MEDS Clinical Medicine (2025)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2025.060106
ISSN 2616-1907 Vol. 6 Num. 1

Modified Dixon sequential method to determine the effective dose of oliceridine combined with remimazolam besylate for painless gastroscopy: protocol for a clinical trial

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Keywords: Oliceridine, Sedation, Gastroscopy, Effective dose, Protocol

Abstract: This study is designed to explore the 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) of oliceridine combined with remimazolam required for sedation procedures in adult patients undergoing gastroscopy. The improved Dixon sequential method will be adopted in the study, with an initial dose of 15 μg/kg oliceridine combined with 0.3 mg/kg remimazolam, with a gradient dose of 1.5 μg/kg for oliceridine. If the administration of medications do not meet the requirements for gastroscopy procedure and the improved alertness/sedation score is greater than 2 points within 5 minutes after administration, indicating insufficient dose of oliceridine. The oliceridine dose escalation proceeds to the next. Otherwise, descend a gradient. The study will be terminated after seven crossovers. The ED50, ED95 and corresponding 95% confidence intervals (CIs) will be calculated for oliceridine by the probit method.

1. Introduction

Gastroscopy is widely used to diagnose or treat esophageal and gastric diseases in China. Sedation procedure in gastroscopy has become an important medical option in routine clinical care. The frequently used sedative scheme is propofol or remimazolam combined with opioid drugs [1]. However, due to its narrower therapeutic range, apnea, hypoxemia and hypotension during the sedation procedure, opioid drugs are the more demanding agent to administer, thus a safer analgesic drug for gastroscopy procedure is urgently needed [2]. Oliceridine, a novel μ opioid agonist, was approved in the USA for use in adults for the management of acute pain severe enough to require an intravenous opioid analgesic [3] [4]. Unlike other opioid agonists currently in use, oliceridine is selective to the G protein pathway, with low potency for β-arrestin recruitment, which may lead to fewer opioid-related adverse events. The mechanism action could lead effective analgesia improved safety gastrointestinal tolerability than conventional opioids [5]. Therefore, oliceridine may be regarded as a potentially better prospect in gastroscopy sedation.

Oliceridine combined with remimazolam may be an emerging approach in intravenous moderate and deep sedation, owing to these pharmacological advantages [6]. It is reported that oliceridine has

the potential to revolutionize gastrointestinal endoscopy sedation [7]. The exposure to oliceridine increases with an increase in the dose from 0.15 to 7 mg and such an increase is nonlinear by about 15%. As a result, when used as sedative, dose adjustments are necessary. Presently, there are few research reports on the use of oliceridine for moderate and deep sedation for painless gastroscopy. It is urgent to explore the ideal dosage of oliceridine in painless gastroscopy, a non operating room sedation process.

Therefore, we believe that it is necessary to determine the dosage of oliceridine according to body weight. This study investigated whether oliceridine, given at different dosages according to body weight, could achieve similar efficacy, with the incidence of adverse events also observed in sedation for gastroscopy.

2. Materials and Methods

2.1 Study Design

This study is designed to detect the ED_{50} and ED_{95} of oliceridine combined with remimazolam required for sedation procedures in adult patients undergoing gastroscopy. The study was approved by the Medical Ethics Committee of the Deyang People's Hospital on March 28, 2024 (2024-04-028-K01), and the study protocol (version 2.0) was registered in the Chinese Clinical Trial Registry (ChiCTR2400093416). The subjects will be recruited in Deyang People's Hospital.

All researchers will be trained to conduct the study in a standard and uniform protocol. The researchers will explain this study to the eligible subjects and present them with informed consent forms. After signing the relevant documents, candidates will be included into the procedure and they can withdraw at any time. This study will be performed in accordance with the Declaration of Helsinki.

Modified Dixon sequential therapy will be used in this study. We set the initial oliceridine dose at 15 μg/kg combined with 0.3 mg/kg remimazolam, with a gradient dose of 1.5 μg/kg for oliceridine. Consequently, the effective dose gradient of oliceridine (μg/kg) is 15-16.5-18-19.5-21-22.5-24-25.5-27-28.5 by elevating 7 cross points of drug concentration on the initial dose of 15 μg/kg. The dosage of oliceridine administered to each patient depends on the analgesia effect during the gastroscopy procedure based on the previous patient. If the result of the previous patient is "insufficient", then the oliceridine dose escalation proceeds to the next. Otherwise, descend a gradient. We consider the analgesia to be effective if the modified observer's assessment of alertness/sedation scale (MOAA/S) score < 2 within 5 min after intravenous injection, and conversely as ineffective.

2.2 Inclusion and Exclusion Criteria

Patients scheduled for selective painless gastrointestinal endoscopy are eligible for participation in this study if they: (1) have an ASA physical status I-II, regardless of gender; (2) are 18-64 years old; (3) have a body mass index (BMI) between 18 and 28 kg/m^2.

The exclusion criteria are as follows: (1) patients with a Mallampati Modified Scale score equal to 4 points; (2) patients with poorly controlled hypertension by antihypertensive drugs; (3) patients with a history of continuous use of anticonvulsant, sedative, analgesic drugs; (4) patients with a history of alcohol or opioid abuse; (5) patients with a complication of acute asthma attack or alleosis; (6) patients with a history of allergy to remimazolam, emulsions or opioids; (7) patients with known or suspected gastrointestinal obstruction; (8) pregnant or lactating women; (9) patients with a history of severe cardiac, cerebral, pulmonary, hepatic, renal, or metabolic diseases.

If patients meet one of the following situation, the cases will be stopped: (1) failing to complete

gastroscopy smoothly; (2) severe hypoxemia, allergic reactions and anesthesia accidents.

2.3 Study methods and Allocation

All participants will be asked to fast before the examination in accordance with the guidelines. No preoperative medicine will be administered. Once the patient enters the anesthesia preparation room, the baseline vital signs will be collected in the left lying position, including noninvasive blood pressure (NIBP), electrocardiogram (ECG), heart rate (HR), pulse oxygen saturation (SpO_2), and respiratory rate (RR). Peripheral venous access will be opened immediately before painless gastroscopy. A bag of 500 ml physiological saline solution will be slowly infused.

Ten minutes before the start of gastroscopy, every subject will take orally 10 ml of lidocaine gel. After entering the gastroscopy room, patients will be routinely monitored for basic vital signs in the left lateral position. Patients will be continuously monitored with SpO_2, ECG, NIBP and RR during sedation, with oxygen inhaled at a rate of 4 L/min through a respiratory mask. For sedation induction, the initial dose of 15 μg/kg oliceridine will be intravenously injected more than 30 s, combined with a bolus of 0.3 mg/kg remimazolam besylate within 60 s, subsequently. One minute later, if the MOAA/S score reaches smaller than 2 points, gastroscopy procedure begins. Otherwise, additional dose of propofol (0.4 mg/kg for once) will be administered and this gradient dose of oliceridine is “insufficient”, then the oliceridine dose escalation proceeds to the next. If the gradient dose of oliceridine is “sufficient”, the oliceridine dose escalation recedes to the last. During gastroscopy procedure, the depth of sedation will always be maintained below 3 scores of MOAA/S, with additional dose of propofol (0.4 mg/kg for once) administered if necessary. The formal test begins with the first crossover wave and lasts until seven crossovers.

The NIBP will be kept within 20% of the baseline value by metaraminol or nicardipine injected intravenously. Atropine (0.3 ~ 0.5 mg/bolus) will be administered when HR is below 50 beats/min, with a maximum dose of 2 mg. The treatments for simple airway maneuvers, such as head-tilt/chin lift and jaw-thrust, will be performed by the anesthesiologist when the SpO_2 is below 90%. If the low SpO_2 isn’t alleviated by the previously mentioned treatments, manual ventilation by anesthesia machine will be consequently applied and emergency tracheal intubation or laryngeal mask insertion will be performed if necessary. Other perioperative security incidents are also noted and treated in accordance with the clinical operation standards of Deyang People's Hospital.

Table 1: The 10-point Likert scale

Sore	Meaning
10	Outstanding
9	Excellent
8	Very good
7	Good
6	Above average
5	Average
4	Below average
3	Less than acceptable
2	Unacceptable
1	Highly unacceptable

After completing the gastroscopy procedure, patients will be transferred into the post anesthesia recovery room with continuous monitoring. When the patient get a Steward score ≥4 and stable vital signs, allowed to leave the anesthesia recovery room accompanied by their family members. Adverse events will be documented by the nurse anesthetist. Attending anesthesiologists will

participate in the treatment of these side effects. In addition, satisfaction of the patients, endoscopists and anesthesiologists will also be determined by a 10-point Likert scale (1=highly unacceptable, 10=outstanding) [8] (Table 1) before the patient leaving the anesthesia recovery room.

2.4 Observation indices

The main observations include: oliceridine dose, total propofol dose, and MOAA/S score within 5 min after sedation induction. Secondary observations include: blood pressure, heart rate and SpO_2 at patients entering the gastroscopy room (T0), sedation induction completed (T1), 1, 3, 5 min after the start of gastroscopy operation (T2), (T3), (T4), patient leaving the anesthesia recovery room (T5). The duration of gastroscopy, recovery time, anesthesia recovery room stay time, systems incidence of security events and adverse reactions of various systems (apnea, respiratory depression, hypoxemia, hypotension, nausea, vomiting, dizziness), satisfaction scores of patients and endoscopist will also be recorded.

2.5 Data collection and management

Baseline demographic data including age, height, body weight, gender, BMI, ASA score, modified Mallampati score, blood pressure, heart rate and SpO_2 will be recorded when subjects enter the anesthesia preparation room. The data recorded during gastroscopy are as follows: blood pressure, heart rate and SpO_2 at T0, T1, T2, T3, T4, T5, successful incidence of sedation by oliceridine combined with remimazolam besylate, oliceridine dose, total propofol dose, and MOAA/S score within 5 min after sedation induction, duration of gastroscopy, recovery time, anesthesia recovery room stay time, systems incidence of security events and adverse reactions of various systems, satisfaction scores of patients and endoscopist. All data will be input and stored in the SPSS software by an independent researcher. Two research members will be responsible for managing the data. All the researchers will be trained, such as the eligibility evaluation, privacy protection, and interview skills before the study.

2.6 Recruitment plan

Patients who plan to undergo a painless gastroscopy are required to accept a preoperative evaluation of anesthesia clinic at the Deyang People's Hospital. After evaluation, the study protocol, risks and benefits will be explained to the eligible patients in detail without persuasive advertising. The related documents were reviewed and approved by the Ethics Committee of Deyang People's Hospital. To promote participant retention and completion of follow up, we will inform them that the time points of phone calls during recruitment period and reserve at least 2 records of contact number. Recruitment is planned to begin on September 1, 2024 and end on January 31, 2025.

2.7 Statistical analysis

SPSS 26.0 (SPSS, Inc., IL, USA), GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA), and Origin Pro 2021 (Origin Lab Co., Northampton, MA, USA) will be used for all statistical analyses. Normally distributed data will be summarized as mean ± standard deviation (SD), compared between two groups (positive group and negative group) using the student t-test. While non-normally distributed data will be expressed as median. Categorical data will be shown as frequency and percentages. The ED_{50}, ED_{95} and corresponding 95% confidence intervals (CIs) will be calculated for oliceridine by the probit method. Plotting oliceridine sequential diagrams and

dose–effect relationship curves. Significance is set as a two-sided *P* value < 0.05.

3. Results

The first patient has been enrolled on September 23, 2024. As of December 2024, a total of 30 participants were enrolled out of 200 who received screening. The data analysis is expected to be carried out after all patients enrolled, about in February 2025, with an approximate publication of results by May 2025.

4. Discussion

Remimazolam is a rapidly metabolized benzodiazepine and approved for procedural sedation and general anesthesia [9]. It has advantages of light respiratory depression and hemodynamic fluctuations in painless gastroscopy [10]. Therefore, it is particularly suitable for the sedation process of painless gastroscopy [11]. Oliceridine is selective to the G protein pathway, with low potency for β-arrestin recruitment, which may lead to fewer opioid-related adverse events. The combination of oliceridine and remimazolam has the potential for ideal painless sedation during gastroscopy procedures. But, there are few research reports on the use of oliceridine for painless gastroscopy. This study is designed to explore the ED_{50} and ED_{95} of oliceridine combined with remimazolam required for sedation procedures in adult patients undergoing gastroscopy.

Oliceridine has no known active metabolites, with the clinical effect in terms of analgesia seen in about 5 min and factors such as age and gender have no significant impact in terms of pharmacokinetics [4] [12]. Compared to traditional opioids, oliceridine has attracted attention for its lower adverse reactions, respiratory depression and gastrointestinal issues [13]. It is considered a promising medication for addressing the current limitations in opioid therapy. Some studies suggest that oliceridine doses of 1-3 mg are probably effective in reducing acute pain. In lower doses, it may also show a better side effects profile with lesser nausea and vomiting. But the ideal dose is still unknown. It is necessary to explore the ED_{50} and ED_{95} of oliceridine for gastroscopy sedation in clinic practice.

In the present study, the modified Dixon sequential method is used to determine the ED_{50} and ED_{95} of oliceridine since it is simple and efficient with a small sample size. Referring to the dose of remimazolam required for sedation, 0.3 mg/kg will be adopted in this study. A MOAA/S score < 2 will be used as a valid sedation score in this study. After seven crossover waves, the both positive and negative responses subjects will be analyzed. The ED_{50} and ED_{95} of oliceridine compounded with remimazolam for sedation procedures in adult patients undergoing gastroscopy will be calculated.

5. Conclusion

The ED_{50} and ED_{95} of oliceridine combined with remimazolam required for gastroscopy sedation will be detected according to the results. Positive results would provide an optimal sedation plan for painless gastroscopy in clinical practice.

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