Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Effective Dose of Oliceridine Fumarate Co-Administered with Remimazolam in Suppressing Gastroscope Insertion Responses for Adults

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Objective: To determine the 50% effective dose (ED50) and 95% effective dose (ED95) of oliceridine in suppressing gastroscope insertion responses during painless gastroscopy when combined with 0.3 mg/kg remimazolam.

Methods: This prospective study enrolled 52 patients scheduled for elective painless gastroscopy. The initial dose of oliceridine was 15 ug/kg, with sequential 1.5 ug/kg adjustments based on response. ED50 and ED95 were calculated using the modified Dixon's up-and-down method and Probit regression analysis. Vital signs, adverse events, anesthesia induction time, recovery time, and satisfaction scores (patients, anesthesiologists, and endoscopists) were recorded.

Results: When combined with 0.3 mg/kg remimazolam, the ED50 and ED95 of oliceridine for suppressing insertion responses were 12.717 ug/kg and 18.818 ug/kg, respectively. The time from drug administration to successful scope insertion was 2 (2, 3) minutes, and the recovery-to-discharge time was 21 (16.5, 22.5) minutes. Vital signs remained stable throughout the procedure, with no hypoxemia, hypotension, or arrhythmias. No anesthesia-related adverse events (eg, nausea, vomiting and dizziness) occurred. Satisfaction scores were high: 10 (10, 10) for patients, 10 (9, 10) for anesthesiologists, and 9 (8, 10) for endoscopists.

Conclusion: Oliceridine combined with 0.3 mg/kg remimazolam effectively suppresses gastroscope insertion response at ED50 and ED95 doses of 12.717 ug/kg and 18.818 ug/kg, respectively. This optimized regimen provides hemodynamic stability, rapid recovery and high procedural satisfaction, with no observed adverse events. These findings support its clinical utility as a safe and efficient anesthetic protocol for painless gastroscopy.

Trial Registration: Chinese Clinical Trial Registry (ChiCTR2400093416).

Keywords: painless gastroscopy, gastroscope insertion response, oliceridine, remimazolam, ED50, ED95, modified Dixon's sequential method

Introduction

Digestive endoscopy can facilitate early detection of digestive tract cancer.[1] Sedation-based digestive endoscopy significantly improves the comfort of patients while ensuring the successful completion of diagnosis and treatment procedures, thereby enhancing lesion detection rates.[2] In the implementation of painless procedures, respiratory complications are predominant, ranging in severity from mild drops in oxygen saturation to severe respiratory depression requiring emergency intervention. The incidence of hypoxemia during painless endoscopy has been reduced by optimizing the medication regimen of anesthetic drugs, strengthening monitoring, and optimizing oxygen delivery

Received: 11 March 2025
Accepted: 1 June 2025
Published: 10 June 2025

strategies. For instance, compared with the propofol-based sedation, remimazolam regimen significantly reduced the risk of postoperative respiratory depression (risk ratio=0.2);[3] Compared with traditional nasal catheter oxygen inhalation, the use of high flow nasal oxygen can significantly improve the respiratory safety during painless endoscopy (risk ratio=0.3).[4] Guidelines recommend a comprehensive strategy to prevent and improve hypoxemia, including adequate oxygen supply, optimizing the administration plan, selecting the drug with light respiratory inhibition, keeping the airway open and continuous monitoring.[5,6]

Oliceridine, a μ-opioid receptor agonist, is selective for the G-protein pathway and has less potency of recruitment for β-arrestin than morphine.[7,8] As activation of β-arrestin pathway is associated with adverse events such as nausea, vomiting and respiratory depression, oliceridine theoretically causes fewer side effects compared to other opioids.[9] Based on these characteristics, many scholars believe that oliceridine is expected to revolutionize the analgesic regimen of painless endoscopy.[10–12] However, the clinical evidence is limited. Two Chinese studies reported the use of oliceridine in digestive endoscopy.[13,14] Li et al[13] compared the effects of 0.02 mg/kg oliceridine and 0.1 ug/kg sufentanil when combined with 1.5 mg/kg propofol. The results indicated that the effectiveness was comparable between the groups, but lower incidences of subclinical respiratory inhibition, nausea and vomiting were observed in the oliceridine group. Jia et al[14] demonstrated that the effective dose of oliceridine to inhibit gastroscope insertion reaction had no significant difference between the elderly and adults.

Herein, we aimed to investigate the 50% effective dose (ED50) and 95% effective dose (ED95) of oliceridine in suppressing gastroscope insertion reaction when combined with remimazolam.

Methods

Ethics and Registration

The protocol of this study was reviewed and approved by the Ethics Committee of Deyang People's Hospital on 28/3/2024, with an ethics approval number of 2024–04-028-K01. This trial was registered in the Chinese Clinical Trial Registry on 04/12/2024, with a registration number of ChiCTR2400093416. All the investigators explained this study to all subjects and got written informed consent. Enrolled patients understood this study after investigators' introduction and signed written informed consent. The study group declares the whole study was performed in accordance with the Declaration of Helsinki.

Criteria for the Subjects

Inclusion criteria: (1) Patients who plan to undergo elective painless gastroscopy; (2) American Society of Anesthesiologists (ASA) status I–II; (3) 18 to 64 years; (4) body mass index (BMI) 18–27 kg/m^2.

Exclusion criteria: (1) Difficult airway (modified Mallampati grade IV); (2) Poorly controlled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg); (3) Long-term use of anticonvulsants, sedatives, analgesics, or history of alcohol or opioid abuse; (4) Mental disorders that prevent correct self-expression; (5) Allergy to drugs involved in the study or in the acute phase of asthma; (6) Known or suspected gastrointestinal obstruction; (7) Pregnancy or lactation; (8) Severe systemic diseases, such as coronary heart disease, liver cirrhosis, etc.

Case elimination: (1) Difficulties of endoscopic operation that lead to prolonged examination duration; (2) Severe complications such as hypoxemia and circulatory fluctuations that need first aid and that break the study protocol.

Study Procedure

The investigators introduced this study to eligible patients after pre-anesthesia assessment. Patients who agreed to participate in the study were enrolled. The subjects were allowed to quit at any time.

On the day of the examination, after entering the anesthesia preparation area of the endoscopy center, the patient's information was verified by the anesthesia nurse. An 18-gauge venous indwelling needle catheter was established in the right upper limb and connected to a three-way stopcock for standby access. Approximately 5–10 minutes prior to the initiation of gastroscopy, the patient was instructed to gargle with 10 g of lidocaine hydrochloride mucilage (containing 0.2 g lidocaine) while maintaining a head-tilt position. The medication of lidocaine was administered in divided doses

slowly to ensure sufficient contact time with the pharyngeal mucosa, thereby achieving effective topical anesthesia and lubrication to reduce pharyngeal reflexes induced by endoscopic stimulation. Upon entering the examination room, the tripartite verification protocol was implemented by the gastroenterologist, anesthesiologist, and endoscopy nurse.

The patient was placed in the left lateral position, with a blood pressure cuff attached to the left upper arm. Peripheral oxygen saturation (SpO_2), heart rate (HR), and non-invasive blood pressure (NIBP, with a measurement interval of 1 minute and manual measurement as needed) were monitored routinely. A mask and nasal cannula for double-lumen oxygen inhalation (6 L/min) were placed. Oliceridine was intravenously injected (initial dose 15 ug/kg, step dose 1.5 ug/kg, maximum dose 3 mg), followed by a slow intravenous injection of 0.3 mg/kg remimazolam after 30 seconds. Within 1 minute after drug administration, if the modified alertness/sedation score (MOAA/S) was ≤ 2 points, a senior endoscopist started to insert the gastroscope (Olympus GIF H290). If the patient experienced choking, hiccups, or other endoscope insertion reactions, resulting in failed insertion, propofol would be administered as a single dose of 30 mg.

If the patient's significant body movement or other reasons during the gastroscopy examination prevent the procedure from continuing, the researcher would use the rescue drug propofol to complete the operation. A single dose of 0.3 to 0.5 mg of atropine was injected intravenously to treat bradycardia (HR < 50 beats/min; 8 ug of norepinephrine was given to deal with the systolic blood pressure drops (> 30% of the baseline, or < 90 mmHg, or the mean arterial pressure (MAP) < 55 mmHg); in case of respiratory depression and airway obstruction, the jaw was lifted, and a nasopharyngeal airway, gastroscopy laryngeal mask or endotracheal intubation was placed when necessary.

After the examination, the patient was transferred to the post-anesthesia care unit (PACU) for spontaneous recovery. Vital signs were monitored until the Aldrete score ≥ 9 (including the states of consciousness, breathing, circulation, SpO□ and mobility). The discharge criteria included the Aldrete score ≥ 9 for 2 consecutive times (interval: 5 mins), and no nausea, vomiting, dizziness and other complaints.

Modified Dixon's Up-and-Down Method

The initial dose of oliceridine was 15 ug/kg and the step dose was 1.5 ug/kg. If the patient had choking cough, frowning or body movements, the case was defined as positive, indicating that the dose of oliceridine was insufficient, and the dose was increased for the next patient. Otherwise, absence of these responses was negative, triggering a one-step dose reduction for the next patient. The recruitment was stopped when 7 crossover points (positive to negative) occurred.

Outcomes

The primary outcomes are the ED50and ED95 of oliceridine to inhibit gastroscope insertion reaction when combined with 0.3 mg/kg remimazolam.

The secondary outcomes included: (1) The MAP, HR and SpO_2 of the patients at the time of entering the examination room (T0), 1 minute after drug administration (T1), the first time of endoscope insertion (T2), the first minute of gastroscopy (T3), the end of gastroscopy (T4), and at the time of discharge (T5); (2) The duration of gastroscopy, induction time of anesthesia and recovery time; (3) The occurrence of complications (such as hypoxemia, hypotension, nausea and vomiting, dizziness, etc).; (4) The satisfaction score of patients, anesthesiologists and endoscopists (with a total score of 10, the higher the score, the more satisfied with the anesthetic procedure).

Statistical Analysis

Based on the modified Dixon's sequential methodology, the study maintained patient recruitment until achieving two critical criteria: a minimum of 6 pairs demonstrating positive-to-negative transitions and a cohort size exceeding 20 participants.[15,16] This dual threshold ensures statistical validity through adequate crossover event documentation and population representation. In this study, patient recruitment was stopped when 7 crossovers occurred.

SPSS 26.0 was used for statistical analysis. Statistical significance was defined as $P < 0.05$. The measurement data of normal distribution, such as height, MAP and HR, were expressed as mean ± standard deviation ($\chi \pm s$), while nonnormal data as median (25^{th} percentile, 75^{th} percentile). Categorical indicators, such as the incidence of adverse events, were expressed as number (percentage).

Statistical evaluation of circulatory and respiratory parameters for all patients incorporated two analytical approaches: Longitudinal hemodynamic changes underwent assessment via one-way repeated measure analysis of variance with Bonferroni-adjusted post hoc comparisons for temporal variations; while comparative analysis between baseline and subsequent time points employed paired *t*-test. The ED50and ED95 of oliceridine were estimated by the Probit analysis. Comparisons between positive cases and negative cases were performed. The *t*-test was for normal data, the rank sum test for nonnormal data, and χ^2 for categorical data.

Results

The study flowchart is shown in Figure 1. When there were 7 crossover events, we recruited 52 subjects (21 males, 40.38%). The basic characteristics are shown in Table 1. All patients were taken into final analysis.

Vital Signs of the Patients at Different Time Points

The changes in vital signs of patients at different times during the study are shown in Table 2. One minute after anesthesia induction, HR and MAP were significantly decreased compared with that upon entering the examination room ($p = 0.012$, $p < 0.001$, respectively). During the insertion of gastroscope, HR increased by approximately 10.5 beats/min compared with before, with a significant difference ($p < 0.001$), while the slightly elevated blood pressure showed no significant difference compared with before ($p = 0.163$). There were no significant changes in HR and MAP during the examination process ($p > 0.05$). After the recovery from anesthesia, HR and MAP returned to the levels before the examination. SpO_2 showed no significant changes at all observation points ($p > 0.05$).

Comparisons Between the Positive and Negative Cases

There were 26 positive patients and 26 negative patients. The demographic data, including age, height, weight, BMI and ASA status were comparable between the two groups (Table 3). The dose of oliceridine, and satisfaction score of the anesthesiologists and endoscopists were significantly lower in positive cases (12 (10.5, 13.5) vs 13.5 (12, 15), $p = 0.005$; 9 (8, 10) vs 10 (10, 10), $p < 0.001$; 9 (8, 9) vs 10 (10, 10), $p < 0.001$; respectively) (Table 3). The induction time of positive patients was significantly longer

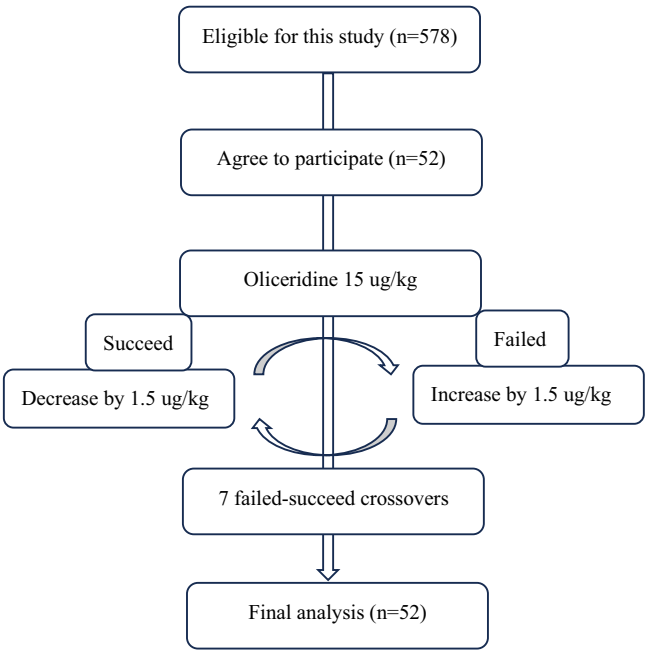

Figure 1 Flowchart of this study. When there were 7 crossover events, 578 patients were assessed for eligibility, and 450 of them met the criteria. Finally, 52 subjects agreed to participate our study.

Table 1 Demographic Characteristics of the Subjects

	Male (n=21)	Female (n=31)	Total (n=52)
Age, years	49.62±10.40	51.42±7.75	50.69±8.86
Height, cm	169.33±5.40	156.42±4.13	161.63±7.90
Weight, kg	67.26±9.23	54.99±8.15	59.95±10.46
BMI, kg/m^2	23.41±2.63	22.45±3.00	22.84±2.87
ASA status			
I, n	4	5	9
II, n	17	26	43
Hypertension, n	2	4	6
Other comorbidity, n	0	0	0

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2 Changes in Vital Signs During the Study

Time	SpO_2, %	HR, beats/min	MAP, mmHg
T0	100 (99, 100)	79.04±10.79	96.31±10.60
T1	100 (100, 100)	74.27±9.98*	86.73±10.35*
T2	100 (100, 100)	84.71±10.83*#	88.94±12.04*
T3	100 (100, 100)	79.23±11.32#	85.50±11.22*
T4	100 (100, 100)	80.27±9.98#	85.37±8.39*
T5	100 (99, 100)	78.56±9.32#	93.75±9.39#

Notes: T0: Entering the examination room; T1: 1 minute after anesthesia induction; T2: At the first insertion of gastroscope; T3: The first minute of gastroscopy operation; T4: At the end of gastroscopy operation; T5: At the time of leaving the hospital. *: Significantly different from T0 ($p < 0.05$); #: Significantly different from T1 ($p < 0.05$).
Abbreviations: HR, heart rate; MAP, mean arterial pressure.

Table 3 Comparison Between the Positive and Negative Cases

	Positive (n=26)	Negative (n=26)	*p*
Age, years	49.46±8.85	51.92±8.88	0.322
Height, cm	161.46±7.25	161.81±8.64	0.876
Weight, kg	60.00±10.35	59.89±10.77	0.971
BMI, kg/m^2	22.90±2.75	22.78±3.03	0.882
ASA status			
I, n	5	4	0.714
II, n	21	22	
Oliceridine, ug/kg	12 (10.5, 13.5)	13.5 (12, 15)	0.005
Induction time, min	3 (2, 3)	2 (2, 2)	0.001
Endoscopy time, min	3 (2, 3)	3 (2, 3)	0.437
Recovery time, min	21 (16.75, 22.25)	21 (16.75, 23)	0.978
Patients' satisfaction	10 (10, 10)	10 (10, 10)	1
Anesthesiologists' satisfaction	9 (8, 10)	10 (10, 10)	<0.001
Endoscopists' satisfaction	9 (8, 9)	10 (10, 10)	<0.001

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

than that of negative ones (3 (2, 3) vs 2 (2, 2), $p = 0.001$) (Table 3). However, the recovery time and patients' satisfaction score were not significantly different (21 (16.75, 22.25) vs 21 (16.75, 23), $p = 0.978$; 10 (10, 10) vs 10 (10, 10), $p = 1$; respectively) (Table 3).

ED50 and ED95 of Oliceridine

The up-and down chart of oliceridine is shown in Figure 2, with 26 cases of positive and negative reactions respectively. According to the SPSS Probit analysis, the model equation is: Probit (p) = −3.429 + 0.27x; The result of Pearson's chi-squared goodness-of-fit test: $\chi 2 = 8.484$, $p = 0.132$, indicating a good model fit. When combined with 0.3 mg/kg of remimazolam, the ED50 of oliceridine for inhibiting the endoscope insertion response is 12.717 ug/kg, and the ED95 is 18.818 ug/kg. The dose-effect relationship curve is shown in Figure 3.

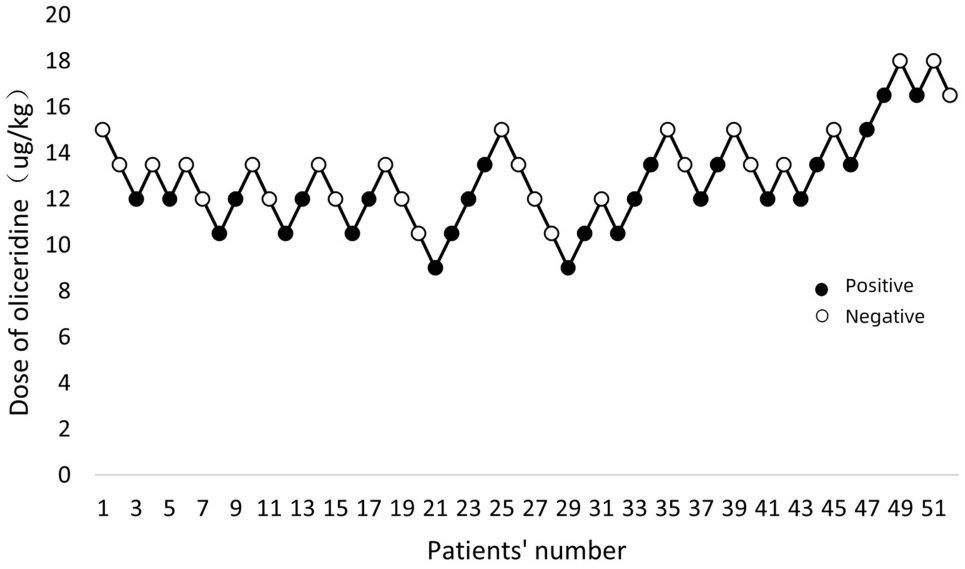

Figure 2 The sequential response of the 52 patients to gastroscope insertion with the modified Dixon's up-and-down method. The black dot represents "positive", referring to the current dose is insufficient to inhibit inserting response. The white dot represents "negative", indicating the current dose is sufficient to inhibit insertion response.

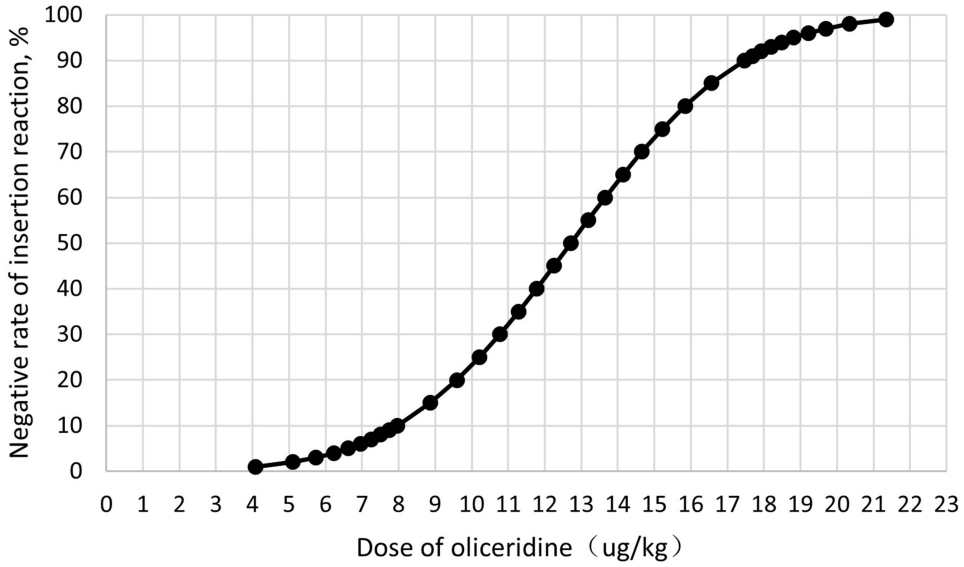

Figure 3 Dose-response curve for oliceridine according to the Probit analysis.

Safety and Adverse Events

All patients successfully completed the study. No patient had hypoxemia, hypotension, bradycardia or other kinds of cardiocerebral events during the study procedure. Postoperative adverse events, such as nausea, vomiting, agitation, dizziness and confusion, were also not observed.

Discussion

In the present study, we investigated the use of oliceridine combined with remimazolam for gastroscopy. Our results show its safety of the investigated doses and the effectiveness of proper doses. By the modified Dixon's up-and-down method, the Probit analysis estimated that the ED50 and ED95 of oliceridine to inhibit gastroscope insertion response were 12.717 ug/kg and 18.818 ug/kg respectively.

When performing painless gastroscopy, adequate sedation depth is necessary to provide good operating conditions for endoscopists, especially during gastroscope insertion. However, drug-related adverse effects, such as hypotension, hypoxia and bradycardia, increase the difficulty of intraoperative management and the risk to patients. This contradiction necessitates the use of anesthetics with fewer side effects.

Remimazolam is a short-acting intravenous benzodiazepine with rapid onset, fast metabolism (not dependent on organs), no significant accumulation of active metabolite, quick recovery, good pharmacological reversibility, and few side effects (hypotension, hypoxia, injection pain, etc).[17,18] Since its coming on the market, a large number of clinical trials have been conducted to investigate its clinical use. For upper gastrointestinal endoscopy, a phase IIb randomized trial demonstrated that a single dose of 0.1–0.2 mg/kg of remimazolam was well tolerated and effective.[19] A Phase III trial indicated that 5 mg remimazolam was non-inferior to 1.5 mg/kg propofol in terms of sedation success rate (97.34% vs 100%).[20] However, the time to achieve adequate sedation with remimazolam was prolonged by about 50 seconds compared with propofol).[20] In addition, we found in daily practice that choking during gastroscope insertion was common when 0.2mg/kg remimazolam was used. Therefore, in our previous study, we used 0.2–0.3 mg/kg remimazolam for gastrointestinal endoscopy and demonstrated no significant increase in cardiopulmonary suppression.[21] In the present study, the dose of remimazolam was set at 0.3 mg/kg.

All 52 patients included in this study completed the trial without any dropout due to severe drug-related complications, indicating that the combination of 0.3 mg/kg remimazolam and 9–18 ug/kg oliceridine for painless gastroscopy anesthesia is highly safe. Secondly, the vital signs of the patients did not change significantly during the anesthesia process, and no hypotension caused by cardiovascular system inhibition or hypoxemia caused by respiratory system inhibition was observed. One minute after anesthesia induction, the MAP decreased significantly compared with that upon entering the room (86.73 ± 10.35 vs 96.31 ± 10.60 mmHg), but this decrease was not clinically significant. A large sample study involving over 30,000 non-cardiac surgery patients observed the impact of MAP less than 55–75 mmHg on postoperative acute kidney injury and myocardial infarction.[22] The results indicated that intraoperative MAP less than 55 mmHg was a risk factor for postoperative acute kidney injury and myocardial infarction, and the risk ratio increased significantly with the prolongation of hypotension.[22] Numerous large sample studies have shown that intraoperative MAP < 60–70 mmHg is associated with acute kidney injury, myocardial injury, myocardial infarction, and death.[23–26] Therefore, the international organization PeriOperative Quality Initiative (POQI) released the latest guidelines in 2024, recommending maintaining intraoperative MAP above 60–70 mmHg, especially for high-risk populations.[27] In this study, the mean of MAP at each observation time point was greater than 85 mmHg, and no cases of hypotension were observed. In terms of respiration, the respiratory depression effects of remimazolam and oliceridine are relatively weak.[28,29] In this study, the SpO_2 of the patients fluctuated between 94% and 100%, and no hypoxemia occurred. Regarding adverse reactions during the recovery period, nausea, vomiting, drowsiness, and dizziness are relatively common.[21,30] However, no such adverse reactions were observed in this study. These results support the use of co-administration of remimazolam and oliceridine for painless gastroscopy anesthesia.

In this study, the novel opioid oliceridine was used to inhibit the gastroscope insertion reaction. Through the modified Dixon sequential method, when combined with 0.3 mg/kg remimazolam, the ED50 of oliceridine is estimated to be 12.717 ug/kg and the ED95 is 18.818 ug/kg. Jia et al[14] first explored the ED50 of oliceridine combined with 1.5mg/kg

propofol in inhibiting the insertion reaction in patients of different age groups (18–65 years group and >65 years group). The results showed that the ED50 of the adult group was 15 ug/kg and that of the elderly group was 12 ug/kg, but there was no statistical difference.[14] In the present study, our research population was between 18 and 65 years old, and the sedative drug was 0.3mg/kg remimazolam. The ED50 of oliceridine was slightly smaller than 15 ug/kg. This may be explained by the different types and doses of sedatives. Zhu et al[31] conducted a multicenter study comparing the anesthetic effects of remimazolam and propofol for painless gastroscopy, and the results showed that the successful induction rate of 0.2 mg/kg remimazolam was not inferior to that of 1.5 mg/kg propofol. Therefore, the anesthesia intensity of 0.3 mg/kg remimazolam is higher than that of 1.5 mg/kg propofol. Thus, the analgesic requirement decreased accordingly. Li et al[13] compared the anesthetic effects of 20 ug/kg oliceridine and 0.1ug/kg sufentanil when combined with 1.5 mg/kg propofol in painless gastroscopy. Their findings support the advantages of oliceridine, such as safety, effectiveness and rapid recovery.[13]

Similar to other studies using the modified Dixon's up-and-down methodology, this study has some limitations. Firstly, the ED50 and ED95 of oliceridine obtained in this study are derived under the premise of using 0.3 mg/kg remimazolam as the compound. Therefore, changing the type of sedative or its dosage would likely yield divergent ED50 and ED95. Secondly, this study lacked a control group, and thus it was impossible to determine which dosage is better. These limitations inherently stem from the research purpose and methodology of this study. In the future, we will conduct randomized controlled trials to provide more evidence to support the role of oliceridine in painless gastroscopy.

Conclusion

In summary, co-administration of remimazolam and oliceridine is viable for gastroscopy. Combining 12.717 or 18.818 ug/kg oliceridine with 0.3 mg/kg remimazolam demonstrates effective attenuation of the gastroscope insertion reaction in 50% or 95% of adult patients with limited adverse events. Further studies should confirm the advantages of oliceridine in endoscopy through randomized controlled trials.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics Statement

This study was reviewed and approved by the Ethics Committee of Deyang People's Hospital. The patients provided their written informed consent before being enrolled into this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Funding

This study is funded by the Wu Jieping Foundation (Grant number: 320.6750.2024-05-55).

Disclosure

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflicts of interest.

References

1. Xin L, Gao Y, Cheng Z, et al. Utilization and quality assessment of digestive endoscopy in China: results from 5-year consecutive nationwide surveys. *Chin Med J*. 2022;135(16):2003–2010. doi:10.1097/CM9.0000000000002366
2. Qiu L, Yao L, Hu P, et al. Analysis of the detection rate and clinical characteristics of early gastric cancer by painless gastroscopy and ordinary gastroscopy. *Medicine*. 2024;103(18):e38120. doi:10.1097/MD.0000000000038120
3. Zhao MJ, Hu H-F, Li X-L, et al. The safety and efficacy between remimazolam and propofol in intravenous anesthesia of endoscopy operation: a systematic review and meta-analysis. *Int J Surg*. 2023;109(11):3566–3577. doi:10.1097/JS9.0000000000000638
4. Gu WJ, Wang H-T, Huang J, et al. High flow nasal oxygen versus conventional oxygen therapy in gastrointestinal endoscopy with conscious sedation: systematic review and meta-analysis with trial sequential analysis. *Dig Endosc*. 2022;34(6):1136–1146. doi:10.1111/den.14315

5. Gotoda T, Akamatsu T, Abe S, et al. Guidelines for sedation in gastroenterological endoscopy (second edition). *Dig Endosc*. 2021;33(1):21–53. doi:10.1111/den.13882
6. Sidhu R, Turnbull D, Haboubi H, et al. British society of gastroenterology guidelines on sedation in gastrointestinal endoscopy. *Gut*. 2024;73(2):219–245. doi:10.1136/gutjnl-2023-330396
7. Markham A. Oliceridine: first approval. *Drugs*. 2020;80(16):1739–1744. doi:10.1007/s40265-020-01414-9
8. Manglik A, Lin H, Aryal DK, et al. Structure-based discovery of opioid analgesics with reduced side effects. *Nature*. 2016;537(7619):185–190. doi:10.1038/nature19112
9. Faouzi A, Varga BR, Majumdar S. Biased opioid ligands. *Molecules*. 2020;25(18):4257. doi:10.3390/molecules25184257
10. Goudra B, Singh PM. Oliceridine and its potential to revolutionize GI endoscopy sedation. *Saudi J Anaesth*. 2020;14(3):349–354. doi:10.4103/sja.SJA_813_19
11. Finlay JE, Leslie K. Sedation/analgesia techniques for nonoperating room anesthesia: new drugs and devices. *Curr Opin Anaesthesiol*. 2021;34(6):678–682. doi:10.1097/ACO.0000000000001057
12. Lee JM, Park Y, Park JM, et al. New sedatives and analgesic drugs for gastrointestinal endoscopic procedures. *Clin Endosc*. 2022;55(5):581–587.
13. Ge Li YG, Liu W, Liu S, Guo Y, Xihua L. Efficiency of the application of oliceridine or sufentanil in painless gastroscopy. *J Clin Anesthesiol*. 2024;40(12):1259–1263.
14. Jia Jia GL, Zhang B, Zhang J, Zhang W. Effect of age factor on potency of oliceridine in inhibiting responses to gastroscopic implantation when combined with propofol. *Chin J Anesthesiol*. 2024;44(12):1456–1459.
15. Pace NL, Stylianou MP, Warltier DC. Advances in and limitations of up-and-down methodology: a précis of clinical use, study design, and dose estimation in anesthesia research. *Anesthesiology*. 2007;107(1):144–152. doi:10.1097/01.anes.0000267514.42592.2a
16. Görges M, Zhou G, Brant R, et al. Sequential allocation trial design in anesthesia: an introduction to methods, modeling, and clinical applications. *Paediatr Anaesth*. 2017;27(3):240–247. doi:10.1111/pan.13088
17. Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent. *Front Pharmacol*. 2021;12:690875.
18. Kilpatrick GJ, McIntyre MS, Cox RF, et al. CNS 7056: a novel ultra-short-acting Benzodiazepine. *Anesthesiology*. 2007;107(1):60–66.
19. Borkett KM, Riff DS, Schwartz HI, et al. A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. *Anesth Analg*. 2015;120(4):771–780. doi:10.1213/ANE.0000000000000548
20. Chen S-H, Yuan T-M, Zhang J, et al. Remimazolam tosilate in upper gastrointestinal endoscopy: a multicenter, randomized, non-inferiority, phase III trial. *J Gastroenterol Hepatol*. 2021;36(2):474–481. doi:10.1111/jgh.15188
21. Zhou R, Fu L, Liu S, et al. Influences of propofol, ciprofol and remimazolam on dreaming during anesthesia for gastrointestinal endoscopy: a randomized double-blind parallel-design trial. *Drug Des Devel Ther*. 2024;18:1907–1915. doi:10.2147/DDDT.S455915
22. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology*. 2013;119(3):507–515. doi:10.1097/ALN.0b013e3182a10e26
23. Ahuja S, Mascha EJ, Yang D, et al. Associations of intraoperative radial arterial systolic, diastolic, mean, and pulse pressures with myocardial and acute kidney injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology*. 2020;132(2):291–306. doi:10.1097/ALN.0000000000003048
24. Mathis MR, Naik BI, Freundlich RE, et al. Preoperative risk and the association between hypotension and postoperative acute kidney injury. *Anesthesiology*. 2020;132(3):461–475. doi:10.1097/ALN.0000000000003063
25. Roshanov PS, Sheth T, Duceppe E, et al. Relationship between perioperative hypotension and perioperative cardiovascular events in patients with coronary artery disease undergoing major noncardiac surgery. *Anesthesiology*. 2019;130(5):756–766. doi:10.1097/ALN.0000000000002654
26. Hallqvist L, Granath F, Fored M, et al. Intraoperative hypotension and myocardial infarction development among high-risk patients undergoing noncardiac surgery: a nested case-control study. *Anesth Analg*. 2021;133(1):6–15. doi:10.1213/ANE.0000000000005391
27. Saugel B, Fletcher N, Gan TJ, et al. PeriOperative quality initiative (POQI) international consensus statement on perioperative arterial pressure management. *Br J Anaesth*. 2024;133(2):264–276.
28. Barbosa EC, Espírito Santo PA, Baraldo S, et al. Remimazolam versus propofol for sedation in gastrointestinal endoscopic procedures: a systematic review and meta-analysis. *Br J Anaesth*. 2024;132(6):1219–1229. doi:10.1016/j.bja.2024.02.005
29. Simons P, van der Schrier R, van Lemmen M, et al. Respiratory effects of biased ligand oliceridine in older volunteers: a pharmacokinetic-pharmacodynamic comparison with morphine. *Anesthesiology*. 2023;138(3):249–263. doi:10.1097/ALN.0000000000004473
30. Amornyotin S. Sedation-related complications in gastrointestinal endoscopy. *World J Gastrointest Endosc*. 2013;5(11):527–533. doi:10.4253/wjge.v5.i11.527
31. Zhu H, Su Z, Zhou H, et al. Remimazolam dosing for gastroscopy: a randomized noninferiority trial. *Anesthesiology*. 2024;140(3):409–416. doi:10.1097/ALN.0000000000000485