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Research Article

Determining the 90% Effective Dose of Remimazolam Inhibiting Responses to Upper Gastrointestinal Endoscopy Insertion in Adults: A Double-Blind Study Utilizing a Biased Coin Up-and-Down Sequential Method

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Background. Remimazolam, a benzodiazepine sedative with clinical advantages, is used for anesthesia during GI endoscopy. However, the accurate clinical dosage remains understudied. This study aims to investigate the 90% effective dose (ED90) of remimazolam in inhibiting responses to upper GI endoscopy insertion and evaluate its efficacy and safety for upper GI endoscopic diagnosis and treatment. *Methods*. A total of 54 adult patients undergoing upper GI endoscopy under procedural sedation were included, and they were anesthetized with an intravenous bolus of remimazolam. The first patient was given a dose of 0.3 mg/kg of remimazolam and was next randomized according to a biased coin design (BCD) method, and each patient received a dose of remimazolam depending on the response of the previous patient. A positive reaction was defined as no choking cough, nausea and vomiting, and/or motor response during placement of the upper GI endoscope into pharyngeal cavity or within 3 minutes after placement; otherwise, it was a negative reaction. If positive, randomize the next patient's dose of remimazolam to be unchanged or decrease by 0.05 mg/kg. If negative, increase the next patient's dose of remimazolam by 0.05 mg/kg. According to the study protocol, at least 45 patients with positive reactions were needed to suspend the trial while monitoring anesthesia-related adverse events. *Results*. The ED90 of remimazolam for upper gastrointestinal endoscopy insertion was 0.556 mg/kg (95% CI: 0.399–0.578). All patients maintained stable circulation and no serious adverse events were observed during sedation. Patient satisfaction was 4.89 ± 0.69 points, anesthesiologist satisfaction was 4.57 ± 0.96 points, and endoscopist satisfaction was 4.67 ± 0.87 points (full score 5 points, minimum 1 point). *Conclusion*. The use of remimazolam for upper gastrointestinal endoscopy was safe and effective, with a single intravenous bolus at an ED90 dose of 0.556 mg/kg inhibiting responses to the procedure.

1. Introduction

Upper gastrointestinal (GI) endoscopy may elicit varying degrees of discomfort in patients, with some experiencing intolerance to the procedure [1–3]. Currently, sedation for GI endoscopy procedures typically involves midazolam or propofol. While propofol is favored in clinical practice due to its rapid onset and short half-life, it still poses safety concerns [4–6]. Substantial clinical studies have shown that adverse reactions, including injection site pain, cardiovascular and respiratory depression, as well as the potential for aspiration pneumonia and hypoxia, remain significant [7, 8]. As for midazolam, although with the advantages of rapid onset, anterograde amnesia, and no injection pain, its half-life is around 1.8 to 6.4 hours, and its metabolites have some sedative effect, ultimately producing a sedative effect for a relatively long time, leading to delayed resuscitation and high incidence of respiratory depression [9–11]. The

proximity of upper gastrointestinal endoscopy to the respiratory tract may increase the likelihood of respiratory-related adverse events during sedation [12, 13].

Remimazolam is a novel benzodiazepine with rapid onset, short duration of action and recovery time, no accumulation, metabolism independent of hepatic and renal function, inactive metabolites, and reduced risk for respiratory and circulatory depression. [4, 14–21]. Remimazolam is more suitable for short surgeries and contributes to rapid patient recovery due to its metabolism by organ-independent tissue esterases into inactive metabolites and reversibility with flumazenil [16, 20, 22].

The aim of this study was to assess the effectiveness and safety of intravenous remimazolam in painlessly diagnosing and treating upper gastrointestinal endoscopy insertion among adults by determining its ED90.

2. Materials and Methods

2.1. Study Population. The present study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhejiang University and Shulan Hospital. In addition, it was registered at clinicaltrials.gov (ID: ChiCTR2200062535). Prior to undergoing gastroscopy, all patients provided informed consent.

A total of 54 patients were treated with upper GI endoscopy under sedation in the Shulan Hospital from January 2022 to August 2022. The inclusion criteria were as follows: (1) male and female aged 18 to 65 years; (2) American Society of Anesthesiologists (ASA) I-II; (3) body mass index (BMI) 20 to 25 kg/m^2; (4) no language disorder; and (5) able to cooperate well with examinations. Patients were excluded if (1) they had chronic pain with long-term use of analgesics, psychiatric drugs (e.g., opioids, NSAIDS, sedatives, antidepressants); (2) they were addicted to alcohol; (3) they had history of abnormal surgical anesthesia recovery; (4) they had history of hypertension and systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg; (5) they had chronic lung disease and SPO2 < 95%; (6) they had history of central nervous system diseases; (7) they used sedative drugs within 24 hours before surgery; (8) there was expected difficult airway, allergy, or contraindications to related anesthetic drugs; (9) emergency examination; (10) they were pregnant or parturient; (11) there was clinical or imaging evidence of gastric obstruction, intestinal anatomical changes, high risk of bleeding, or unstable circulation; and (12) they participated in other clinical studies within 3 months.

2.2. Procedure. All patients started fasting and liquid fasting at 8 hours and 3 hours before the surgery, and preoperative medication was not applied. After admission, the patient received continuous ECG, blood pressure monitoring of the right upper limb, and pulse oxygen saturation monitoring of left index finger. Venous access to the left upper limb was opened with a continuous drip of 0.9% sodium chloride injection at 5-6 ml/kg/h. After oral administration of lidocaine gel, the patient was placed in the left lateral decubitus position. The patient was given oxygen inhalation via nasal catheter at 3 L/min, and relevant emergency drugs and equipment were prepared.

Induction started after the first blood pressure measurement. A preset dose of 30 ml of remimazolam was slowly injected intravenously by an experienced anesthesiologist to complete the injection within 30 to 40 seconds. Anesthesiologists evaluated the anesthetic effect and observed the adverse reactions. Gastroscopic procedures were initiated by a senior gastroenterologist when the patient's modified observer's assessment of alert/sedation (MOAA/S) score was ≤3. The patient's body movement response during upper GI endoscopic placement was observed and recorded.

Vital signs such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse oxygen saturation (SpO2), and respiratory rate (RR) (impedance pneumography) were monitored every 5 minutes throughout the process. In addition, circulatory and respiratory parameters were observed and recorded before induction (T0), after induction (T1), at the time of upper GI endoscopy insertion (T2), and at the time of endoscope withdrawal (T3). The presence of movement or other anesthesia-related complications was also recorded.

After the operation, the patient was admitted to the postanesthesia care unit (PACU). The full-time anesthesia nurse observed and recorded the patient's vital signs as well as MOAA/S score, pain score, nausea, vomiting, dizziness, gait, and other conditions, and scored the patient, anesthesiologist, and operating physician's satisfaction. The criteria for PACU discharge was an Aldret score of 10, and the moment of discharge was observed and recorded. During postoperative follow-up, each patient was followed up by telephone by the same nurse at 24 hour after discharge.

Remedial measures: If there were physical activity reactions during the upper GI endoscopy placement that affected the examination, it was judged as anesthesia failure. Remedial sedation with remimazolam was performed at a rescue dose of 0.05 mg/kg. An endoscopic operation was performed and evaluated after 1 minute of observation. If adequate sedation could not be achieved with three additional remimazolam, an intravenous injection of propofol medium/long chain fat emulsion (1-2 mg/kg) was given for rescue to complete the examination.

2.3. Clinical Outcomes and Safety Assessments. The primary outcome was the successful insertion of the upper endoscope into the cardia. Secondary outcomes were body movement, respiratory depression (i.e., RR < 10 beats/min), hypoxemia (i.e., SpO2 < 90%), hiccups, hypotension (i.e., a reduction of 20% in the baseline systolic pressure), hypertension, and arrhythmia.

During anesthesia, symptomatic treatment should be performed when there are adverse reactions such as hypotension, hypoxia, and arrhythmia. When hypotension occurred, it was corrected by rapid infusion of 0.9% sodium chloride injection in 200 ml; if failed, appropriate vasoactive drugs were given according to the situation, such as

ephedrine 6 mg or phenylephrine 40 μg intravenous bolus. When bradycardia (HR < 50 beats/min) occurred, atropine injection 0.5 mg intravenous injection was given. When hypoxemia or respiratory depression occurred, oxygen flow increased, the jaw was supported, and endoscopic operation suspended while giving mask pressurized oxygen if necessary.

This study used a blind design. The dose of remimazolam for each patient receiving deep sedation/anesthesia was prepared by a specialist and handed to the anesthesiologist who performed the anesthesia. The anesthesiologist, patient, surgeon, and follow-up nurse all did not know the actual dose of remimazolam. Positive reaction was defined as no choking cough, nausea and vomiting, and/or motor response during placement of the upper GI endoscope into the pharyngeal cavity or within 3 minutes after placement, representing successful anesthesia; otherwise, it was a negative reaction, that is, failed anesthesia. Anesthesia results were determined and recorded by the anesthesiologist performing the anesthetic procedure.

To determine the ED90, a minimum of 45 positive responses were necessary [23]. Therefore, we prospectively enrolled patients until 45 successful sedations were achieved and opened a set of 44 sealed envelopes containing random concentration assignments for these successful sedations. According to biased coin up-and-down (BCUD), when the patient was successfully placed endoscopically, the latter patient received the allocation of the dose of remimazolam for deep sedation/anesthesia by biased coin randomization (target probability $\Gamma = 0.9$), and the random number was generated by the R software. The next patient had a probability of $b = (1\text{-}\Gamma)/\Gamma = 0.11$ to reduce the dose of remimazolam by one unit (0.05 mg/kg), and a probability of 1-b = 0.89 to remain unchanged. After a patient with a positive response opened cards labeled with −1 or 0 (obtained by biased coin randomization, with 0 indicating that the dose of remimazolam used in the next patient was unchanged, and −1 indicating that the dose was reduced by 0.05 mg/kg) in 44 envelopes sequentially until 45 patients had positive responses, the study was terminated.

2.4. Statistical Analysis. Continuous variables were expressed as the mean ± standard deviation (SD) or median and interquartile range (IQR) for normally distributed and non-normally distributed ones, separately. Categorical variables were described as frequencies and percentages. Repeated-measures data analysis of variance was used for comparison of measurement data at different time points.

Numerical differences between groups were assessed by the *t*-test. Pooled adjacent violators algorithm (PAVA) of isotonic regression was used to obtain the adjusted positive rate. PAVA had three estimated values $\widehat{\mu}_1$, $\widehat{\mu}_2$, and $\widehat{\mu}_3$, among which linear interpolation $\widehat{\mu}_3$ was more accurate than the other two [27]. The rules were as follows: if $\Gamma \le p_1^*$, then $\widehat{\mu}_3 = x_1^*$; if $p_1^* < \Gamma \le p_K^*$, then $\widehat{\mu}_1 = \max_{x_k \in \Omega_x}(x_k\colon p_k^* \le \Gamma)$, $\widehat{\mu}_2 = (x_k\colon |p_k^* - \Gamma| \longrightarrow \min, x_k \in \Omega_x)$, $\widehat{\mu}_3 = (\Gamma - p_k^*)/(p_{k+1}^* - p_k^*)(x_{k+1} - \widehat{\mu}_1) + \widehat{\mu}_1$; if $\Gamma > p_K^*$, then $\widehat{\mu}_3 = x_K^*$. The R software was used to calculate $\widehat{\mu}_3$ estimation. 95% confidence interval (CI) of $\widehat{\mu}_3$ was calculated from bootstrap samples after repeating 2000 times.

The above statistical analyses were conducted using SPSS, Version 26.0 and R software, Version 4.0.3, and figures were plotted using GraphPad prism 8.

3. Results

3.1. Patient Characteristics. A total of 54 patients were included in this study. The mean age was 41.4 years, and there were 20 (37%) females. 74.1% and 25.9% patients had ASA I and II, separately. There were 38.9% patients undertaking simple gastroscopy and 61.1% patients undergoing GI endoscopy (see Table 1 for details).

3.2. Procedure Characteristics. The BCUD sequence of remimazolam dose was shown in Figure 1, and ED90 was 0.556 mg/kg with a 95% CI of 0.399–0.578 mg/kg. Table 2 displays the positive response of all patients to each actual dose of remimazolam, as well as the adjusted positive response by PAVA.

Table 3 summarized anesthesia-related adverse reactions. All 54 patients completed the endoscopic procedure, of which 53 completed the follow-up. 7 patients experienced hypotension, 1 patient experienced bradycardia, 13 patients experienced hiccups, and none experienced respiratory depression or hypoxia.

3.3. Anesthesia Satisfaction. A total of 53 satisfaction surveys were completed by patients, as well as anesthesiologist and endoscopist, and the score ranged from 1 to 5. The overall patient satisfaction score was 4.89 ± 0.69, the anesthesiologist satisfaction score was 4.57 ± 0.96, and the endoscopist satisfaction score was 4.67 ± 0.87. In addition, there were 4 cases with anesthesia satisfaction less than 4 points, of which 3 patients had anesthesia failure (i.e., negative reactions) because of the BCUD method in this study (see Table 4 for details).

3.4. Anesthesia Recovery. There were 21 (38.9%) patients undertaking simple gastroscopy and 33 (61.1%) patients undertaking GI endoscopy. The recovery time of all patients was within 30 minutes (Table 5).

3.5. Circulatory and Respiratory during Anesthesia. There were 4 important observation time points: before induction (T0), after induction (T1), at the time of upper GI endoscopy insertion (T2), and at the time of endoscope withdrawal (T3). Changes in SBP at each observation time point were shown in Figure 2, with a mild decrease in blood pressure after induction. Repeated measures data analysis of variance at different time points suggested a significant difference in SBP between T1/T2/T3 and T0 ($P < 0.05$), but no significant difference among T1, T2, and T3. The changes in HR at each observation time point are shown in Figure 3. HR increased after induction, but the mean HR at each time point was within the normal range. The results of repeated

Table 1: Patient characteristics.

Items	Values
Gender, female	20 (37%)
Age, years	41.4 ± 10.2
Height, cm	163.6 ± 8.5
Weight, kg	58.3 ± 9.4
BMI, kg/m^2	21.8 ± 3.3
ASA grade	
I	40 (74.1%)
II	14 (25.9%)
Surgery type	
Gastroscopy	21 (38.9%)
GI endoscopy	33 (61.1%)

Note. BMI = body mass index; ASA = American Society of Anesthesiologists.

measures analysis of variance showed that there was no statistical difference in the changes in heart rate at each time point. The changes in RR at each observation time point was shown in Figure 4. There was no significant change in RR during the whole diagnosis and treatment process, as well as at each time point.

4. Discussion

Remimazolam selectively has a high affinity for GABAAR without obvious selectivity for receptor subtypes or off-target activity. It triggers chloride ion influx after binding to receptors, leading to hyperpolarization of the nerve cell membrane and thus inhibiting neuronal activity, which finally results in sedation, anterograde amnesia, and anticonvulsant effects [24]. As a metabolite of remimazolam, CNS7054 inherits the same properties but with an approximately 300-400-fold decrease in affinity to the receptor and is therefore considered inactive [25]. Recent studies have demonstrated that Remimazolam is noninferior to propofol for sedation during upper gastrointestinal procedures [26, 27].

Currently, there is no precise recommended dosage for the administration of remimazolam in upper gastrointestinal endoscopic anesthesia. To date, only a few clinical studies have utilized the Dixon-Mood up-down sequential method (DM-UDM) to determine the ED50 of remimazolam for inhibiting various surgical stimuli. Simply extrapolating ED50 calculated by DM-UDM will have a large error, so statisticians always recommend BCD to obtain a higher quantile of ED [28]. Current studies prefer the estimates from the nonparametric PAVA in combination with Efron's bootstrapping procedure in order to provide standard errors and CIs for more reliable statistical performance [28]. Based on the package program developed by R statistical software, the PAVA algorithm can be implemented to solve isotonic regression and more comprehensive positive sequence optimization problems.

The results of isotonic regression in this study have demonstrated that the ED90 of remimazolam for inhibiting body movements during upper GI endoscopy insertion is 0.556 mg/kg, with a 95% CI ranging from 0.399 to 0.578 mg/kg. These findings shed light on the accurate selection and application of remimazolam dosage in clinical practice. In this study, BCD randomization resulted in 45 positive (successful anesthesia) and 9 negative (failed anesthesia) reactions. The average number of remimazolam additions in failure cases was 1.56 (95% CI 1.15–1.96), all of which completed the upper GI endoscopic sedation requirements within three additional times, indicating that remimazolam is a safe and effective option for implementing endoscopic sedation procedures. Nonetheless, the BCD method facilitates direct determination of the minimum effective dose at any quantile, thereby prompting further investigation into clinically significant ED95 and ED99 with a larger sample size.

In this study, the only statistically significant difference observed among all circulatory and respiratory parameters at each time point was in the change of the blood pressure after induction. A total of 7 patients (13%) had mild hypotension, which was improved after rapid fluid replacement in 6 patients and improved by intravenous injection of neosynephrine in 1 patient. Bradycardia occurred in 1 patient, which was relieved after intravenous injection of 0.5 mg atropine. It is noteworthy that no instances of severe hypoxemia or respiratory depression were observed in this study, indicating a superior safety profile associated with the use of remimazolam anesthesia alone. Furthermore, there were no adverse events reported such as injection pain, postoperative nausea and vomiting, or dizziness-all of which are indicative of the high level of comfort afforded by remimazolam despite the relatively small sample size.

In this study, 14 patients (25.9%) had hiccups during endoscopic anesthesia for diagnosis and treatment. Hiccup occurrence is mainly associated with upper GI procedures, but prospective studies have shown that compared with nonsedation upper GI endoscopy, sedation (e.g., midazolam) is strongly linked to an increased incidence of hiccups [29]. In addition, patients diagnosed with esophagitis were more likely to have hiccups when undergoing sedative endoscopy, but such patients were not included in this study. Clinically, most hiccups are benign and self-limiting with acute onset, and usually cease within minutes [30]. Nevertheless, sudden hiccups may become a potential safety hazard during endoscopic procedures under sedation. Despite Thompson's review did not have sufficient evidence to conclude that any specific drug-induced drug-related hiccups existed, glucocorticoids and benzodiazepines were the most common suspect drugs for drug-induced hiccups [31, 32]. The mechanism of benzodiazepine-induced hiccups remains unclear; One possible explanation for the occurrence of hiccups as a result of midazolam administration is its influence on the supraspinal mechanism [33]. Another factor contributing to hiccups caused by midazolam may be direct stimulation of the inspiratory muscles, particularly diaphragmatic contraction [29]. In contrast, Fujii et al. conducted an animal study and stated that midazolam reduced the contractility of the diaphragm in a dose-dependent manner [34]. Furthermore, intravenous midazolam has been used successfully in patients with advanced hiccups [35]. The discrepancy between these results

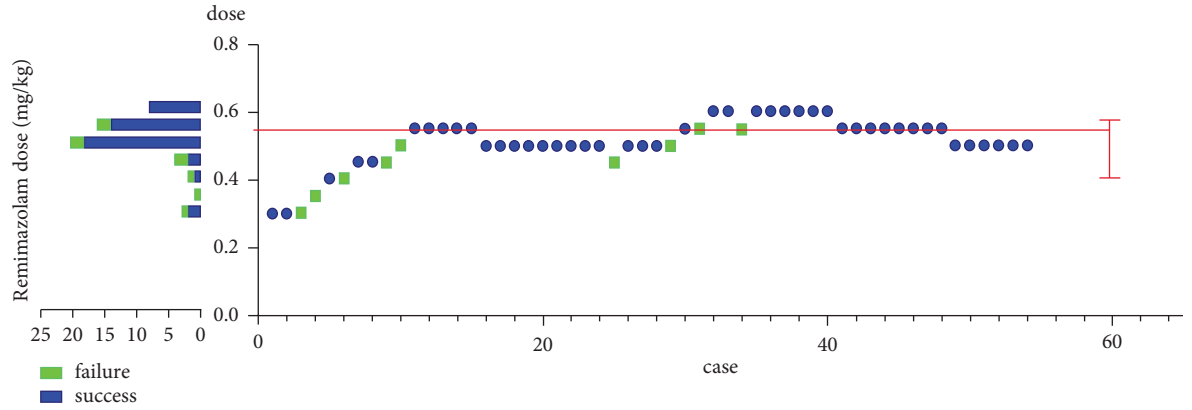

Figure 1: The right side of ordinate showed the complete BCUD sequential data. The green dots ((●)) indicated a negative reaction (anesthesia failure), while the blue dots ((●)) indicated a positive reaction (anesthesia success). The red line ((━)) indicated the estimated value of ED90 and its 95% CI. The right side of the ordinate showed that sample size could concentrate around the target concentration when using BCUD. Thus, even the study with a small sample could effectively obtain the ED90 estimation.

Table 2: True positive rate of different doses of remimazolam and adjusted positive rate after isotonic regression.

Remimazolam dose (mg/kg)	Number of successfully placed endoscopes (*n*)	Total cases (*n*)	True positive rate	Adjusted positive rate
0.30	2	3	0.667	0.333
0.35	0	1	0.000	0.333
0.40	1	2	0.500	0.500
0.45	2	4	0.500	0.500
0.50	17	20	0.900	0.888
0.55	14	16	0.875	0.888
0.60	8	8	1.000	1.000

Table 3: Anesthesia-related complications.

Adverse reactions	*n*
Hypotension	7 (13.0%)
Anoxia	0
Respiratory depression	0
Injection pain	0
Hiccup	13 (24.1%)
Nausea and vomiting	0
Bradycardia	1 (1.9%)
Other: postoperative leg twitching for 18 minutes	1 (1.9%)

Table 4: Anesthesia satisfaction score.

Anesthesia satisfaction score (points)	Patient (*n*)	Anesthesiologist (*n*)	Endoscopist (*n*)
5	52	41	45
4	1	8	4
3	0	2	4
2	0	2	0
1	0	0	0

may reflect the complex etiology of hiccups, and further clinical studies should focus on exploring their etiology.

In this study, the overall patient satisfaction score was 4.89 ± 0.69, anesthesiologist satisfaction score was 4.57 ± 0.96, and endoscopist satisfaction score was 4.67 ± 0.87. In addition, there were 4 cases with anesthesia satisfaction less than 4 points, of which 3 patients had anesthesia failure (i.e., negative reactions) because of the BCD method in this study. The above results suggested the recognition of the use of remimazolam in anesthesia during the

Table 5: Operation time and anesthesia recovery time.

Events	Time (min)
Gastroscopy operation time	14.4 ± 4.1
GI endoscopy operation time	5.9 ± 4.5
Gastroscopy anesthesia recovery time	18.7 ± 11.9
GI endoscopy anesthesia recovery time	20.7 ± 12.0

Notes. Anesthesia recovery time was the time from endoscope withdrawal to Aldrete score of 10. Operation time was the time from endoscope insertion to endoscope withdrawal.

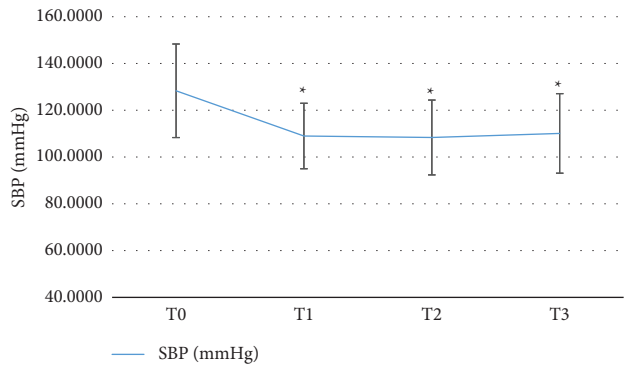

Figure 2: Changes in SBP at each observation time point. *represented statistically significant difference from T0 ($P < 0.05$).

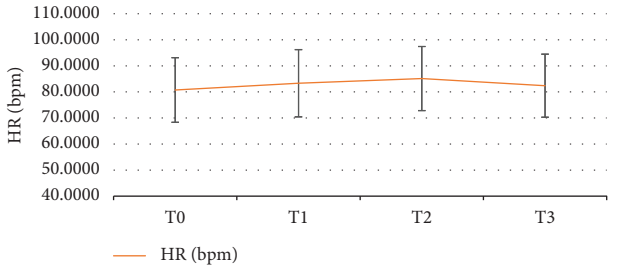

Figure 3: Changes in HR at each observation time point without any significant differences.

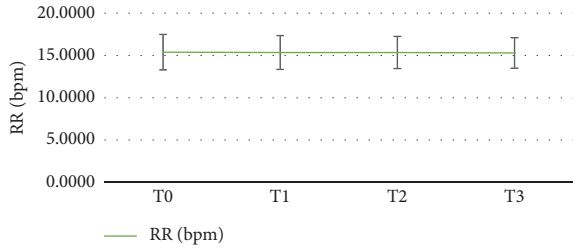

Figure 4: Changes in RR at each observation time point without any significant differences.

upper GI endoscopy. We included patients undergoing both gastroscopy and GI endoscopy. The mean recovery time was around 20 minutes with a relative short time to PACU discharge, indicating the application of remimazolam is especially suitable for the need for safe and rapid outpatient surgery.

There is one limitation in this study since we only investigated the dose of remimazolam for painless gastroscopy in the general adult population. Further studies are required in the light of gender difference, elderly, and obese patients, as well as ASA III and above patients.

5. Conclusion

The use of remimazolam in patients undergoing upper GI endoscopy was safe and effective, and ED90 of a single intravenous bolus remimazolam inhibiting responses to upper GI endoscopy insertion was 0.556 mg/kg with 95% CI between 0.399 and 0.578 mg/kg.

Data Availability

The data that support the findings of this study are available from the corresponding author, Xianhui Kang, upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Pengfei Yin and Xian Zhao are the co-first authors.

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