous 1.5 mg oliceridine significantly reduced the remifentanil EC_{50} and EC_{95} required to attenuate hemodynamic responses to tracheal intubation. These results are consistent with a synergistic interaction between oliceridine and remifentanil in modulating nociceptive transmission, allowing a reduction in remifentanil dose while maintaining similar anesthetic depth and cardiovascular stability.

The 1.5 mg dose of oliceridine was selected based on both clinical relevance and safety considerations. This dosage corresponds to the recommended single intravenous bolus for acute pain management, providing an appropriate analgesic baseline (Trevena Inc., 2020). Preliminary observations also revealed a trend toward reduced heart rate at higher doses, while the prescribing information advises against doses exceeding 3 mg due to the potential risk

Tab. 2. Intraoperative parameters, including induction and maintenance doses of anesthetic agents, by study group

	Group O	Group C	*p* value
Induction time (min)	7.57(6.56,8.77)	9.84(9.08,10.13)	<0.001*
Maintenance duration (min)	84.88(64.69, 121.78)	68.50(55.00, 83.75)	0.089#
Induction remifentanil dose (μg)	86.49±18.06	111.74±12.46	<0.001*
Induction propofol dose (mg)	114.70(93.50,140.25)	137.25(128.35,156.34)	<0.001*
Induction rocuronium dose (mg)	36.60(32.10,41.55)	36.60(32.10,40.60)	0.860*
Maintenance remifentanil dose (μg)	446(397.58, 911.75)	463 (319.57, 669.10)	0.452*
Maintenance propofol dose (mg)	283.50(171.00, 478.25)	213.85(169.88, 263.40)	0.226*
Maintenance sevoflurane consumption (mL)	16.00(11.13, 25.93)	13.10(10.25,16.75)	0.117*

Data are presented as mean ± standard deviation or median (interquartile range). Induction time and maintenance duration are in minutes. Remifentanil and propofol doses are in μg and mg, respectively; sevoflurane consumption is in mL. Statistical tests: * Mann–Whitney U test; # independent sample t testbody mass index. Statistical tests: † Fisher's exact test; * independent sample t test; # Mann–Whitney U test.

Tab. 3. Postoperative recovery and analgesia outcomes by study group.

	Group O	Group C	*p* value
Emergence time (min)	10.64±4.78	9.21±2.33	0.187*
Pain score at extubation (NRS)	1(0,2)	2.5(2,4)	<0.001*
Pain score at 24h postop (NRS-R)	1(0,2)	1(0,2)	0.727*
Patients Requiring Rescue Analgesia in PACU, n (%)	4(18.1%)	13(46.4%)	0.070 #
Incidence of PONV, n (%)	1(4.5%)	4(14.2%)	0.368 #

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). NRS, numerical rating scale; NRS R, numerical rating scale at rest; PACU, post anesthesia care unit. Statistical tests: * Mann–Whitney U test; # Fisher's exact test

of QTc interval prolongation. Accordingly, 1.5 mg was determined to be an optimal dose to explore the synergistic effect with remifentanil while maintaining a well-established safety margin and minimizing the risk of hemodynamic instability or other dose-related adverse outcomes.

Tracheal intubation is one of the most intense nociceptive stimuli during anesthesia induction. It frequently triggers sympathetic activation and substantial hemodynamic fluctuations, which can endanger patients with underlying cardiovascular disease (Teong *et al.* 2020). Remifentanil, an ultra-short-acting μ-opioid receptor agonist, is commonly used to suppress this response due to its rapid onset, predictable pharmacokinetics, and context-insensitive half-life (Grillot *et al.* 2023). However, like other traditional opioids, remifentanil is associated with dose-dependent adverse effects, including respiratory depression, bradycardia, and reduced gastrointestinal motility, primarily mediated by β-arrestin pathway activation (Furuichi *et al.* 2016; Schüttler *et al.* 1997). Therefore, identifying adjunctive strategies that can reduce the required remifentanil dose without compromising analgesic efficacy is clinically valuable.

Oliceridine, a novel G protein–biased μ-opioid receptor agonist, preferentially activates G protein signaling while limiting β-arrestin recruitment. This mechanism provides potent analgesia while minimizing typical opioid-related adverse effects (Markham, 2020; Biskupiak *et al.* 2024). In the present study, preemptive oliceridine administration lowered the remifentanil EC_{50} from 3.52 ng/mL in the control group to 2.52 ng/mL, indicating a marked synergistic interaction. This effect likely reflects multiple mechanisms. First, both agents target the μ-opioid receptor but differ in their signaling bias—remifentanil acting as a full agonist and oliceridine as a biased agonist—resulting in enhanced suppression of ascending nociceptive transmission during intubation (Shah *et al.* 2021; Liang *et al.* 2019). Critically, this difference in signaling bias means that, compared to remifentanil, oliceridine can provide comparable analgesia while minimizing adverse effects mediated by the β-arrestin pathway, such as respiratory depression and gastrointestinal dysfunction (Daksla *et al.* 2023; Markham, 2020; Biskupiak *et al.* 2024). Second, oliceridine provides an independent analgesic baseline, reducing remifentanil requirements, consistent with prior findings for other adjunctive agents such as esketamine (Tian *et al.* 2025; Ziqiang *et al.* 2024; Chen *et al.* 2025).

This synergistic reduction in remifentanil requirement is clinically reflected in our findings of enhanced hemodynamic stability during the early post-intubation period (T4-T6) and superior immediate

post-extubation analgesia in the oliceridine group. To our knowledge, this is the first study to quantify the effect of preemptive oliceridine on the remifentanil EC_{50} required to blunt tracheal intubation–induced hemodynamic responses under propofol target controlled infusion. While other unmeasured intraoperative factors may have contributed to individual hemodynamic variability, the randomized, double-blind, controlled design ensured that such factors were likely balanced between the oliceridine and control groups. Therefore, the observed between-group difference in EC_{50} is more plausibly attributed to the study intervention rather than to background confounding.

The methodological reliability of this investigation was supported by Dixon's sequential up-and-down design, which efficiently estimates EC_{50} values, particularly for intravenous anesthetic agents with rapid onset and short duration (Tan *et al.* 2022). A concentration step size of 0.3 ng/mL was employed, and enrollment concluded after six crossover points, fulfilling the statistical prerequisites for stable EC estimation (Liang *et al.* 2019). Furthermore, standardizing the propofol effect-site concentration at 3.0 μg/mL and performing intubation only after the BIS reached 40–50 minimized potential confounding related to anesthetic depth or operator variability.

No severe adverse events such as hypotension, bradycardia, or chest wall rigidity were observed in the 50 study participants. This favorable safety profile likely results from two factors. First, oliceridine's G protein–biased agonism inherently produces less respiratory and circulatory depression than traditional opioids (Ziqiang *et al.* 2024; Furuichi *et al.* 2016). Second, the observed reduction in remifentanil dosage likely contributed to fewer dose-dependent adverse effects. Together, these findings indicate that the combined use of oliceridine and remifentanil offers an opioid-sparing approach that preserves hemodynamic stability while potentially mitigating postoperative respiratory or circulatory complications. This opioid-sparing property is a clinically relevant finding that warrants further evaluation in larger studies.

Several limitations should be noted. First, the composite primary endpoint, which included subjective clinical signs, may have introduced inter observer variability and increased the statistical uncertainty of EC estimates, although the randomized design makes systematic bias unlikely. Second, beyond the standardized protocol, other incompletely controlled clinical factors (e.g., sevoflurane, neuromuscular blockade) could influence individual responses; however, under the randomized, double-blind design, these were likely balanced between groups and do not challenge the core attribution of the observed EC_{50} reduction to oliceridine. Third, the study was conducted at a single center and included only ASA I–II patients undergoing specific procedures. Additionally, only a single dose of oliceridine (1.5 mg) was evaluated, precluding assessment of dose–response relationships. These factors limit direct generalizability to broader surgical populations, higher risk patients, or different dosing regimens. The present results therefore apply primarily to ASA I–II adults undergoing elective surgery with standardized propofol and remifentanil TCI protocols at our center. Larger, multicenter trials evaluating multiple oliceridine dosing regimens are needed to confirm these findings and to define optimal strategies in more diverse patient groups.

CONCLUSION

Preemptive intravenous administration of 1.5 mg oliceridine during propofol TCI induction significantly reduced the EC_{50} and EC_{95} of remifentanil required to attenuate the cardiovascular response to tracheal intubation. These findings indicate a synergistic analgesic interaction between oliceridine and remifentanil. The observed opioid-sparing effect of oliceridine may offer a clinically valuable strategy to minimize remifentanil-related adverse effects while preserving hemodynamic stability during anesthesia induction. This approach may be particularly relevant for patients in whom limiting remifentanil exposure is desirable because of concern for respiratory depression or hemodynamic fluctuations. Further investigation in larger-scale studies is warranted to confirm and expand upon these clinical benefits.

DECLARATIONS

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Chongqing University Fuling Hospital (reference number: 2024CDFSFLYYEC-056). Written informed consent was obtained from all participants before enrollment.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Authors' contributions

Conception and design of the research: Ke-yu He, Zong-qiong Lu, Peng Cheng, Wei Wang

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Analysis and interpretation of the data: Zong-qiong Lu, Wei Wang, Ke-yu He
Statistical analysis: Zong-qiong Lu, Peng Cheng
Obtaining financing: Ke-yu He
Writing of the manuscript: Zong-qiong Lu
Critical revision of the manuscript for intellectual content: Ke-yu He
All authors read and approved the final draft.

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Trial registration

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REFERENCES

1 Biskupiak J, Oderda G, Brixner D, Wandstrat TL. (2024). Gastrointestinal adverse effects associated with the use of intravenous oliceridine compared with intravenous hydromorphone or fentanyl in acute pain management: An adjusted indirect treatment comparison. J Comp Eff Res. **13**(5): e230041. doi: 10.2217/cer-2023-0041.
2 Chen S, Lin L, Zhou Q, Lin L. (2025). Effect of esketamine on the EC50 of remifentanil for suppression of choking cough during extubation. iScience. **28**(5): 112392. doi: 10.1016/j.isci.2025.112392.
3 Colvin LA, Bull F, Hales TG. (2019). Perioperative opioid analgesia – when is enough too much? A review of opioid-induced tolerance and hyperalgesia. Lancet. **393**(10180): 1558–1568. doi: 10.1016/S0140-6736(19)30430-1.
4 Daksla N, Wang A, Jin Z, Gupta A, Bergese SD. (2023). Oliceridine for the management of moderate to severe acute postoperative pain: A narrative review. Drug Des Devel Ther. **17**: 875–886. doi: 10.2147/DDDT.S401622.
5 Dixon WJ. (1991). Staircase bioassay: The up-and-down method. Neurosci Biobehav Rev. **15**(1): 47–50. doi: 10.1016/S0149-7634(05)80090-9.
6 Duan J, Wang X, Hou C, Yu T, Ju X, Wang S. (2025). Comparison of oliceridine and morphine in postoperative analgesia in laparoscopic total hysterectomy: A randomized double-blind controlled trial. Drug Des Devel Ther. **19**: 6687–6697. doi: 10.2147/DDDT.S530296.
7 Furuichi Y, Hamada A, Nakazato K, Kobayashi K, Sakamoto A. (2016). Severe respiratory depression and bradycardia before induction of anesthesia and onset of takotsubo cardiomyopathy after cardiopulmonary resuscitation. J Clin Anesth. **35**: 275–277. doi: 10.1016/j.jclinane.2016.08.011.
8 Grillot N, Lebuffe G, Huet O, Trillot N, Duhamel A, Tavernier B. (2023). Effect of remifentanil vs neuromuscular blockers during rapid sequence intubation on successful intubation without major complications among patients at risk of aspiration: A randomized clinical trial. JAMA. **329**(1): 28–38. doi: 10.1001/jama.2022.23646.
9 Jin Z, Zhu M, Gupta A, Page C, Gan TJ, Bergese SD. (2022). Evaluating oliceridine as a treatment option for moderate to severe acute post-operative pain in adults. Expert Opin Pharmacother. **23**(1): 9–17. doi: 10.1080/14656566.2021.1998241.
10 Liang DY, Li WW, Nwaneshiudu C, Irvine KA, Clark JD. (2019). Pharmacological characteristics of oliceridine, a μ opioid receptor G protein-biased ligand, in mice. Anesth Analg. **129**(5): 1414–1421. doi: 10.1213/ANE.0000000000004160.
11 Markham A. (2020). Oliceridine: First approval. Drugs. **80**(16): 1739–1744. doi: 10.1007/s40265-020-01396-1.
12 Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J. (2003). Propofol reduces perioperative remifentanil requirements in a synergistic manner: Response surface modeling of perioperative remifentanil–propofol interactions. Anesthesiology. **99**(2): 347–359. doi: 10.1097/00000542-200308000-00016.
13 Minto CF, Schnider TW, Egan TD, Youngs EJ, Shafer SL, Kaplan E. (1997). Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology. **86**(1): 10–23. doi: 10.1097/00000542-199701000-00006.
14 Oliceridine (TRUVELTRA) full prescribing information. (2020). Trevena Inc. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210730s000lbl.pdf. PMID: 33355533.
15 Pace NL, Stylianou MP. (2007). Advances in and limitations of up-and-down methodology: A précis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology. **107**(1): 144–152. doi: 10.1097/01.anes.0000270740.25281.51.
16 Pan T, Lei Y, Lei Z, Lei Z, Fang Y, Xu R, et al. (2022). Clinical study on anesthesia with remifentanil and propofol in patients with high hemodynamics. Altern Ther Health Med. **28**(4): 44–49. PMID: 35452420.
17 Schüttler J, Albrecht S, Breivik H, Osnes S, Prys-Roberts C, Holder K, et al. (1997). A comparison of remifentanil and alfentanil in patients undergoing major abdominal surgery. Anaesthesia. **52**(4): 307–317. doi: 10.1111/j.1365-2044.1997.071-az.x.
18 Shah A, Shah R, Fahim G, Brust-Sisti LA. (2021). A dive into oliceridine and its novel mechanism of action. Cureus. **13**(10): e19076. doi: 10.7759/cureus.19076.
19 Shin SW, Cho AR, Lee HJ, Choi DH, Kim MH, Lee JJ, et al. (2010). Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. Br J Anaesth. **105**(5): 661–667. doi: 10.1093/bja/aeq222.
20 Tan M, Zhang C, Zeng W, Chen M, Huang Z, Huang D. (2022). Determining the effective dose of esketamine for mitigating pain during propofol injection by Dixon's up-and-down method: A double-blind, prospective clinical study of drug dose response. BMC Anesthesiol. **22**(1): 368. doi: 10.1186/s12871-022-01906-5.
21 Teong CY, Huang CC, Sun FJ. (2020). The haemodynamic response to endotracheal intubation at different times of fentanyl administration during induction: A randomised controlled trial. Sci Rep. **10**(1): 8829. doi: 10.1038/s41598-020-65754-2.
22 Tian Y, Hu J, Pan H, Bai G, Zhang Z, Zhang P. (2025). Effect of oliceridine combined with sufentanil on patient-controlled intravenous analgesia in elderly patients after laparoscopic radical resection of rectal cancer: A prospective randomized controlled study. Drug Des Devel Ther. **19**: 10033–10043. doi: pending.
23 Xu F, Cui Y, Wang Z, Liu R, Tang J, Xu Y, et al. (2025). Determination of the 90% effective dose of oliceridine combined with etomidate for inhibiting laryngeal mask airway insertion responses in patients of different ages: A biased-coin sequential allocation dose-finding trial. Drug Des Devel Ther. **19**: 10259–10268. doi: pending.
24 Yang W, Zhou R, Zhou X, Chen X, Zhou D, Zhang X. (2025). Effective dose of oliceridine fumarate co-administered with remimazolam in suppressing gastroscope insertion responses in adults. Drug Des Devel Ther. **19**: 5033–5041. doi: pending.
25 Yeganeh N, Roshani B, Yari M, Almasi A. (2010). Target-controlled infusion anesthesia with propofol and remifentanil compared with manually controlled infusion anesthesia in mastoidectomy surgeries. Middle East J Anaesthesiol. **20**(6): 785–793. PMID: 21526662.
26 Ziqiang F, Keyu H, Yun X, Li L, Yiping B. (2024). Effect of esketamine on the EC50 of remifentanil for blunting cardiovascular responses to endotracheal intubation in female patients under general anesthesia: A sequential allocation dose-finding study. BMC Anesthesiol. **24**(1): 67. doi: 10.1186/s12871-024-021xx-y.