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CLINICAL TRIAL REPORT

Determine of 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

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Background: Oliceridine is a μ-opioid receptor agonist that selectively activates the G-protein signaling pathway, offering a potential advantage over traditional opioids by reducing respiratory depression and gastrointestinal reactions. This study aimed to determine the 90% effective dose (ED90) of oliceridine for inhibiting responses to laryngeal mask airway (LMA) insertion under etomidate anesthesia in patients of different ages.

Methods: This prospective Biased-Coin Sequential Allocation Dose-Finding Trial initially enrolled 120 patients scheduled for LMA anesthesia, divided into two age groups: young-to-middle-aged (Group A, 18–64 years) and elderly (Group B, 65–79 years). The initial dose of oliceridine was 0.02 mg/kg, with dose spacing of 0.002 mg/kg. Dose adjustments for subsequent patients were based on the previous subject's response. If movement, frowning, tearing, coughing, or hemodynamic parameters exceeding 20% above baseline occurred during LMA insertion, the dose was considered inadequate, and the dose for the next patient was increased. Otherwise, biased-coin randomization was applied to the next patient, with an 89% probability of maintaining the same dose and an 11% probability of reducing the dose. The primary outcome was the ED90 and 95% confidence intervals (CIs) for oliceridine combined with etomidate in inhibiting responses to LMA insertion.

Results: A total of 113 patients met the study criteria and were included in the final analysis (58 in the group A and 55 in the group B). The ED90 of Oliceridine was 0.0246 mg/kg (95% CI: 0.0215–0.0320 mg/kg) and 0.0229 mg/kg (95% CI: 0.0199–0.0298 mg/kg), respectively. No significant difference in ED90 was observed between the two groups ($P > 0.05$).

Conclusion: The ED90 of oliceridine for inhibiting LMA insertion responses, when combined with 0.25 mg/kg etomidate, was 0.0246 mg/kg in young-to-middle-aged patients and 0.0229 mg/kg in elderly patients.

Trial Registration: The study was registered with the Chinese Clinical Trial Registry (ChiCTR2500095893) on January 25, 2025.

Plain Language Summary: Determining the optimal drug dose that balances effectiveness and safety is a central challenge in anesthesia research. Adaptive dose-finding methods, such as the biased-coin up-and-down design, allow researchers to estimate effective doses efficiently while exposing fewer patients to suboptimal levels. In this prospective trial, we investigated oliceridine, a novel μ-opioid receptor agonist that preferentially activates G-protein signaling and may cause fewer respiratory and gastrointestinal side effects than traditional opioids. The study aimed to identify the 90% effective dose (ED90) of oliceridine required to suppress patient reactions during laryngeal mask airway (LMA) insertion under etomidate anesthesia in adults of different ages. The results demonstrate that oliceridine combined with etomidate provides consistent suppression of airway reflexes and stable anesthesia

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induction in both younger and older adults. These findings support its role as a safe, precise, and modern opioid adjunct for balanced anesthesia practice.

Keywords: oliceridine, 90% effective dose, biased coin design, mask airway insertion response, elderly patients

Introduction

The laryngeal mask airway (LMA), an important supraglottic device, is widely recognized as a less invasive alternative to endotracheal intubation.[1] It offers easier insertion, greater comfort, and a lower risk of postoperative laryngeal complications, particularly in ambulatory and short-duration surgeries.[2] However, LMA insertion can still trigger adverse airway reflexes such as coughing, body movements, laryngospasm, and hemodynamic instability, potentially increasing perioperative complications.[3,4] Additionally, elderly patients, due to age-related cardiovascular decline, increased drug sensitivity, and underlying comorbidities, experience greater hemodynamic fluctuations and higher anesthesia risks during induction.[5,6] Therefore, rational selection of anesthetic drugs and precise dosage adjustments during anesthesia induction are crucial for optimizing patient safety and minimizing complications.

Etomidate is a widely used intravenous induction agent known for its hemodynamic stability and minimal respiratory depression.[7,8] However, as a sole agent for LMA insertion, it often fails to adequately suppress airway reflexes, typically requiring the addition of opioids. The combination of sedative and analgesic agents is commonly employed to ensure sufficient suppression of airway reflexes and provide optimal conditions for LMA insertion. This combination not only enhances the effectiveness of anesthesia but also minimizes the required dosages of individual drugs, potentially reducing their side effects while improving patient comfort and safety during the procedure.

Oliceridine, a novel G protein-biased μ-opioid receptor agonist, provides potent analgesia by selectively activating G protein signaling pathways while minimizing β-arrestin recruitment.[9] This mechanism helps reduce opioid-related adverse effects (ORAEs) such as nausea, vomiting, and respiratory depression. A recent meta-analysis showed that oliceridine, at equivalent analgesic doses, significantly reduces the incidence of postoperative nausea and vomiting compared to morphine.[10,11] Furthermore, oliceridine has a favorable safety profile, with no significant need for dosage adjustments in patients with mild to moderate renal or hepatic impairment, suggesting broad clinical applicability.[12]

Although recent studies have explored the effective dose of oliceridine in suppressing gastroscope insertion responses and painless hysteroscopy,[13–15] its efficacy in combination with etomidate for suppressing LMA insertion responses during anesthesia induction remains unexplored. Therefore, this study uses a biased coin up-and-down sequential allocation design to determine the 90% effective dose (ED90) of oliceridine for inhibiting LMA insertion across different age groups under etomidate anesthesia, aiming to provide evidence-based guidance for precise clinical dosing.

Materials and Methods

Trial Design

This prospective, dose-finding trial study was conducted at a single site, with approval from the ethics committee of Changshu No. 2 People's Hospital, China (identifier 2025-KY-K16). All participants provided written informed consent prior to enrollment. The study took place from February 10, 2025, to May 20, 2025, and was registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn/) on January 25, 2025, under identifier ChiCTR2500095893. The study was conducted in accordance with the principles of the Declaration of Helsinki and reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Participants

A total of 113 patients scheduled for LMA anesthesia were enrolled after initial screening. The inclusion criteria were: age 18–79 years, ASA classification I–III, and BMI between 18 and 35 kg/m^2. Exclusion criteria included a history of anesthesia drug allergies, severe cardiovascular disease, significant organ dysfunction, arrhythmia, chronic use of sedatives or analgesics, alcoholism, poorly controlled hypertension, and anticipated difficult airways. Withdrawal criteria

were: failed LMA insertion on the first attempt, insertion time exceeding 30 seconds, or a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score ≥2 following anesthetic induction. The MOAA/S scale is a validated 6-point clinical tool used to assess sedation levels based on a patient's response to stimuli. The scale is as follows: 5 – Responds readily to their name in a normal tone (alert); 4 – Lethargic response to their name; 3 – Responds only after their name is called loudly or repeatedly; 2 – Responds only to mild prodding or shaking; 1 – Responds only to painful trapezius squeeze; 0 – No response to painful trapezius squeeze. Participants were divided into two age groups: young-to-middle-aged (18–64 years, Group A) and elderly (65–79 years, Group B).

Study Protocol

Patients are required to fast for 8 hours and refrain from drinking for 4 hours before surgery, with no specific preoperative medications. Upon entering the operating room, intravenous access was established, and routine monitoring of heart rate (HR), blood pressure (BP), electrocardiogram (ECG), and pulse oximetry (SpO_2) was initiated. Invasive arterial blood pressure monitoring was subsequently established, and oxygen was administered via a mask at 5 L/min for 3 minutes prior to anesthesia induction.

Anesthesia induction was initiated with an intravenous bolus of Oliceridine at 0.02 mg/kg, followed one minute later by Etomidate at 0.25 mg/kg, administered over 30–50 seconds. Rocuronium at 0.8 mg/kg was then given once the patient's MOAA/S score was <2. After achieving satisfactory muscle relaxation, a senior anesthesiologist inserted a LMA Supreme (Zhejiang Haisheng Medical Device Co., Ltd.), with size 4.0 used for males and size 3.0 for females. Baseline vital signs were recorded before anesthesia induction (T0), followed by the lowest BP and HR values post-induction (T1). The highest BP and HR values were recorded within 2 minutes after LMA insertion (T2).

ED90 of Oliceridine was determined using the biased coin sequential allocation design. The initial dose for the first patient was 0.02 mg/kg, and subsequent doses were based on the previous patient's response, with a dose spacing of 0.002 mg/kg. Positive responses were defined as any signs of movement, frowning, tearing, coughing, or hemodynamic parameters (BP or HR) exceeding 20% above baseline after LMA insertion, in which case the dose was increased by 0.002 mg/kg. In the case of a negative response, biased coin randomization was applied for the next patient's dose, with an 89% probability of maintaining the current dose and an 11% probability of dose reduction. The randomization was determined using a computer-generated number between 1 and 100. If the number was between 1 and 11, the dose was reduced; for all other numbers, the dose remained unchanged. During anesthesia induction, vasopressor administration is indicated if BP or heart rate HR decreases by more than 30% from baseline, with systolic blood pressure (SBP) < 90 mmHg, mean arterial pressure (MAP) < 60 mmHg, or HR < 50 bpm. Conversely, if BP or HR increases by more than 30% from baseline, or if SBP ≥ 180 mmHg or HR ≥ 100 bpm, the depth of anesthesia should be increased first, with Urapidil or Esmolol administered as necessary.

Study Outcomes

The primary outcome was the determination of the ED90 of Oliceridine for anesthesia induction to suppress LMA insertion responses in both young-to-middle-aged and elderly patients. Secondary outcomes included changes in BP and HR during anesthesia induction, as well as the incidence of adverse reactions, including myoclonus, hypotension, bradycardia, hypertension, and tachycardia.

Sample Size

The up-and-down dose-finding method used in this study is a small sample design, for which precise sample size calculation tools are currently unavailable. Recent studies suggest that 30–40 participants are required to estimate the 50% effective dose, while 50–60 participants are recommended to estimate the 90% effective dose to ensure reliable results.[16] Based on these guidelines, 60 participants were selected per group, with a total of 120 participants enrolled in the study.

Statistical Methods

Data analysis and graphing were performed using SPSS 27.0, R 4.3.2, and GraphPad Prism 9.4.1. The normality of continuous variables was assessed with the Kolmogorov–Smirnov test. Quantitative data with a normal distribution are expressed as mean (SD) and compared using the independent samples *t*-test, while non-normally distributed data are presented as median (interquartile range) and compared with the Mann–Whitney *U*-test. Qualitative variables were compared using the Chi-square test or Fisher's exact test, as appropriate.

The ED90 of Oliceridine was calculated using central isotonic regression, and 95% confidence intervals (CIs) were obtained from 2000 bootstrap replications. The ED90 values between the two groups were compared using the confidence interval method; no significant difference was considered if the 95% confidence intervals overlapped.[17]

Repeated measures data, such as HR and BP, were analyzed using repeated measures analysis of variance (ANOVA). Comparisons between groups at the T0 time point were conducted using the independent *t*-test. For the T1 and T2 time points, repeated measures analysis of covariance (ANCOVA) was employed, with baseline T0 levels included as covariates for adjustment.

P-value of <0.05 was considered statistically significant.

Results

Characteristics of Patients

Out of 120 patients enrolled in the trial, seven were excluded due to failure of the initial LMA insertion or an insertion time exceeding 30 seconds, resulting in 113 patients eligible for analysis, with 58 in group A and 55 in group B. Figure 1 presents the patient inclusion flowchart, and Table 1 outlines the demographic characteristics of the participants.

Dose-Response

Figure 2 illustrates experimental trajectories of each subject's response (positive or negative) during LMA insertion in both group A and group B. The x-axis represents the sequence of subjects in the study, while the y-axis represents the dose level of Oliceridine. Both groups included 8 subjects who exhibited positive responses during LMA insertion. Table 2 shows the total number of subjects and negative responses at each Oliceridine dose level, along with the observed and PAVA-adjusted response rates for both groups, calculated using the centered isotonic regression method. Centered isotonic regression estimated the ED90 of Oliceridine for inhibiting the response during LMA insertion to be 0.0246 mg/kg (95% CI: 0.0215–0.0320) in Group A and 0.0229 mg/kg (95% CI: 0.0199–0.0298) in Group B. Although the ED90 in Group B was lower than in Group A, the 95% CI overlapped, indicating that the difference was not statistically significant.

Comparison of Hemodynamic Variables

The hemodynamic variables (SBP, DBP, MAP, and HR) measured during anesthesia induction are presented in Figure 3 and Supplementary Tables 1–4 of the Supplementary Material.

Blood Pressure (SBP, MAP)

The repeated measures analysis of variance (ANOVA) revealed significant differences between groups in SBP and MAP at T0, T1, and T2 ($p < 0.001$). At baseline (T0), both SBP and MAP were significantly lower in Group A compared to Group B ($p < 0.001$). After adjusting for baseline levels as covariates, there were no significant differences in SBP and MAP between the two groups at T1 and T2 ($p > 0.05$), indicating that the changes in blood pressure between the groups became similar after controlling for baseline differences.

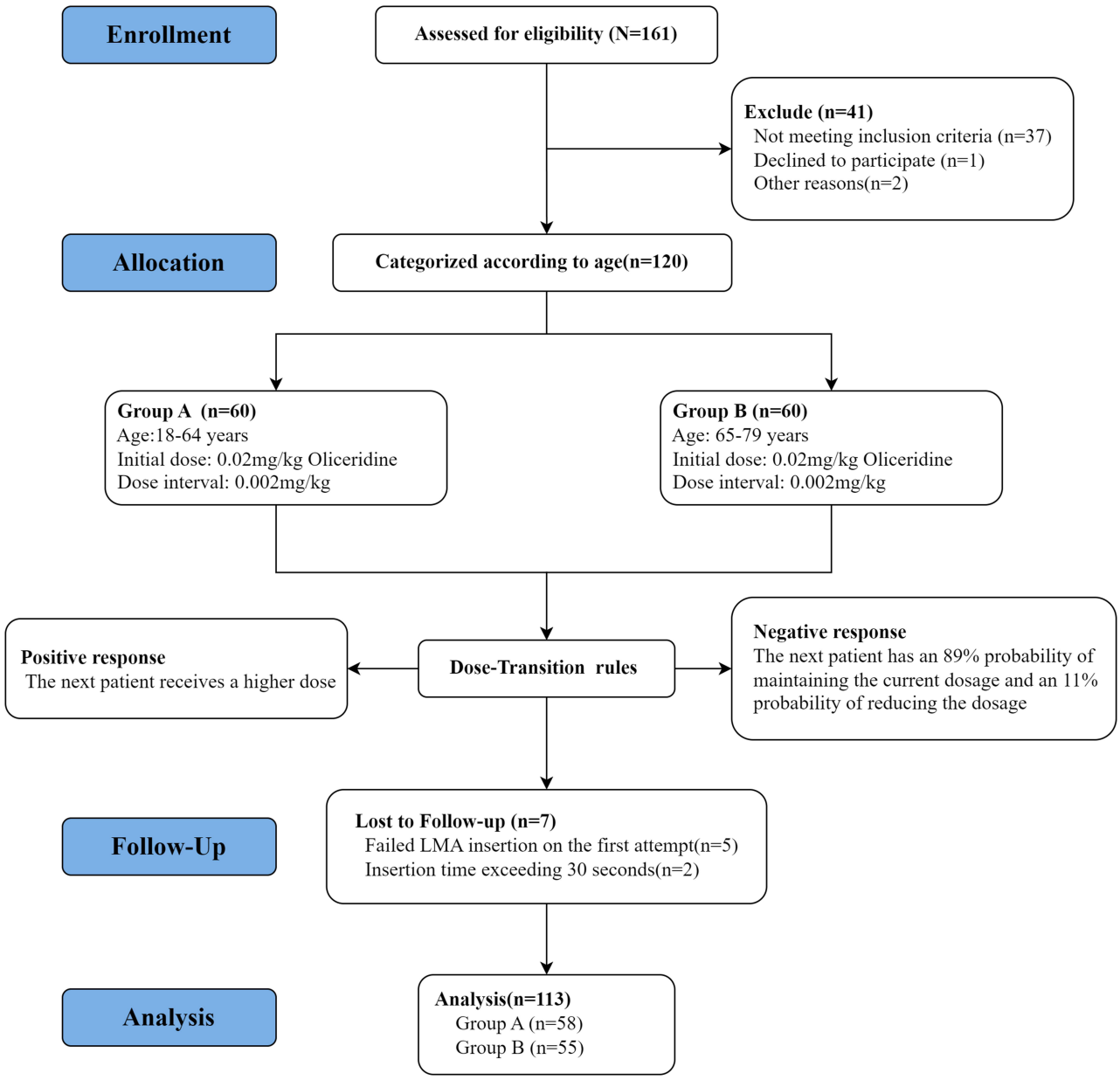

Figure 1 Flow diagram of participant inclusion.

Heart Rate (HR)

Analysis of heart rate revealed a significant interaction between group and time points ($F = 6.704$, $p = 0.002$), warranting a separate effect analysis. Compared to baseline (T0), HR was significantly higher in Group A at T2 and significantly lower in Group B at T1 ($p<0.05$). Compared to T1, HR increased significantly in both Group A and Group B at T2. However, there were no significant differences in HR between the two groups at T0. After adjusting for baseline differences, HR was significantly lower in Group B than in Group A at both T1 and T2 ($p < 0.05$).

The mean difference, adjusted least square means difference, and 95% confidence intervals for BP and HR are provided in the Supplementary Material.

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Table 1 Demographic Characteristics

Variable	Group A (N=58)	Group B (N=55)
Age (years)	48.7±12.2	71.5±4.5
Male n(%)	32 (55.2)	33 (60.0)
Female n(%)	26 (44.8)	22 (40.0)
Height (cm), mean(SD)	165.7±7.7	163.9±7.4
Weight (kg)	65.1±10.8	65.0±8.6
BMI (mg/kg^2), mean(SD)	23.7±3.4	24.2±2.7
ASA physical status n(%)		
I	7 (12.1)	0 (0)
II	42 (72.4)	34 (61.8)
III	9 (15.5)	21 (38.2)
Comorbidities n(%)		
Hypertension	12 (20.1)	35 (63.6)
Diabetes	7 (12.1)	14 (25.5)

Adverse Reactions

The incidence of myoclonus following anesthesia induction was 7% in Group A and 8% in Group B. Additionally, 2 cases in Group A and 3 cases in Group B required the administration of a vasopressor. Group A had 1 case of atropine administration. No other serious adverse events were observed during anesthesia induction in either group.

Discussion

This study successfully identifies the ED90 of oliceridine for inhibiting responses to LMA insertion when combined with etomidate, in both young-to-middle-aged and elderly patients. The ED90 of oliceridine was determined to be 0.0246 mg/kg (95% CI: 0.0215–0.0320) for the younger cohort (Group A) and 0.0229 mg/kg (95% CI: 0.0199–0.0298) for the elderly cohort (Group B). While the ED90 for elderly patients was slightly lower, statistical analysis revealed no significant difference between the two groups, indicating that oliceridine is equally effective in both age groups.

ED90 lies at the inflection point of the sigmoidal dose-response curve. Doses below this threshold significantly elevate the risk of treatment failure, while doses above it provide only marginal improvements in success rates and may increase the likelihood of side effects.[18–20] Thus, accurately determining ED90 is crucial for optimizing both safety and efficacy in clinical practice. This study used a biased-coin sequential allocation design, a reliable method for estimating ED90 in anesthesiology.[21–23] Dose adjustments were made based on each subject's response: the dose was increased after a positive response, and either maintained (89% probability) or decreased (11% probability) after a negative response. This strategy ensured identification of the target dose while minimizing the risk of exposing patients to excessively high or low doses.

To estimate the target dose, a dose-response curve is typically constructed using regression analysis based on actual dose and response data, with logistic and probit models commonly employed.[24,25] However, up-and-down designs often involve a limited range of doses, potentially failing to fully capture the dose-response relationship. Isotonic regression, a non-parametric method, assumes that response rates do not decrease with increasing doses, offering more stability in estimating ED90 without assumptions about the curve's shape.[26] A limitation of isotonic regression is the tendency for resulting curves to exhibit unrealistic flat intervals, reducing estimation precision. Oron and Flournoy improved the algorithm by introducing the centered isotonic regression method, which eliminates most flat intervals, thereby improving accuracy by reducing estimation errors.[16] Therefore, this study employed centered isotonic regression combined with bootstrapping to calculate ED90 and its 95% confidence intervals, providing reliable and precise estimates of the effective dose.

Elderly patients are generally more sensitive to anesthetic drugs and typically require lower doses compared to young and middle-aged patients. The results of this study show that although the ED90 in the elderly group is lower than in the young and middle-aged group, the difference is not statistically significant. This may be due to the synergistic effects of

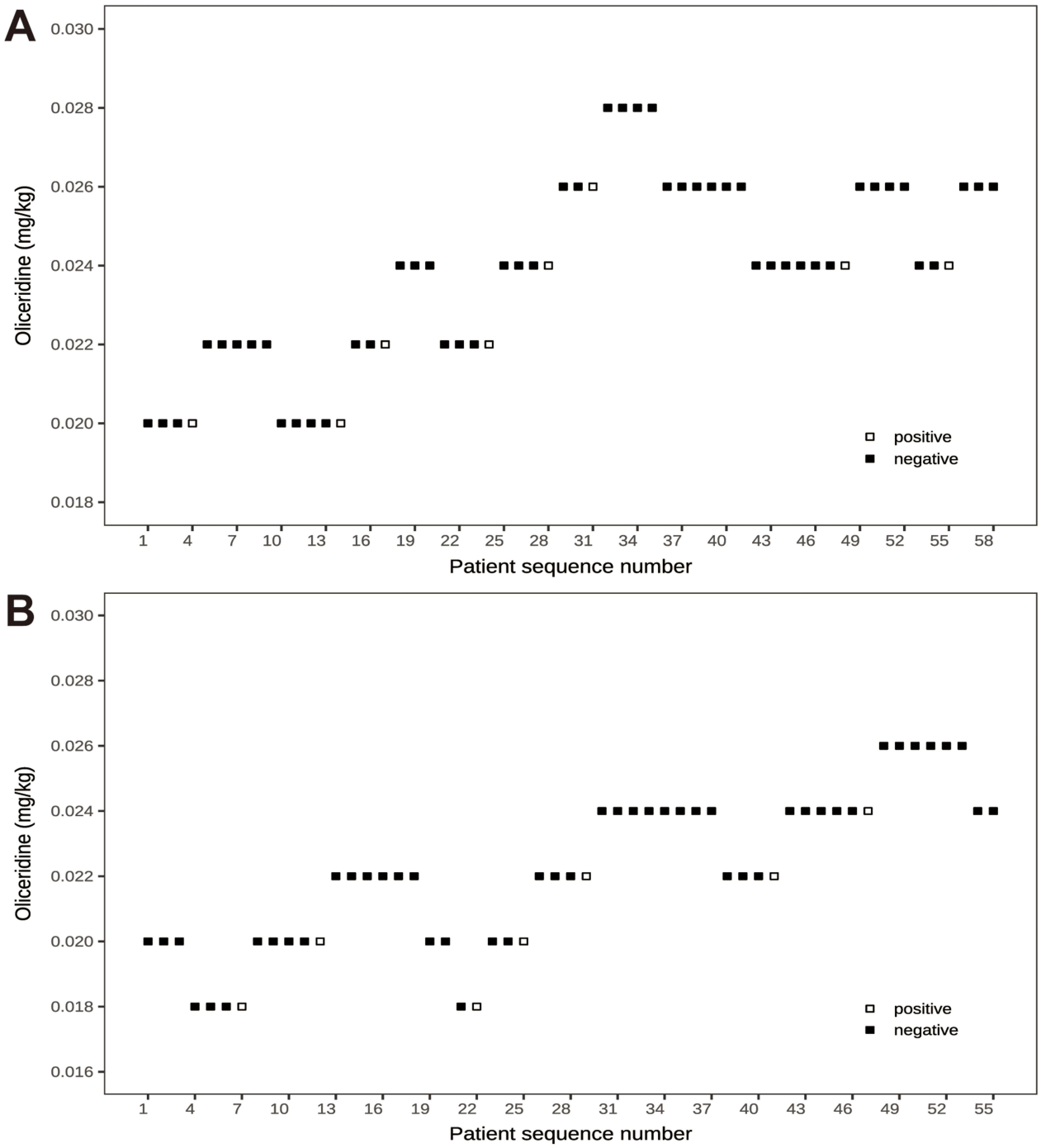

Figure 2 Experimental trajectories of an ED90-finding by biased coin up-and-down design. (**A**) Experimental trajectories for group A (n = 58) with 5 dose levels. (**B**) Experimental trajectories for group B (n = 55) with 5 dose levels. The black square indicates a negative response, and the white square indicates a positive response.

analgesic and sedative drugs, which reduce stimulation during Laryngeal Mask Airway (LMA) insertion, thereby minimizing the difference in analgesic requirements between the two age groups.[27] Therefore, although the ED90 is lower in elderly patients, this difference may be influenced by the synergistic effects of the drugs and the depth of sedation, warranting further exploration in future studies.

Hemodynamic analysis revealed that elderly patients exhibited significantly higher baseline SBP and MAP compared to younger counterparts, likely reflecting age-related vascular elasticity. However, after adjustment for baseline values,

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Table 2 Observed Response Rates and PAVA-Adjusted Rates for Oliceridine Using the Centered Isotonic Regression Method in Group A and Group B

Group	Dose-Level (mg/kg)	Number of Case	Negative Response	Response Rates	PAVA-Adjusted Response Rates
Group A					
	0.020	9	7	0.778	0.790
	0.022	12	10	0.833	0.848
	0.024	17	14	0.824	0.883
	0.026	16	15	0.938	0.935
	0.028	4	4	1	0.980
Group B					
	0.018	6	4	0.667	0.707
	0.020	13	11	0.846	0.854
	0.022	16	14	0.875	0.879
	0.024	15	14	0.933	0.934
	0.026	5	5	1	0.992

post-induction blood pressure remained comparable between groups, suggesting that the combination of oliceridine and etomidate exerts similar hemodynamic effects across age ranges. In terms of heart rate, no significant change from baseline was observed in the young-to-middle-aged group at T1, whereas the elderly group exhibited a significant reduction, indicating diminished cardiovascular compensatory capacity with age—likely attributable to attenuated

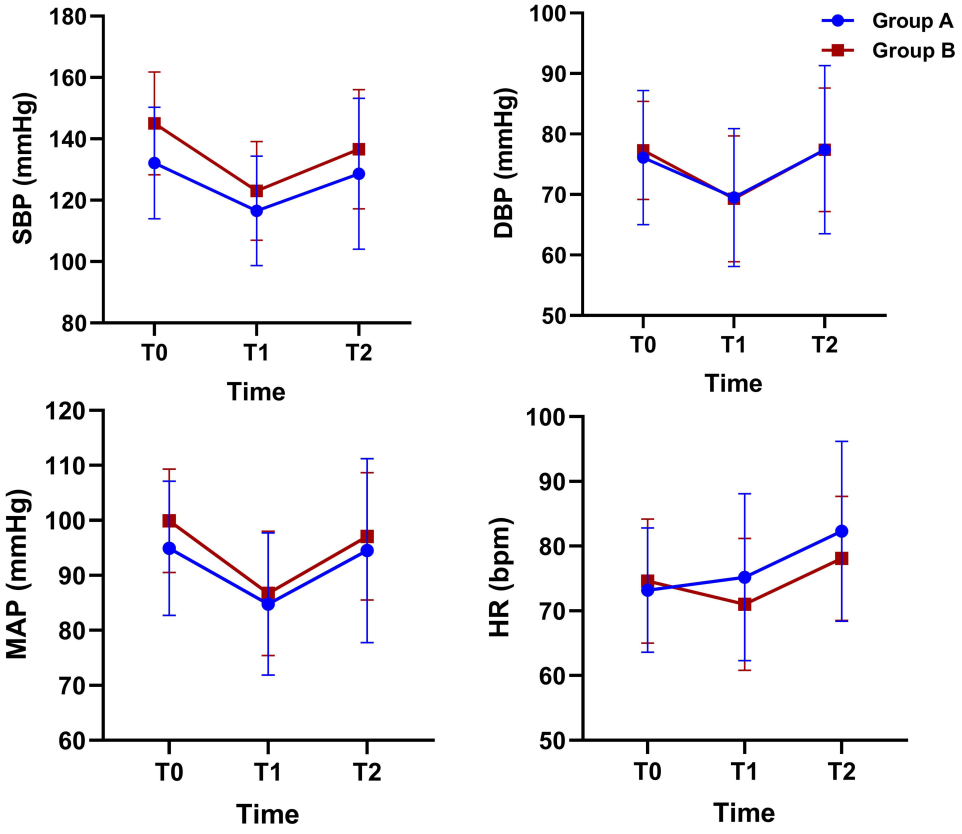

Figure 3 Changes in the blood pressure and heart rate during anesthesia induction between two group. T0: Baseline measurements before anesthesia induction (calm state). T1: Minimum values before LMA insertion. T2: Maximum values within 2 minutes after LMA insertion.
Abbreviations: SBP, Systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, Heart rate.

autonomic responsiveness. These findings underscore the need for vigilant monitoring in elderly patients during induction.

Several limitations of this study must be acknowledged. First, the trial excluded patients with severe comorbidities, which limits the generalizability of the findings to these populations. Second, the age range of the younger-to-middle-aged cohort was broad, potentially introducing pharmacodynamic variability. Additionally, the study only assessed changes during anesthesia induction, without evaluating postoperative recovery outcomes. Future research should include more complex patient populations, with a finer age stratification, to better assess pharmacodynamic differences across age groups.

Conclusion

In conclusion, this study demonstrates that oliceridine, when combined with etomidate, is an effective and safe option for suppressing LMA insertion responses in both young-to-middle-aged and elderly patients. The ED90 of oliceridine is 0.0246 mg/kg for young-to-middle-aged patients and 0.0229 mg/kg for elderly patients.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author Jianfeng Pu upon reasonable request.

Ethics Statement

The study protocol and informed consent form have been approved by the Ethics Committee of Changshu No. 2 People's Hospital (Approval No. 2025-KY-K62). All participants were required to provide written informed consent prior to participation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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