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Determination of ED_{90} and ED_{99} of Oliceridine combined with Propofol in inhibiting responses to gastroscope insertion: a biased coin up-and-down design

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Abstract

Background Gastroscopy is a common medical procedure, but the insertion of the endoscope often causes significant discomfort and anxiety in patients, necessitating effective sedation strategies. Traditional sedatives, such as propofol, are widely used for procedural sedation but can lead to adverse effects, including respiratory depression and cardiovascular instability at higher doses. Oliceridine, a novel opioid analgesic, has emerged as a potential alternative due to its biased agonist properties, which may provide effective analgesia with a more favorable side effect profile. The potential for its combination with propofol warrants further investigation.

Methods The ED_{90} and ED_{99} were calculated using a biased coin design and central ordered regression. Measurements: The primary outcome measure was the occurrence of body movements or coughing responses during gastroscopy.

Results A total of 49 patients were included in this study, with anesthesia successfully achieved in 45 cases and failed in 4 cases. The calculated ED_{90} and ED_{99} for Oliceridine combined with Propofol to suppress the response during gastroscopy were22.5 and 23.8 $\mu g \cdot kg^{-1}$, respectively.

Conclusions The combination of 2 $mg \cdot kg^{-1}$ Propofol and 23.8 $\mu g \cdot kg^{-1}$ Oliceridine is effective in suppressing the responses during the gastroscopy procedure.

Trial registration The study was registered in the Chinese Clinical Trial Registry (ChiCTR2400092318) on November 14, 2024.

Keywords Oliceridine, Gastroscopy, ED_{99}

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Introduction

Painless gastroscopy is an important method widely used for screening, diagnosing, and treating digestive system diseases. Patients frequently experience discomfort and pain during insertion of the endoscope. The administration of sedatives and analgesics can enhance patient comfort, ensuring a safer and more accessible procedure. Common drug combinations for painless gastroscopy include Propofol and opioids. While Propofol offers rapid and precise sedation, opioids can alleviate the discomfort and pain associated with the insertion and examination processes. However, both Propofol and opioids can lead to respiratory depression, and the combination of their side effects may result in serious consequences for patients.

Oliceridine is a novel opioid that effectively relieves pain while exhibiting a significantly lower incidence of complications such as respiratory depression compared to conventional opioids. The combination of Oliceridine and Propofol may provide ideal sedation and analgesia while minimizing related complications.

In clinical practice, establishing the correct dosage for drug combinations is crucial for ensuring safety and efficacy. The ED_{90} and ED_{99} represent the doses at which 90% and 99% of patients achieve the desired effect, which is significant for guiding clinical usage and formulating individualized treatment plans. Traditional methods for determining dosages are often time-consuming and challenging for efficient clinical application; therefore, utilizing a biased coin design in dose determination offers a more flexible and efficient option. This method adjusts the allocation ratio dynamically, allowing for quick identification of appropriate drug dosages while maintaining trial validity.

This study aims to determine the ED_{90} and ED_{99} of Oliceridine combined with Propofol using a biased coin design during the process of gastroscopy, providing a scientific basis for clinical practice.

Methods

Patients aged 18–65 years, regardless of gender, with an ASA classification of I-II were included. Exclusion criteria included allergies to the drugs used in this study, severe liver or kidney impairment, acute gastrointestinal bleeding, severe psychiatric disorders, acute upper respiratory infections, poorly controlled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg), severe thoracic and spinal deformities, and significant coagulation abnormalities.

Anesthesia method

Patients were instructed to fast for 4 h for liquids and 8 h for solids before the painless gastroscopy. A routine intravenous access was established upon entry, and the patients' vital signs were monitored with nasal oxygen provided at a rate of 4 $L{\cdot}min^{-1}$. All procedures were performed by the same anesthesiologist and endoscopist using Propofol (Xi'an Libang Pharmaceutical Co., Ltd., Batch No. H9990282) and Oliceridine (Jiangsu Enhua Pharmaceutical Co., Ltd., Batch No. H20233509). The gastroscopy was conducted when the OAA/S(Observer's Assessment of Alertness/Sedation) score was ≤2(The OAA/S scale is a five-point scoring system used to assess a patient's level of alertness and sedation. Scores range from 1 to 5, with higher scores indicating greater alertness. Specifically: 1 represents general anesthesia; 2 indicates responsiveness only to physical shaking, slurred speech, and deep sedation; 3 denotes responsiveness to mild prodding or shaking, slurred speech, and relaxed lower eyelids; 4 reflects the ability to respond to name calls but with slower responses, slurred or significantly slowed speech, relaxed expression, and shiny, slightly droopy eyes; and 5 signifies full alertness.)All patients received 2 $mg{\cdot}kg^{-1}$ of Propofol. The first patient received 20 $\mu g{\cdot}kg^{-1}$ of Oliceridine; if there were no body movements or coughing responses during gastroscopy, the anesthesia was considered successful. In this case, the next patient had an 11% probability of reducing the dosage by one increment (increment of 2 $\mu g{\cdot}kg^{-1}$ Oliceridine) and an 89% probability of maintaining the current dosage. If there was a reaction, the dosage for the subsequent patient was increased by one increment. This process continued until 45 successful anesthesia cases were reached, at which point the trial was terminated (see Fig. 1).

If the patient coughs or moves during the painless gastroscopy, add propofol 0.5 mg/Kg Immediately and record the total amount of the added drug.If a patient's oxygen saturation fell below 90%, chin lifting, abdominal compression, or positive pressure oxygenation via a mask was administered. If the heart rate fell below 50 beats per minute, 0.3–0.5 mg of Atropine was given, and if the mean arterial pressure dropped more than 30% from baseline, 5–10 mg of Ephedrine was administered.

Primary outcome

The occurrence of body movements or coughing responses during the insertion of the endoscope.

Secondary outcomes

Intraoperative heart rate, mean arterial pressure, and oxygen saturation of the patients.

Adverse reactions

The incidence of nausea, vomiting, abdominal discomfort, and drowsiness within 24 h post-anesthesia.

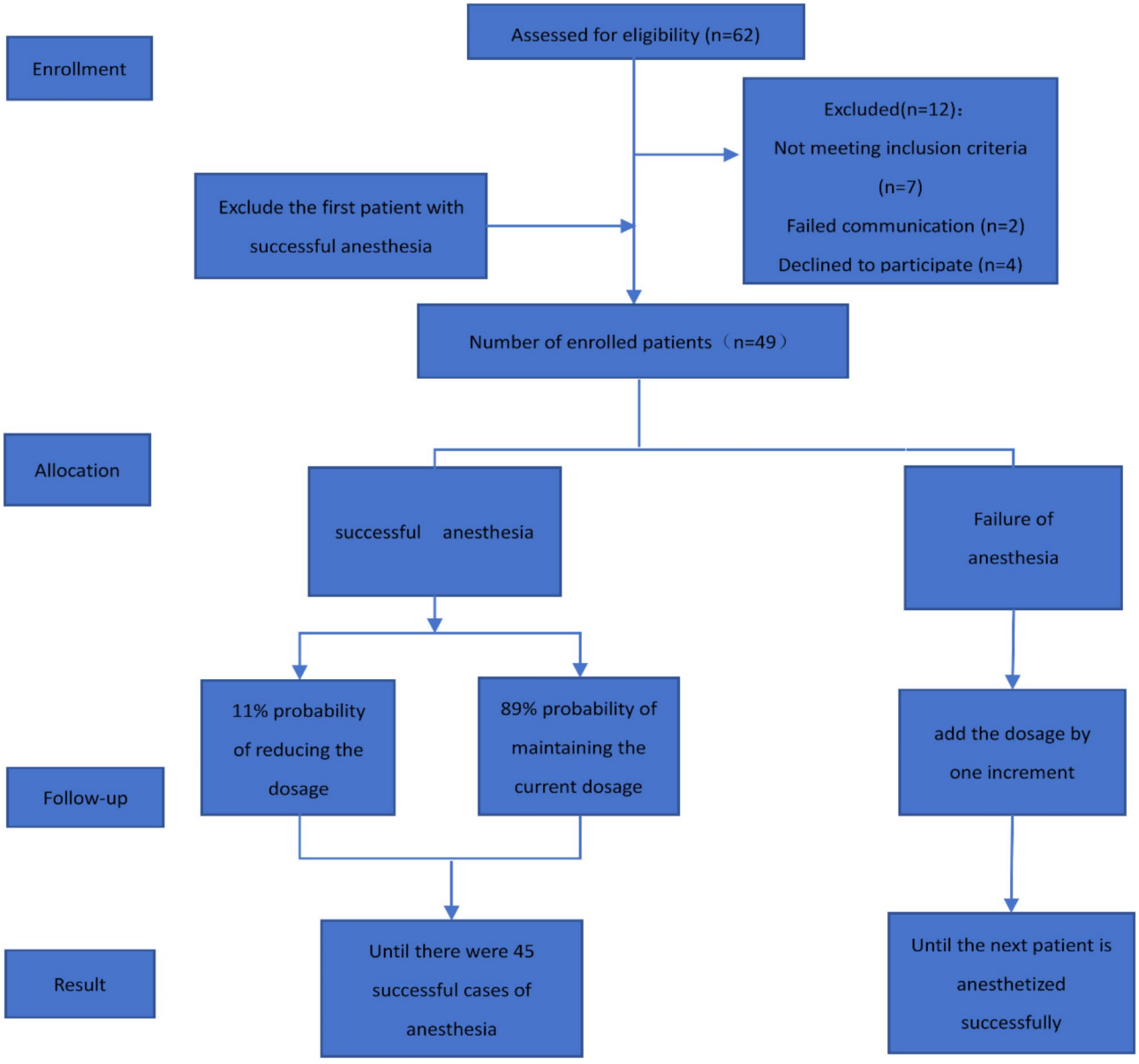

Fig. 1 Consort diagram

Statistical analysis

ED_{90} and ED_{99} were calculated using central ordered regression. Statistical analysis was performed using R version 4.2.2. Normally distributed continuous data are expressed as mean ± standard deviation ($\bar{x}$±s), while non-normally distributed data are presented as median (M) and interquartile range (IQR). Categorical data are expressed as counts (%). A p-value of < 0.05 was considered statistically significant.

Sample size calculation

This study utilized a biased coin design, setting $\Gamma = 0.1$ (indicating a 10% probability of anesthesia failure) and $b = \Gamma/(1\text{-}\Gamma) = 0.11$ (indicating an 11% probability of reducing dosage after a successful second case and an 89% probability of maintaining the dosage), terminating the trial after 45 successful anesthesia cases. The sample size required for successful central ordered regression must be a multiple of 9 and greater than 40; thus, the estimated sample size was 54 cases.

Results

A total of 49 patients were included in this study, with anesthesia successfully achieved in 45 cases and failed in 4 cases (Table 1).

The calculated ED_{90} and ED_{99} for Oliceridine in combination with Propofol to suppress the response during

Table 1 Demographic characteristics of patients ($n=49$)

Parameter	Value
Sex (n)	
Male	24
Female	25
ASA Classification (n)	
I	13
II	36
Age (years)	47.7 ± 10.8
Weight (kg)	62.6 ± 11.2

gastroscopy were 22.5 and 23.8 $\mu g \cdot kg^{-1}$, respectively (Fig. 2).

In this study, 5 patients (10%) experienced respiratory depression during the gastroscopy(No effective chest fluctuation was observed in 3 patients, and upper respiratory tract obstruction occurred in 2 patients), and 3 patients (6%) had a blood pressure drop greater than 30%. All cases were well managed without serious complications such as suffocation or arrhythmia. Follow-up phone calls within 24 h post-operation showed that 3 patients were lost to follow-up, while 47 patients did not experience any nausea, vomiting or abdominal discomfort within 24 h. All patients showed no symptoms of drowsiness after being discharged from the resuscitation room. Except for 4 patients who had failed anesthesia and whose heart rates were the fastest over 100 beats per minute, the heart rates of the remaining patients were all between 50 and 100 beats per minute, the relief was achieved by adding 0.5 mg/kg of propofol. Apart from the 4 patients with failed anesthesia who received an additional dose of 0.5 mg/kg propofol, no other patients required additional sedative or analgesic medications.

Discussion

The results of this biased coin design sequential trial indicate that the ED_{90} and ED_{99} for Oliceridine in combination with Propofol to suppress the response during gastroscopy are 22.5 $\mu g \cdot kg^{-1}$(95% confidence interval 18.3 $\mu g \cdot kg^{-1}$–25.6 $\mu g \cdot kg^{-1}$) and 23.8 $\mu g \cdot kg^{-1}$(95% confidence interval 23.6 $\mu g \cdot kg^{-1}$-26.1 $\mu g \cdot kg^{-1}$), respectively.

As one of the most common outpatient procedures, painless gastroscopy allows patients to return home a few hours after the examination. Therefore, selecting opioids with minimal side effects is crucial for ensuring postoperative safety. Oliceridine is a G protein-biased μ-opioid that significantly reduces the incidence of respiratory depression and postoperative cognitive dysfunction compared to traditional opioids, as well as decrease the occurrence of postoperative cognitive dysfunction [1–3]. Moreover, the inactive metabolites of Oliceridine make it safer for patients with liver and kidney dysfunction and suitable for those with severe renal impairment and mild to moderate liver dysfunction [3]. In the field of pain management, Oliceridine acts more quickly, has better tolerance, fewer side effects, and lower addiction potential compared to morphine, ultimately reducing treatment costs for patients over the long term, making it a viable alternative to traditional opioid therapies [4–7]. This study utilized the Biased Coin Design (BCD)

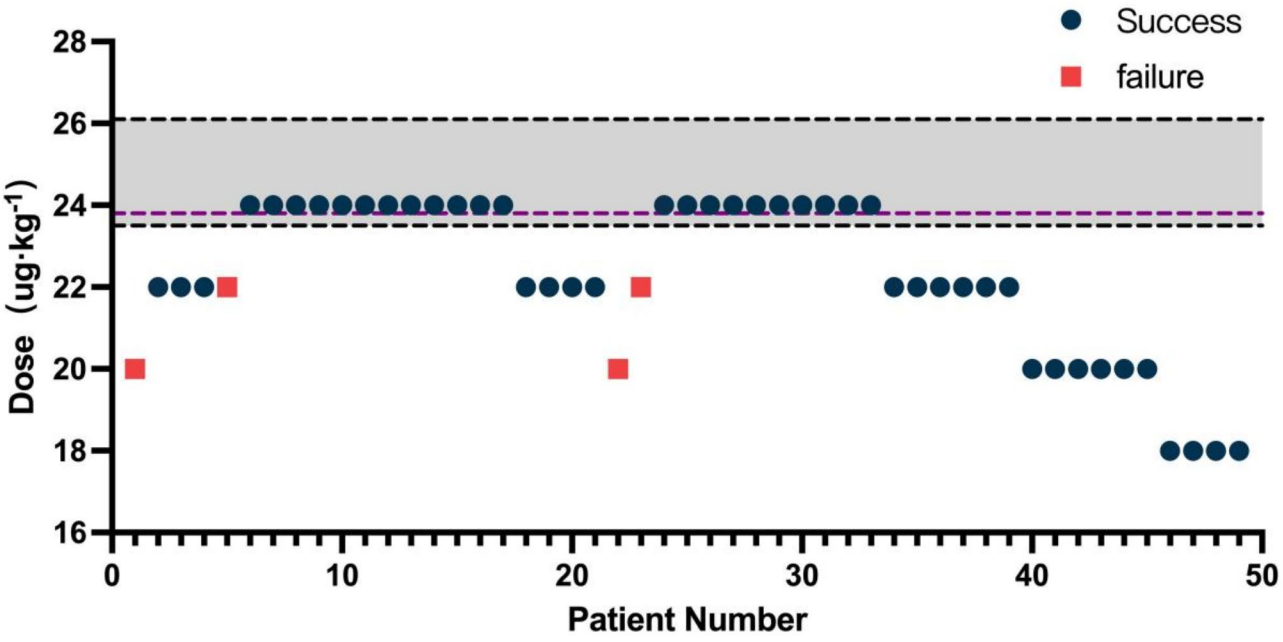

Fig. 2 Patient sequential diagram (Purple dashed line indicates the ED_{99} dose; gray area between the black dashed lines represents the 95% confidence interval of ED_{99})

to explore the ED_{90} and ED_{99} of oliceridine combined with propofol in suppressing the response to gastroscope insertion. Since the study design did not include a control group with traditional opioids (such as fentanyl or morphine), it was not possible to directly compare the differences in the incidence of adverse reactions between different opioids in painless gastroscopy. Existing research suggests that oliceridine may reduce the incidence of postoperative nausea and vomiting (PONV) compared to traditional opioids [8–12]. However, the occurrence of nausea and vomiting after gastroscopy is influenced by multiple factors, including not only the use of opioids but also mechanical stimulation of the gastrointestinal tract by the gastroscope, procedure duration, and the dosage of sedative agents. Therefore, the specific impact of oliceridine on the incidence of PONV after gastroscopy requires further investigation while controlling for relevant variables. This study utilized biased coin design with central ordered regression to calculate the ED_{90} for Oliceridine in combination with Propofol to suppress the response during gastroscopy. This method is more precise compared to Dixon's sequential method and may be more reliable for calculating the 95% confidence interval than resampling bootstrapping algorithms [13]. The biased coin design can produce effective doses to any decimal place by adjusting the value of Γ and sample size; however, our study did not directly seek ED_{99} but derived it from the dose-response curve of ED_{90}, as setting $\Gamma = 0.01$ would require a total sample size of over 500 cases.

In this study, 5 patients (10.2%) experienced respiratory depression, with 4 cases resolving by chin lifting, and 1 case recovering to 100% SpO_2 after 1 min of chin lifting and high-flow nasal oxygen at 10 $L{\cdot}min^{-1}$ null. Three patients (6.1%) experienced a blood pressure drop greater than 30%, which was alleviated by intravenous Ephedrine (5–10 mg). During the 24-hour follow-up, 3 patients were lost to follow-up, and none of the remaining patients experienced nausea, vomiting, or other complications within 24 h.

This study provides a theoretical basis for the dosage of Oliceridine in painless gastroscopy and expands the options for anesthesia protocols in this context, offering dosage references for comparing Oliceridine with other opioids in painless gastroscopy.

Limitations

The incidence of complications with varying doses of Oliceridine may not be representative. This study primarily focused on patients aged 18 to 65 with ASA classifications of I to II, and did not include special populations such as the elderly or obese, who may benefit more from the characteristics of Oliceridine. Therefore, future randomized controlled trials comparing the efficacy and safety of Oliceridine with other commonly used opioids at the ED_{99} dose are warranted.

Conclusion

In summary, this study provides dosage references for individualized sedation and analgesia protocols in painless gastroscopy. The combination of 23.8 $\mu g{\cdot}kg^{-1}$ Oliceridine with 2 $mg{\cdot}kg^{-1}$ Propofol effectively suppresses responses during endoscope insertion. The combined use of Oliceridine demonstrates significant clinical potential in optimizing patient comfort and reducing related complications, warranting further exploration in broader studies.

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Author contribution
Zhiyong Tang and Guangfen Yin contributed equally to this work. Zhiyong Tang and Guangfen Yin designed and performed the experiments, analyzed the data, and wrote the manuscript. Yaohan Yu and Yanwei Fang contributed to the data analysis and interpretation of the results. Yinghong Luo assisted with experimental design and data collection. Shuqin Tian provided critical feedback on the manuscript and assisted with data interpretation. Qingdong Zhang and Qinghang Xuan supervised the project and provided guidance on the experimental design and manuscript revision. All authors reviewed and approved the final version of the manuscript.

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Data availability
Data are available on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki. This study was approved by the Ethics Committee of the First Affiliated Hospital of Dali University on October 8, 2024. Written informed consent was obtained from all participants. The study was registered in the Chinese Clinical Trial Registry (ChiCTR2400092318) on November 14, 2024. Patient recruitment occurred between November 20 and November 30, 2024.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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