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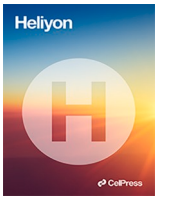

Research article

The efficacy and safety of remimazolam tosilate compared with propofol for endoscopic retrograde cholangiopancreatography under monitored anesthesia care: A single-center randomized controlled clinical trial

Biyun Zhou, Shiyong Li, Ailin Luo, Hongbo Zheng *

Department of Anesthesiology and Pain Medicine, Hubei Key Laboratory of Geriatric Anesthesia and Perioperative Brain Health, and Wuhan Clinical Research Center for Geriatric Anesthesia, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

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ABSTRACT

Background: Although remimazolam tosilate is an ultra-short-acting benzodiazepine that causes less respiratory and circulatory depression than propofol, studies evaluating its efficacy and safety during endoscopic retrograde cholangiopancreatography (ERCP) are limited. This study aimed to compare the efficacy and safety of remimazolam and propofol for ERCP performed under monitored anesthesia care (MAC).

Methods: This study is a randomized controlled clinical trial featuring a noninferiority design. A total of 102 eligible patients undergoing ERCP under MAC were randomly assigned to either the remimazolam tosilate group (R group) or the propofol group (P group) in a 1:1 ratio. Patients in the R group were sedated with remimazolam tosilate, while those in the P group received propofol, both under MAC. The primary efficacy endpoint was the success rate of ERCP completion under MAC. Secondary outcomes included the time to loss of consciousness, sedative effects, and perioperative adverse events at various time points for patients in both groups.

Results: Baseline characteristics of both groups were similar. The successful completion rate for ERCP under MAC was 100 % in the R group and 96.1 % in the P group, resulting in a difference of 3.92 % (95 % CI: −2%, 10 %). This difference met the pre-established criterion of being greater than −8%. The total number of norepinephrine infusions, as well as the incidence of intravenous injection pain, post-induction hypotension, post-induction bradycardia, intraoperative hypotension, respiratory depression, and hypoxemia, were significantly lower in the R group compared to the P group. Conversely, the total number of phloroglucinol uses, body movements, and instances of rapid gastrointestinal peristalsis were significantly higher in the R group than in the P group.

Discussion: Remimazolam-based MAC for ERCP exhibited non-inferior efficacy compared to propofol-based MAC, while also resulting in fewer circulatory and respiratory adverse events during the procedures. Nevertheless, future studies with larger sample sizes are required to evaluate the utility of remimazolam in elderly patients.

* Corresponding author.
E-mail address: zheng1283@163.com (H. Zheng).

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1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is considered the gold standard diagnostic technique for pancreaticobiliary diseases, and an advanced technique for treating pancreatic and biliary diseases [1,2]. Due to the complexity of ERCP, lengthy surgical procedure, patient discomfort, and positioning challenges, an effective and safe anesthesia sedation method is warranted. Monitored anesthesia care (MAC) or general anesthesia with tracheal intubation are prevalent anesthesia techniques for ERCP. While propofol-based MAC is the preferred anesthesia method for ERCP in many countries, injection pain, hypotension, and dose-related respiratory depression are major concerns. Adverse events related to conscious sedation are more commonly observed in elderly patients with comorbidities [3]. With advancements in medical care and an expansion of the indications for ERCP, there has been a corresponding rise in the difficulty, complexity, and duration of these procedures. Given that a significant proportion of ERCP patients are elderly, anesthesiologists must consider not only age-related declines in functional reserve but also the presence of impaired liver function and multiple comorbidities. Therefore, it is paramount to establish an optimal anesthesia technique to prevent respiratory depression or hypotension [3,4]; however, the ideal sedative agent and anesthetic protocol for ERCP remain uncertain.

Remimazolam is a novel ultra-short-acting γ-aminobutyric acid receptor agonist with pharmacodynamics similar to that of midazolam [5,6]. Previous studies have shown that remimazolam possesses a high safety profile with organ-independent metabolism, minimal impact on respiratory and circulatory systems [5,6]. Multiple studies have demonstrated that remimazolam offers significantly greater hemodynamic stability and a lower incidence of respiratory complications compared to propofol during both the induction and maintenance phases of anesthesia in patients undergoing non-cardiac surgery [7,8]. Additionally, in gastrointestinal endoscopies, remimazolam has shown non-inferiority to propofol regarding successful sedation while also exhibiting a lower rate of adverse events [9]. Furthermore, unlike propofol, the sedative effects of remimazolam can be rapidly reversed by the specific antagonist flumazenil [8,10], thus adding an extra layer of safety to clinical applications. Nevertheless, despite these findings, the definitive advantages of remimazolam for ERCP under MAC remain inadequately supported by evidence.

To address the current limitations of anesthesia and sedation during ERCP, we conducted a randomized controlled trial comparing the efficacy and safety of remimazolam and propofol under MAC for ERCP. Our hypothesis was that the success rate of ERCP completion with remimazolam under MAC is not inferior to that of propofol.

2. Methods

2.1. Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (2022-S072) and registered at www.chictr.org.cn (ChiCTR2100044502). Written informed consent was obtained from all patients before enrollment and they agreed to postoperative follow-up.

2.2. Patients

The inclusion criteria were as follows: American Society of Anesthesiologists (ASA) Class I–III, adult patients who underwent ERCP under MAC, and the operation time between 30 min and 4 h. The exclusion criteria were as follows: Allergic or contraindicated to contrast agents, remimazolam, propofol and other drugs; body mass index (BMI) $\geq$ 27 kg/m^2; patients with cardiac insufficiency (EF $<$ 48 %) or severe obstructive ventilatory dysfunction; pregnant or lactating women; patients with mental disorders or a history of epilepsy; and patients with known or potentially difficult airways (Mallampati $\geq$ III) or high risk of regurgitation and aspiration.

2.3. Randomization and intervention

In total, 102 patients were included and allocated into R and P groups using randomly numbered opaque envelopes in 1:1 ratio. Patients were blinded to allocation. Furthermore, due to the distinct color difference between remimazolam and propofol, the anesthesiologist opened the envelope before administering anesthesia to know the grouping plan of each patient. All endoscopists had over 7 years of experience in endoscopy and operated under the supervision of the chief physician.

2.4. Preoperative preparation and medication

The patients underwent routine fasting for 8 h, no water for 4 h. Patients with duodenal obstruction and gastric retention underwent fasting for more than 12 h prior to the procedure. The venous channel was opened after entering the ERCP operating room and the electrocardiogram, heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), and bispectral index (BIS) were continuously monitored. The default frequency for the blood pressure cuff inflation is every 3 min. However, if the patient exhibits hypotension, monitoring shifts to manual continuous observation. Once blood pressure returns to the normal range, the measurement frequency is restored to every 3 min.

Upon entering the room, the patient ingested 10 ml of Dyclonine Hydrochloride Mucilage orally to alleviate throat discomfort and reduce the foam present in the cavity. The patients were positioned in a prone posture, with appropriate elevation of their right shoulders and the head tilted to the right. Oxygen at a rate of 4 L/min was administered through a mask for inhalation. The anesthesiologist inserted a suppository containing 50 mg of diclofenac sodium into the rectum of the patients before administering

anesthesia to decrease postoperative inflammation and pain. Five minutes prior to anesthesia, 0.01 mg/kg of penehyclidine hydrochloride (half dose for patients ≥65 years) and 0.1 mg/kg of dexamethasone sodium phosphate were administered by the anesthesiologist. After fluoroscopic localization, dental pads were placed, and 0.02 mg/kg of butorphanol tartrate was slowly administered.

2.5. Perioperative management

Patients in the remimazolam group received a slow administration of 0.2–0.4 mg/kg of remimazolam using an intravenous pump at a rate of 0.2–0.4 mg/kg/h to maintain the Ramsay sedation score of 5–6. Patients in the propofol group received a slow administration of 1–2.5 mg/kg of propofol using an intravenous pump at a rate of 2–4 mg/kg/h to maintain the Ramsay sedation scale score of 5–6. Patients in both groups were intravenously administered remifentanil hydrochloride at a constant rate of 0.3 μg/kg/h.

The depth of anesthesia was determined using the Ramsay sedation scale score, RR, BIS, and the body movements of patients. Based on literature reports and the expert consensus on sedation/anesthesia for the treatment of digestive endoscopy in China [6,11,12], we set the Ramsay sedation score between 5 and 6, BIS between 50 and 70, and RR between 10 and 18 breaths.

When BIS was ≤50 or RR was ≤9 breaths, the anesthetic drug was decreased by 10 % of the original dosage. When BIS was ≥70 or the patients exhibited somatic movements, an additional 3–6 mg of intravenous remimazolam in the R group or 20–50 mg of intravenous propofol in the P group was administered, and the pumping rate was increased by 10 %.

At the conclusion of the ERCP procedure, sedative medications were discontinued, and the patient was closely monitored until regaining consciousness from anesthesia. Subsequently, the patient exited the ERCP operating room and was transferred to the post-anesthesia care unit (PACU). Delirium was assessed using the 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM, Supplementary Table S1) at 30 min after awakening from anesthesia, as well as on the 1st and 3rd days following surgery [13].

2.6. Prevention and treatment of common intraoperative adverse events

For patients with bradycardia (HR < 50 beats per min), 0.3–0.5 mg of atropine sulfate was administered. In the case of hypoxemia (SpO_2 < 90 %) or respiratory depression, the position of the body and the face mask ventilation were appropriately adjusted [14,15]. Further, a nasopharyngeal airway was placed if the improvement was not distinct, and the pumping rate of anesthesia drugs was adjusted during the same time. Patients with hypotension (MAP <65 mmHg or 30 % reduction in baseline) were administered with methoxyamine hydrochloride or ephedrine hydrochloride more than three times based on their condition and then switched to noradrenaline bitartrate tartrate for intravenous pumping [14,15].

2.7. Outcome measures

In this non-inferiority trial, the primary outcome was to compare the successful completion rate of ERCP performed under MAC between the two groups. The secondary efficacy evaluation assessed the time to loss of consciousness (LoC) from the initiation of drug administration, defined as the first Ramsay sedation scale score of ≥4. Additionally, the evaluation included the sedative effects, satisfaction levels of both patients and endoscopists, rates of intraoperative cardiovascular and respiratory adverse events, and the incidence of postoperative anesthesia-related complications.

2.8. Sample size

We performed a non-inferiority test to evaluate the successful completion rate for ERCP between the two groups. The predefined non-inferiority margin was set at −8% [4,15]. The sample size was calculated using the Power Analysis and Sample Size (PASS) 15.0.5 software [4,15]. Previous studies have reported that the success rate of sedation with remimazolam is 96.93 % and the success rate of sedation with propofol is 99.99 % [17,18]. Therefore, a sample size of 42 patients per group was used to calculate the two-sided type I error rate of 5 % ($\alpha = 0.05$) and 80 % power ($\beta = 0.1$). Considering the potential ineligibility and dropout of patients due to any reason, the total sample size was increased to 102 by 15 %.

2.9. Statistical analysis

Statistical analyses were performed using the SPSS25.0 software. The results are expressed as mean ± SD. Student's *t*-test was performed to determine the differential analysis between the two groups. One-way analysis of variance (ANOVA) was performed to compare multiple groups [15,17,18]. The Mann-Whitney *U* test was employed to compare continuous secondary outcomes, following the verification of the normality assumption using the Shapiro-Wilk test [4,16,17]. Pearson's Chi-square test or Fisher's exact probability test was performed to compare the counting data [15]. A *P*-value of <0.05 was considered statistically significant.

The primary outcome was analyzed using the Full-analysis set (FAS) population, which included all patients undergoing designated pharmacologic interventions and ERCP procedures. Secondary outcomes related to recovery from anesthesia and the incidence of delirium were also assessed using the FAS population; all other secondary outcomes were evaluated in the FAS population comprising all randomized patients. Patients who completed ERCP surgery under MAC were analyzed using the Safety-analysis set (SS) population, while those who completed ERCP surgery under MAC within a specified time frame were analyzed using the Per-Protocol (PP) population [16,17].

3. Results

3.1. Patient demographics and baseline characteristics

From June 2022 to May 2023, a total of 102 patients were screened for eligibility, and all 102 were randomized (n = 51 per group) (Fig. 1). Two patients in the propofol group transitioned from monitored anesthesia care (MAC) to general anesthesia with tracheal intubation and were subsequently excluded from the Safety analysis set (SS) analysis. Additionally, six patients (three from the remimazolam group and three from the propofol group) did not meet the inclusion criteria due to operation time and were excluded from the Per-protocol (PP) analysis. No statistically significant differences were observed between the two groups. Patient demographics and baseline characteristics are presented in Table 1.

3.2. Efficacy outcome

In the FAS analysis, a total of 102 patients were enrolled, achieving a successful completion rate for ERCP of 100 %. The 95 % confidence interval (CI) for the difference between the two groups ranged from −4% to 4 %. In the SS analysis, 100 patients were enrolled; the successful completion rate for ERCP under MAC in the R group was 100 %, while in the P group, it was 96.1 %, resulting in a difference of 3.92 % (95 % CI: −2%, 10 %). These findings met the pre-established criteria of > −8%, confirming the non-inferiority of anesthesia/sedation induced by remimazolam compared to propofol (Table 2).

3.3. Exploratory secondary outcomes

In the FAS analysis, the propofol group demonstrated a significantly shorter time to loss of consciousness, a lower breathing rate, and smaller BIS values compared to the remimazolam group ($P < 0.001$). However, there were no significant variances in terms of the Ramsay sedation scale score, recovery time, and post-anesthesia care unit (PACU) time between the two groups ($P > 0.05$, Table 3)

There were no significant differences between the two groups in terms of bronchospasm, body movements of patients, reflux, or aspiration, and a recovery time of >15 min, Postoperative adverse events, and satisfaction of both patients and endoscopists ($P > 0.05$, Table 4).

In comparison to the propofol group, the remimazolam group exhibited significantly lower incidences of respiratory depression, hypoxemia, injection pain, post-induction hypotension, post-induction bradycardia, and intraoperative hypotension. Furthermore, the remimazolam group required norepinephrine infusion less frequently ($P < 0.05$, Table 4). Additionally, the total number of phloroglucinol uses, body movements, and rapid gastrointestinal peristalsis was significantly higher in the remimazolam group compared to the propofol group ($P < 0.05$, Table 4). The total number of phloroglucinol uses, body movements, and instances of rapid

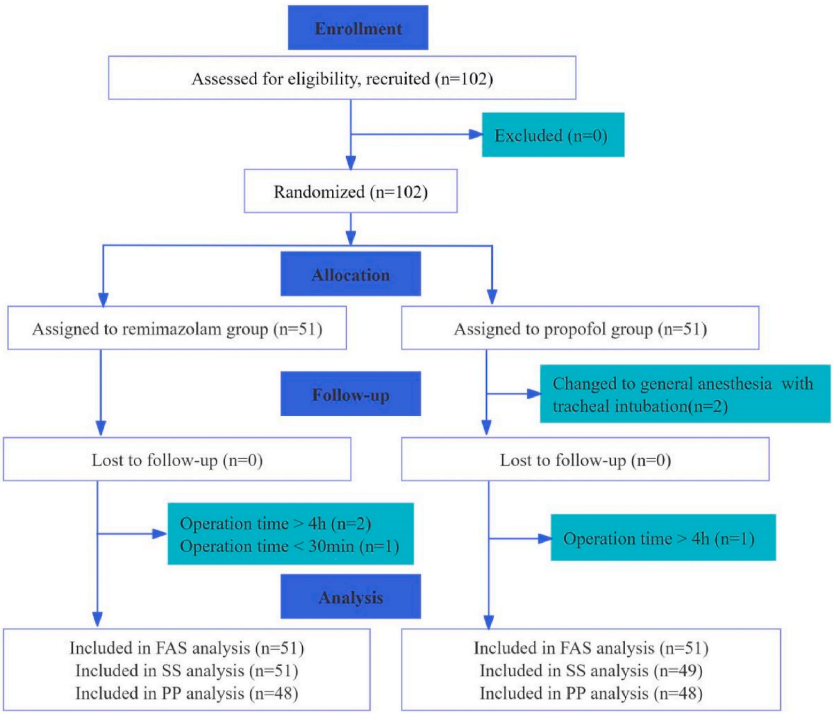

Fig. 1. Patient flowchart with CONSORT guidelines. FAS, Full analysis set; SS, Safety analysis set; PP, Per Protocol.

Table 1
Demographics and baseline characteristics of patients (Full analysis set).

Parameter	R group (n = 51)	P group (n = 51)	*P* value
Age (years)	61.24 ± 12.15	59.98 ± 12.36	0.606
≥70 years old, n (%)	15 (29.4 %)	16 (31.4 %)	1.000
Gender (male/female)	23/28	26/25	0.692
Weight (kg)	59.95 ± 11.86	59.14 ± 9.81	0.705
BMI (kg/m^2)	22.06 ± 3.03	21.73 ± 2.68	0.567
ASA I-II/III, (n)	25/26	27/24	0.843
Types of special diseases, n (%)			
Obstructive jaundice	10 (19.6 %)	11 (21.6 %)	1.000
Choledocholithiasis	14 (27.5 %)	15 (29.4 %)	1.000
Bile duct stenosis after liver transplantation	7 (13.7 %)	9 (17.6 %)	0.786
Medical comorbidities, n (%)			
Hypertension	21 (41.2 %)	23 (45.1 %)	0.842
Diabetes	10 (19.6 %)	12 (23.5 %)	0.810
CHD	11 (21.6 %)	13 (25.5 %)	0.815
COPD	5 (9.8 %)	7 (13.7 %)	0.759
Operation time (min)	75.45 ± 34.06	76.98 ± 33.32	0.819
Anesthesia duration (min)	82.76 ± 34.71	79.16 ± 27.31	0.561

Variables presented as mean ± SD, or number of patients n (%).
CHD: Coronary heart disease; COPD:Chronic obstructive pulmonary disease.

Table 2
Difference of efficacy outcome between the two groups.

Variable	R group	P group	Remimazolam vs Propofol Difference in rates (95%CI)
The successful completion rate for ERCP, Full analysis set	51 (100 %)	51 (100 %)	0.0 % (−4%–4 %)
The successful completion rate for ERCP under MAC, Safety analysis set	51 (100 %)	49 (96.1 %)	3.92 % (−2%–10 %)

Variables presented as number of patients n (%); CI, confidence interval.

Table 3
Comparison of sedative effects between the two groups (Full analysis set).

Variable	R group (n = 51)	P group (n = 51)	*P* value
Time to loss of consciousness (S)	19.08 ± 4.24	14.25 ± 3.96	<0.001
Ramsay Sedation Scale score ≥4			
T1 (Endoscopic procedure initiation)			
Ramsay Sedation Scale score	5.274 ± 0.45	5.177 ± 0.39	0.240
RR	15.09 ± 2.32	12.61 ± 2.02	<0.001
BIS	61.08 ± 5.28	53.47 ± 6.36	<0.001
T2 (During surgery)			
Ramsay Sedation Scale score	5.13 ± 0.35	5.08 ± 0.48	0.482
RR	17.12 ± 7.19	12.41 ± 2.06	<0.001
BIS	57.76 ± 5.30	54.39 ± 4.73	<0.001
T3 (Placement of stents or nasobiliary tubes)			
Ramsay Sedation Scale score	5.88 ± 0.33	5.76 ± 0.43	0.122
RR	15.61 ± 3.09	11.71 ± 1.33	<0.001
BIS	63.35 ± 5.39	57.73 ± 4.83	<0.001
Recovery time (min)	7.31 ± 4.38	6.55 ± 4.06	0.362
PACU time (min)	10.86 ± 4.06	10.68 ± 4.38	0.833

Variables presented as mean ± SD, or number of patients n (%).

gastrointestinal peristalsis were significantly higher in the remimazolam group compared to the propofol group ($P < 0.05$, Table 4). However, the statistical analysis of major events, including baseline characteristics, the incidence of respiratory depression, hypotension, and postoperative complications, demonstrated consistent results in both the FAS and PP populations (Supplementary Tables S2–4).

The Kaplan-Meier curves and log-rank test indicated that the cumulative incidence of mean arterial pressure (MAP) falling below 65 mmHg was significantly lower in the remimazolam group compared to the propofol group ($P < 0.001$, Fig. 2). Furthermore, in patients experiencing intraoperative hypotension, both the total number of norepinephrine infusions and the norepinephrine dose were significantly reduced in the remimazolam group relative to the propofol group ($P < 0.05$, Table 4; Fig. 3).

Table 4
Exploratory secondary outcomes between the two groups (Full analysis set).

Variable	R group (n = 51)	P group (n = 51)	*P* value
Induction of anesthesia			
Injection pain	1 (2.0 %)	30 (58.8 %)	<0.001
Post-induction hypotension	7 (13.7 %)	27 (52.9 %)	<0.001
Post-induction bradycardia	4 (7.8 %)	18 (35.3 %)	0.001
Respiratory-related adverse events			
The mask pressurizes oxygen	4 (7.8 %)	13 (25.5 %)	0.031
Obstruction by the tongue	3 (5.9 %)	12 (23.5 %)	0.023
Hypoxemia	3 (5.9 %)	13 (25.5 %)	0.012
Bronchospasm	1 (2.0 %)	6 (11.8 %)	0.112
Insert nasopharyngeal airway	2 (3.9 %)	11 (21.6 %)	0.015
During surgery			
Intraoperative hypotension	12 (23.5 %)	32 (62.7 %)	<0.001
Total number of norepinephrine infusion	11 (21.6 %)	32 (62.7 %)	<0.001
Norepinephrine dose (μg/kg)	0.59 ± 1.37	2.34 ± 2.56	<0.001
Patients'body movements	15 (29.4 %)	5 (9.8 %)	0.023
Rapid gastrointestinal peristalsis	8 (15.7 %)	1 (2.0 %)	0.031
Total number of phloroglucinola uses	8 (15.7 %)	1 (2.0 %)	0.031
Intraoperative bradycardia	7 (13.7 %)	17 (33.3 %)	0.034
Reflux or aspiration	1 (2.0 %)	3 (5.9 %)	0.617
Recovery time >15 min	5 (9.8 %)	4 (7.8 %)	1.000
Post-operative complications			
Delirium	5 (9.8 %)	4 (7.8 %)	1.000
Pulmonary infection	2 (3.9 %)	3 (5.9 %)	1.000
PONV	5 (9.8 %)	4 (7.8 %)	1.000
Dizziness or headache	3 (5.9 %)	2 (3.9 %)	1.000
Satisfaction			
Patients' satisfaction	50 (98.0 %)	48 (94.1 %)	0.617
Endoscopists' satisfaction	47 (92.2 %)	48 (94.1 %)	1.000

Variables presented as mean ± SD, or number of patients n (%).

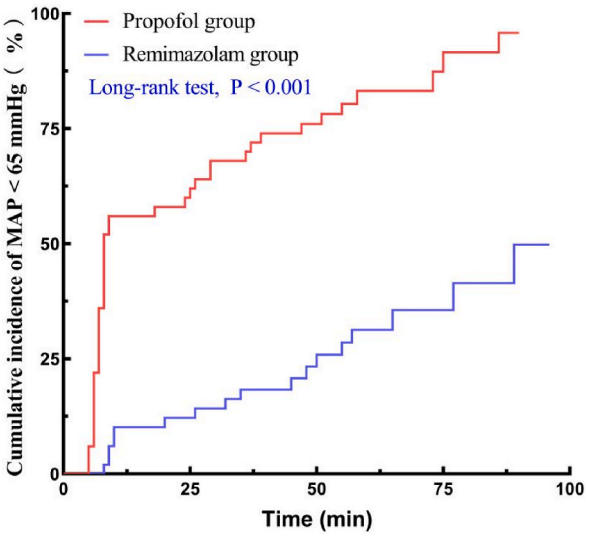

Fig. 2. The Kaplan-Meier curves comparing the cumulative incidence of MAP of <65 mmHg during the study period between the Remimazolam group (blue) and the Propofol group (red). MAP, mean arterial pressure. Note: This analysis considers only the initial occurrence of hypotensive events for each patient, despite the possibility of multiple hypotensive episodes occurring per patient.

4. Discussion

Given the special position of ERCP and the necessity to monitor patients at a distance (radiation area), the selection of anesthetic medication regimen plays a crucial role. Azimaraghi O et al. reported that MAC is the preferred anesthesia plan for ERCP [3,18–22]. In this study, we compared the efficacy and safety of remimazolam and propofol as sedatives for ERCP under MAC. Remimazolam exhibited a sedative and anesthetic effect similar to propofol. Our findings indicate that using remimazolam-based MAC for ERCP may demonstrate equal or potentially superior efficacy propofol, along with a better safety profile. The incidence of sedation-related

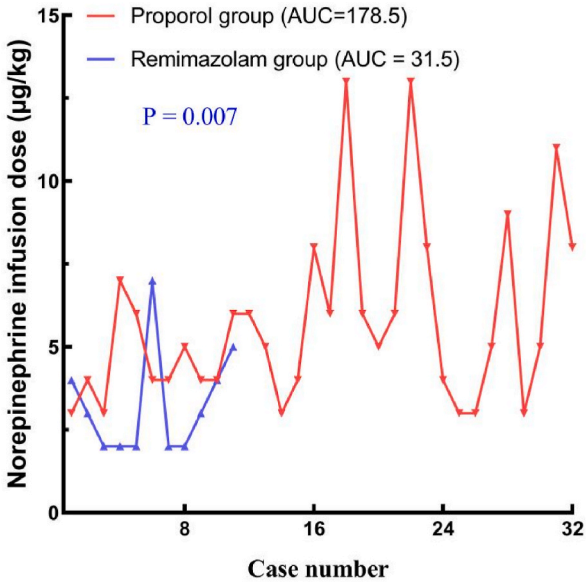

Fig. 3. Norepinephrine infusion in patients with intraoperative hypotension between the Remimazolam group (blue) and the Propofol group (red).

adverse events was significantly lower in the remimazolam group compared with the propofol group, particularly concerning injection pain, hypoxemia, and cardiovascular and respiratory complications. While propofol has the benefit of a significantly shorter onset time compared to remimazolam, this difference does not hold additional clinical significance for ERCP.

The most common cardiovascular events in the R and P groups were intravenous injection pain (2.0 % vs 58.8 %), post-induction hypotension (13.7 % vs 52.9 %), post-induction bradycardia (7.8 % vs 35.3 %), intraoperative hypotension (23.5 % vs 62.7 %), and intraoperative bradycardia (13.7 % vs 33.3 %), with significant differences. Intravenous injection pain was the primary and most prevalent adverse reaction to propofol, impacting patient comfort and heightening surgery and anesthesia fears. Previous studies have indicated that injection pain can be nearly prevented by applying a slight tourniquet, followed by the administration of intravenous lidocaine prior to the initial dose of propofol, or by combining propofol with etomidate [23]. Post-induction hypotension is one of the most prevalent side effects of anesthesia induction [4,7,24,25]. In this study, the incidence of post-induction hypotension in elderly patients (≥70 years old) diagnosed with obstructive jaundice in the P group was notably high at 90.9 %, significantly surpassing the 37.5 % reported in previous studies [24–27]. Therefore, the use of propofol induction should be avoided in elderly patients with obstructive jaundice. In such cases, etomidate is recommended as a suitable alternative, as it has been demonstrated to be effective in preventing hypotension [24,27,28]. Intraoperative hypotension is associated with organ injury and adverse outcomes, including myocardial infarction, cerebral infarction, delirium, and myocardial injury [24,29]. Consistent with the findings of the present study, prior studies have reported superior hemodynamic stability and a lower hypotension risk with the use of remimazolam compared to propofol [4,7,23–29]. The incidence of hypotension requiring vasoactive drugs reached 62.7 % and 21.6 % in the two groups, likely due to a higher proportion of patients with advanced age (≥70 years, 29.4 % vs 31.4 %), obstructive jaundice (19.6 % vs 21.6 %), and choledocholithiasis (27.5 % vs 29.4 %). Furthermore, the higher incidence of post-anesthesia hypotension in these patients may be associated with age-related decreased compensatory mechanisms of various organs, prolonged water fasting, abnormal liver and kidney function, disturbed metabolism of electrolytes, hypoalbuminemia, and elevated bilirubin [30].

Compared to the P group, we also noted that remimazolam decreases the incidence of respiratory depression and hypoxemia; exerts a milder impact on RR; lower the need for airway interventions like mask ventilation and nasopharyngeal airway insertion; and decreases the frequency of the anesthesiologists entered into the radiation area. In this study, two patients in the P group underwent mask-assisted ventilation, but correcting hypoxemia by inserting the nasopharyngeal airway proved challenging. As a result, they received general anesthesia *via* tracheal intubation to successfully complete ERCP. Respiratory depression and hypoxemia can occur during ERCP due to several reasons. For instance, when the patient is in a prone position and the neck is crouching, the duodenoscope can obstruct the oropharynx or cause tracheal compression during the ERCP procedure. Furthermore, obesity and age are independently associated with hypoxemia because ventilation and perfusion do not match with the increase in age or BMI [5]. To ensure patient safety, we utilized the Ramsay Sedation Score and BIS to monitor anesthesia depth, in addition to RR monitoring. Monitoring of RR can compensate for the lack of accurate assessment of the depth of anesthesia under MAC and can rapidly reflect the occurrence of respiratory obstruction, respiratory depression, or tracheal spasm [31,32]. Additionally, the central sedative effect of remimazolam can be antagonized using the benzodiazepine receptor antagonist flumazenil [18], which helps prevent serious adverse events due to the overdose or accumulation of remimazolam and is an important line of defense to ensure patient safety.

In comparison to prior research, our study corroborates the findings of Yang et al. that remimazolam has a less inhibitory effect on intestinal peristalsis than propofol, resulting in a higher incidence of rapid gastrointestinal peristalsis [33]. These findings may be linked to the sedation level and specific pharmacological properties of remimazolam, which could impact intestinal nerve reflexes and

neurotransmitter transmission related to intestinal motility, resulting in reduced suppression of gastric motility and gastrin secretion [33,34]. Additionally, the administration of antibiotics or remimazolam and opioid anesthetics during surgery can cause dysregulation and affect intestinal movement, increasing the frequency of gastrointestinal peristalsis [35,36]. In this study, a total of nine cases were identified—eight in the remimazolam group and one in the propofol group—that exhibited rapid gastrointestinal peristalsis, which interfered with the endoscopist's procedure. To reduce the frequency of gastrointestinal motility, we administered a small intravenous dose of remifentanil and phloroglucinol, ultimately achieving the desired outcome and enhancing the visibility of the surgical field. Studies have demonstrated that the frequency of gastrointestinal peristalsis can be slowed or even inhibited through various methods, including deepening anesthesia, and the administration of remimazolam, phloroglucinol, atropine, glucagon, or a small dose of remifentanil [33,34]. However, rapid gastrointestinal peristalsis is not entirely detrimental; it can contribute to the swift recovery of intestinal function and facilitate the elimination of carbon dioxide from the intestinal lumen during the postoperative period, thereby helping to prevent the occurrence of postoperative hypercarbia, abdominal distension, and abdominal pain [37].

In this study, postoperative complications were documented for the both groups. Delirium stands out as a common issue after surgery in elderly patients [38,39]. It indicates susceptibility to reduced brain reserves and reflects cognitive decline [39]. Intraoperative benzodiazepines are considered an independent risk factor for postoperative delirium [37–39]. Multiple prospective randomized controlled clinical trials have demonstrated that the use of remimazolam in older patients undergoing surgery does not result in a higher incidence of postoperative delirium compared to propofol [38–41]. Our study yielded similar results; after a three-day postoperative observation period, the incidence of postoperative delirium was comparable between the two groups, with no significant difference observed (9.8 % vs. 7.8 %). The demographic data of nine patients with postoperative delirium were analyzed, mainly in the elderly (100 %), obstructive jaundice (7/9, 77.8 %), or bile duct multiple stones (2/9, 22.2 %). The reason for this may be attributed to the higher prevalence of underlying diseases among older patients, anesthetic medications, preoperative liver dysfunction, hypoxemia and vasoactive drug use, and extended duration of the procedure [13,38–41].

While propofol can cause dose-related complications, such as respiratory depression and hypotension, its significance in ERCP cannot be underestimated. Herein, we report that both remimazolam and propofol can be safely and effectively utilized as anesthetics for patients undergoing ERCP without medical comorbidity, sufficient preoperative preparation, and manageable operation time. At the same time, remimazolam offers the advantage of expanding the sedation options for ERCP under MAC and is particularly beneficial for elderly patients with propofol allergies, high respiratory and cardiovascular risks, obstructive jaundice, and multiple complex calculi in the common bile duct.

The present study has some limitations that should be addressed. Firstly, we monitored the depth of anesthesia using the Ramsay sedation scale, RR, and BIS, but we cannot definitively state that the depth of anesthesia was consistently optimal throughout the procedure. Secondly, our study only included patients who underwent ERCP under MAC, with a limited sample size and a single-center trial, thus excluding certain patient populations. A larger sample size is necessary to validate the results of this study. Moreover, our focus was primarily on the clinical effects of the drug, without testing hematological indexes or conducting relevant pharmacokinetic evaluations. Additionally, due to a high proportion of patients with preoperative liver dysfunction and chronic pancreatitis, intraoperative and postoperative blood indices were not collected for analysis, potentially leading to biased results. Furthermore, due to the positioning of the anesthesiologist away from the radiation area during ERCP, and the observation of vital signs through lead glass in the operating room, the drug pumping speed could not be adjusted in real-time based on RR and BIS.

5. Conclusion

Remimazolam-based MAC sedation for patients undergoing ERCP demonstrates comparable efficacy, stable hemodynamic, reduced venous pain, and a superior safety profile compared to propofol. These findings suggest that remimazolam may serve as a viable alternative to propofol for elderly patients undergoing ERCP. Further research should focus on the application of remimazolam for ERCP under MAC in a larger cohort of elderly patients, as well as in multicenter trials.

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Clinical trials registration

Chinese Clinical Trial Registry, ChiCTR2100044502.

Data availability statement

Data included in article/supp. If additional datasets from this study are required, they can be obtained from the corresponding author upon reasonable request *via* email at zheng1283@163.com.

CRediT authorship contribution statement

Biyun Zhou: Writing – review & editing, Writing – original draft, Data curation. **Shiyong Li:** Writing – review & editing, Writing –

original draft, Data curation. **Ailin Luo:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Hongbo Zheng:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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