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Original Article

Effect of remimazolam tosylate on the response to endotracheal intubation under general anesthesia in patients undergoing catheter placement for peritoneal dialysis

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Abstract: Objective: This study aims to observe the effects of remimazolam tosylate on the response to endotracheal intubation under general anesthesia in patients undergoing peritoneal dialysis catheter placement. Additionally, we seek to determine the 95% effective dose (ED95) of remimazolam tosylate for inhibiting the endotracheal intubation response in this patient population. Methods: This prospective study was registered with the China Clinical Trials Center (ChiCTR2200055709), https://www.chictr.org.cn/showproj.html?proj=149640. Patients scheduled for peritoneal dialysis catheter placement under general anesthesia at the First Affiliated Hospital of Nanchang University between January and June 2023 were selected. They were randomly assigned into the remimazolam tosylate group (R group) and the propofol group (P group), with 30 patients in each group. After anesthesia induction and subsequent endotracheal intubation, sedation efficacy and adverse reactions were recorded for both groups. Venous blood samples (1 mL) were collected from patients before anesthesia induction and after endotracheal intubation to measure levels of adrenaline and noradrenaline. The modified Dixon sequential method was used to determine the ED95 of remimazolam tosylate for inhibiting the endotracheal intubation response. Results: Levels of adrenaline and noradrenaline decreased significantly after endotracheal intubation in both the R group and P group, with no significant difference. Vital signs were more stable in the R group compared to the P group. Injection pain during anesthesia induction was reported in 3 patients (10%) in the R group, whereas 18 cases (60%) were observed in the P group. The Dixon sequential experiment included a total of 25 patients, with 13 (52%) showing positive responses and 12 (48%) negative responses. Conclusions: Remimazolam tosylate is effective for inhibiting the systemic response to endotracheal intubation in patients undergoing peritoneal dialysis catheter placement. Additionally, the occurrence rate of hypotension and injection pain during anesthesia induction is significantly lower compared to propofol. The ED95 of remimazolam tosylate for inhibiting the endotracheal intubation response in peritoneal dialysis catheter placement patients is 0.332 mg/kg.

Keywords: Remimazolam tosylate, propofol, endotracheal intubation, peritoneal dialysis placement, 95% effective dose

Introduction

End-Stage Renal Disease (ESRD) patients undergoing peritoneal dialysis catheter placement with general anesthesia present a clinical challenge. ESRD patients are at a higher risk of cardiovascular disease and other comorbidities, with an adjusted all-cause mortality rate at least 10 times higher than non-ESRD populations [1-3]. Anesthesia medications can reduce cardiac output and afterload (systemic vascular resistance) in ESRD patients, sometimes leading to significant hypotension following anesthesia induction [4]. Propofol is the most commonly used sedative and anesthetic agent in ESRD patients [5]. However, propofol can cause injection pain and has side effects such as respiratory and circulatory depression, which may increase the risks of hypoxemia, hypotension, and even cardiac arrest [6].

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Remimazolam besylate, an ultra-short-acting benzodiazepine, has pharmacokinetics and pharmacodynamics similar to remimazolam [7]. It was recently approved for surgical sedation and general anesthesia induction [8]. For ESRD patients and healthy subjects, no significant differences were found in concentration-time curves, plasma clearance rates, and drug metabolism kinetics after a single intravenous injection of 1.5 mg remimazolam besylate [9]. Since remimazolam besylate is primarily metabolized by carboxylesterases in tissues including the liver and lungs, its anesthetic effect is not influenced by renal impairment, making it a possible first-line general anesthesia drug for chronic kidney disease patients [10]. Continuous infusion of remimazolam besylate at 0.15 mg/kg/h in chronic kidney disease patients has shown good sedation effects and satisfaction without an increase in postoperative adverse reactions [11]. However, the effect of this dosage on the response of ESRD patients undergoing peritoneal dialysis catheter placement to general anesthesia and tracheal intubation reactions is currently unclear, and the 95% effective dose (ED95) required to inhibit these reactions in this patient population warrants investigation.

This study aims to observe the effects of remimazolam besylate on tracheal intubation reactions during general anesthesia in patients undergoing peritoneal dialysis catheter placement. Additionally, we will determine the ED95 of remimazolam besylate to inhibit tracheal intubation reactions in these patients using an improved Dixon sequential method. This research seeks to provide clinical evidence for the individualized application of remimazolam besylate in general anesthesia and tracheal intubation for patients undergoing peritoneal dialysis catheter placement.

Materials and methods

This prospective study was registered with the China Clinical Trials Center (ChiCTR2200055709), https://www.chictr.org.cn/showproj.html?proj=149640. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University, with ethics number: IIT2022099. In accordance with ethical guidelines, this clinical trial was conducted after obtaining approval from the relevant ethics committee, and informed consent was obtained from all participants.

The study recruited patients undergoing scheduled peritoneal dialysis catheter placement under general anesthesia with endotracheal intubation at the First Affiliated Hospital of Nanchang University. Both male and female participants were eligible for recruitment, with the study period ranging from January 2023 to June 2023.

Inclusion Criteria: Age between 18 and 65 years, gender not specified; patients scheduled to undergo peritoneal dialysis catheter placement requiring endotracheal intubation; ASA physical status classification III; and patients meeting the diagnostic criteria for chronic kidney failure staging in China, with blood creatinine levels ≥707 μmol/L or creatinine clearance rate <10 ml/min.

Exclusion Criteria: Contraindications or difficult airways for endotracheal intubation; emergency surgeries, patients in shock or coma; acute heart failure; unstable angina, myocardial infarction within the past 6 months; infective cardiac diseases such as myocarditis or endocarditis.

Withdrawal Criteria: Participants can voluntarily withdraw their informed consent at any time; failure of first endotracheal intubation or intubation time exceeding 30 seconds; occurrence of any adverse clinical reactions, abnormal laboratory test results, or other medical conditions that may render participants ineligible to continue benefiting from the study.

Experimental procedures

Upon the patient's entry into the operating room, monitoring of electrocardiography (ECG), heart rate (HR), pulse (BP), pulse oximetry (SpO_2), and mean arterial pressure (MAP) was initiated. Baseline data for HR, BP, SpO_2, and MAP are recorded, along with baseline Bispectral Index (BIS) reading in awake state. Oxygen at 6 L/min was administered via mask, and anesthesia induction was carried out after complete removal of nitrogen. The induction dose for propofol group (P group) is 2.15 mg/kg [12]. For remimazolam tosylate group (R group), the induction dose was set at 0.3 mg/kg according to the instructions. Upon arrival in the

operating room, preoxygenation was performed, followed by the induction of anesthesia using remimazolam tosylate for sedation, which was deemed successful. Subsequently, 4 μg/kg of fentanyl and 0.15 mg/kg of cisatracurium were administered to ensure complete anesthesia induction. An experienced anesthetist utilized a video laryngoscope for intubation if there was no response to the train-of-four (TOF) stimulation three minutes after the administration of fentanyl and cisatracurium.

Blood samples were collected at 5 minutes before induction (Ta) and 2 minutes after intubation (Tb) for remimazolam tosylate group to measure plasma catecholamine levels using sandwich enzyme-linked immunosorbent assay method.

The modified Dixon sequential method sets the initial induction dose of remimazolam tosylate at 0.2 mg/kg, with a dose increment of 0.05 mg/kg. If BIS value was >60 or Observer's Assessment of Alertness/Sedation (OAA/S) score was >1 at 3 minutes after remimazolam tosylate administration, a positive response was noted, and remedial measures were taken immediately. Remedial measures included intravenous injection of 2 mg remimazolam tosylate to deepen anesthesia until BIS≤60 and OAA/S score ≤1, followed by continuation of the induction process. Depending on the criteria, if a positive response was observed, the dose was increased; otherwise, decreased. This process was repeated until the 7th positive-negative crossover point is reached, at which the experiment was terminated.

Criteria for positive endotracheal intubation reaction includes: 1) within 2 minutes of intubation, if HR or MAP increased by more than 20% from baseline values; 2) HR exceeding 120 beats per minute during intubation; 3) systolic blood pressure exceeding 180 mmHg or diastolic blood pressure exceeding 110 mmHg during intubation. Meeting any of these criteria post-intubation indicated a positive reaction, otherwise negative.

Outcome measures

Primary outcome measures: The following values need to be recorded: HR, MAP, SpO_2 at pre-anesthesia induction (T1), 1 minute after administration of remimazolam tosylate and propofol (T2), 3 minutes after administration (T3), immediately post-intubation (T4), and 2 minutes post-intubation (T5), as well as cardiovascular reactions in the remimazolam tosylate group post-medication administration.

Secondary outcome measures: Document occurrences of injection pain post-medication administration, hypoxemia (SpO_2<90%), hypotension (systolic pressure <90 mmHg) [13], coughing, hiccuping, bradycardia, intraoperative awareness, postoperative nausea, vomiting, or any adverse reactions. Additionally, record patient hospital numbers, age, gender, height, weight, blood creatinine levels, history of anesthesia allergies, admission diagnosis, and other clinical data.

Sample size estimation

When exploring the effects of remimazolam tosylate on general anesthesia endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement, sample size was calculated using PASS 11.0 (NCSS-PASS 11), assuming the two groups had similar efficacy, and we estimated that a sample size of 50 patients (25 in each group) would reduce 80% power to 5% in the R group after randomization with a two-sided α level of 0.05. Considering a 20% dropout rate, 30 subjects per group were recruited, totaling 60 participants for the study. Using the modified Dixon sequential method to determine the ED95 of the drug typically requires a sample size ranging from 20 to 40 individuals [14].

Statistical analysis

In this study, statistical analysis was conducted using SPSS 27.0. Normally distributed continuous data were presented as mean ± standard deviation (X±S) and compared between groups using a t-test. Non-normally distributed continuous data were represented by median (M) and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical data were assessed using the chi-square test. The Probit regression analysis was employed to calculate the ED95 of remimazolam tosylate along with its 95% confidence interval (CI). GraphPad Prism 10 software was utilized to create the remimazolam tosylate sequential trial plot and the fitted dose-response curve. A *P* value <0.05 was considered significant.

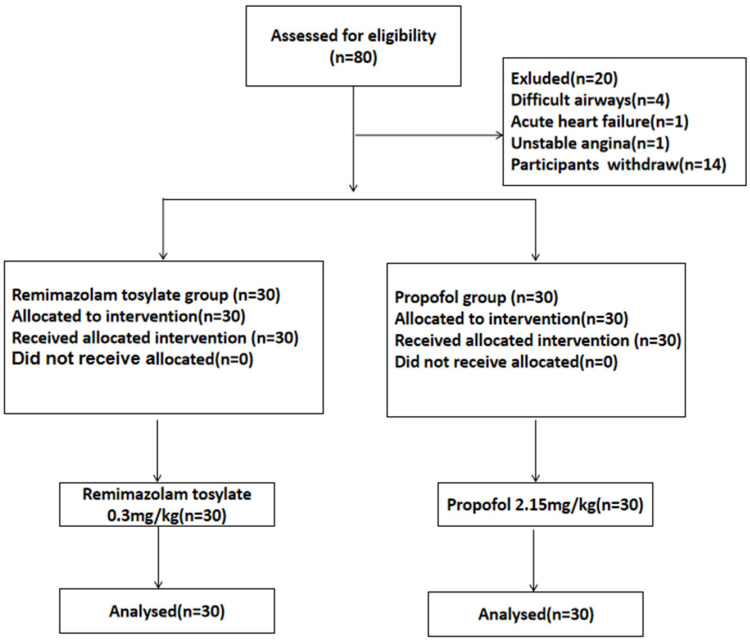

Figure 1. Flow chart of participants in the study.

Results

General conditions of the two groups

A total of 60 patients were enrolled in the study, with 30 patients in the remimazolam tosylate group and 30 patients in the propofol group (**Figure 1**). The general characteristics of the participants are summarized in **Table 1**. There were no significant differences between the two groups regarding gender, age, BMI, blood creatinine levels, hypertension, diabetes, or chronic nephritis. Following administration of remimazolam tosylate or propofol, anesthesia depth was evaluated based on OAA/S score or BIS. An OAA/S score >1 or BIS>60 indicated sedation failure, while values ≤1 or ≤60 were considered successful sedation, with an observation duration of up to 3 minutes. Successful sedation was achieved in 29 cases and unsuccessful in 1 case in the remimazolam tosylate group, and all 30 cases in the propofol group were successfully sedated, showing no significant difference between the groups (P>0.05). The remimazolam tosylate group exhibited a significantly higher incidence of injection pain and hypotension compared to the propofol group (P<0.05), while there were no significant differences in occurrences of hiccuping, body movements, or hypoxemia (P>0.05).

Hemodynamic changes during induction in the two groups

At T1, there were no significant differences in HR or MAP between the two groups (P> 0.05) (**Figure 2**). Both groups maintained 100% SpO_2 at all five time points. Compared to T1, there were no significant differences in HR or MAP at each time point in the R group (P>0.05). In the P group, HR and MAP significantly decreased at each time point compared to T1 (P<0.05). HR and MAP at T2, T3, T4, and T5 in the P group showed significant decreases compared to the R group and between different time points (P<0.05) (**Figure 2**).

Changes in cortisol levels before and after endotracheal intubation in patients in the two groups

At T1, there were no differences in adrenaline and noradrenaline levels between the two groups (**Table 2**). Adrenaline and noradrenaline levels significantly decreased from T1 to T5 in both groups (P<0.05). This indicates that remimazolam tosylate and Propofol effectively inhibited the stress response to endotracheal intubation in patients undergoing peritoneal dialysis catheter placement under general anesthesia.

Determination of the 95% effective dose of remimazolam tosylate in suppressing endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement

A total of 25 subjects were included in the determination of the ED95 trial of remimazolam tosylate in suppressing endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement. Records of the reactions in these patients were collected and a sequential plot was constructed (**Figure 3**). After each subject underwent the trial, 13 cases were positive and 12 cases were negative. The number of cases corresponding to

Table 1. Clinical data of two patient groups ($\bar{X}$±S/M (P25, P75))

Clinical feature	Group R (n=30)	Group P (n=30)	P
Age (years)	45.2±11.3	43.7±14.7	0.899
Gender			
Male	20	14	0.118
Female	10	16	
BMI (kg/m^2)	22.0±3.1	21.3±2.9	0.575
Serum creatinine (umol/L)	888.0 (675.4, 1121.7)	768.4 (679.5, 1955.1)	0.894
Hypertension (cases)	25	21	0.222
Diabetes (cases)	10	15	0.190
Chronic kidney disease (cases)	5	8	0.347
Sedation effect (cases)			
OAA/S>1	0	0	>0.05
OAA/S≤1	30	30	
BIS>60	1	0	0.313
BIS≤60	29	30	
Injection pain (cases)	3 (10%)	18 (60%)	<0.01
Hiccup (cases)	2 (6.6%)	0	0.150
Movement response (cases)	1 (3.3%)	0	0.313
Hypoxemia (cases)	1 (3.3%)	4 (13.3%)	0.161
Hypotension (cases)	0	6 (20%)	0.010

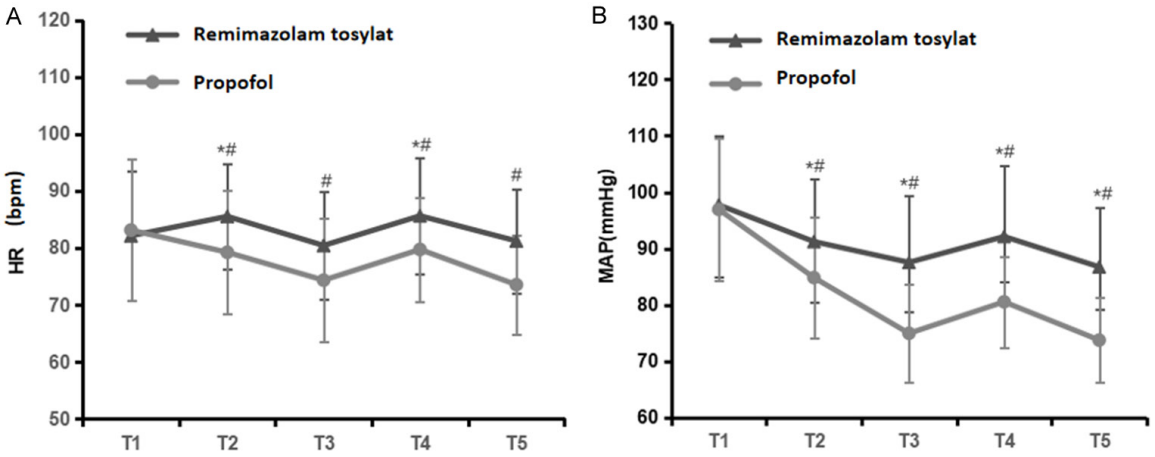

Figure 2. Hemodynamic changes during the induction phase in the two groups. Compared to T1, *P<0.05; Compared to propofol, #P<0.05.

Table 2. Serum hormone levels before and after endotracheal intubation in the two groups ($\bar{X}$±S, n=60)

	Time	Group R	Group P	P
E (pmol/L)	Ta	278.8±35.5	277.1±36.9	0.856
	Tb	259.2±32.6*	247.3±35.0*	0.178
P		0.030	0.002	
NE (pmol/L)	Ta	58.6±4.2	58.4±5.8	0.879
	Tb	55.9±5.8*	55.1±4.2*	0.543
P		0.043	0.014	

Compared to Ta, *P<0.05.

each concentration is shown in **Table 3**. Probit regression analysis and the Pearson goodness-of-fit test with χ^2=0.586 and P=0.746 (P>0.05), indicated that the model closely matched the actual data and confirmed its reliability. Consequently, the Probit regression model for the ED95 of remimazolam tosylate in sup-

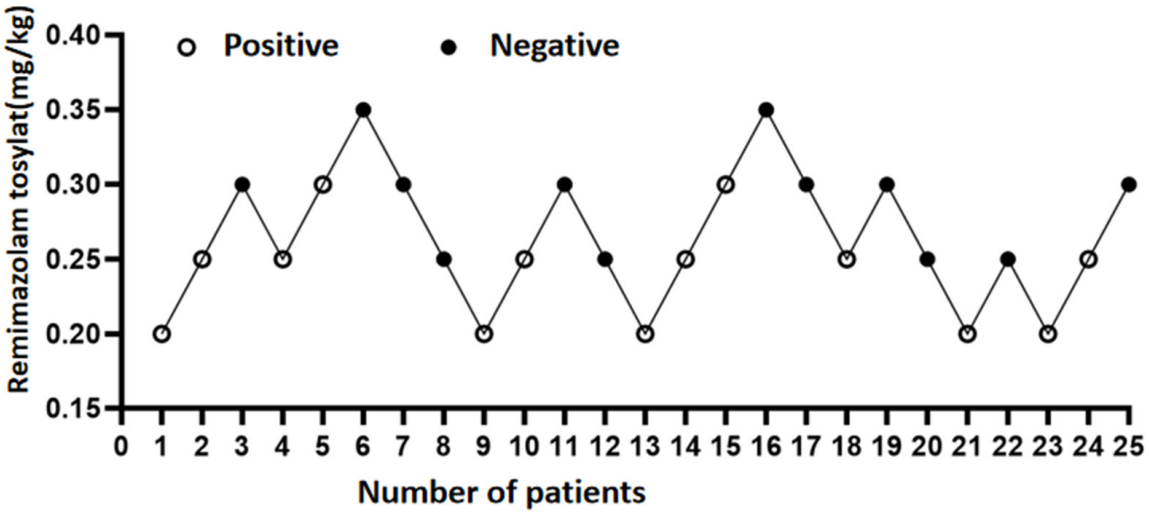

Figure 3. Sequential plot of remimazolam tosylate in suppressing endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement.

Table 3. Number of subjects at each drug concentration

Remimazolam tosylate (mg/kg)	Negative cases (cases)	Total cases (cases)	Efficacy rate (%)
0.2	0	5	0%
0.25	4	10	40%
0.3	6	8	75%
0.35	2	2	100%

pressing endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement was determined as: PROBIT(P) = -6.775 + 25.303 × (concentration) (**Figure 4**). The ED95 of remimazolam tosylate for suppressing endotracheal intubation reactions in these patients was calculated as 0.332 mg/kg, with a 95% confidence interval of 0.299-0.509 mg/kg.

Discussion

The novel ultra-short-acting benzodiazepine remimazolam tosylate is characterized by rapid onset, rapid metabolism, rapid sedative recovery, and the inactivity of its metabolites [15]. Multiple studies have shown that remimazolam tosylate is not inferior to propofol and midazolam in sedative effects, while significantly reducing the incidence of hypotension and injection pain. However, there have been few clinical studies on remimazolam tosylate in patients with ESRD. By exploring the inhibitory effect of remimazolam tosylate on endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement under general anesthesia, we further investigated the ED95 of remimazolam tosylate in suppressing these reactions. This study provided clinical evidence for individualized drug therapy for patients undergoing peritoneal dialysis catheter placement.

The primary source of stress that induces significant circulatory fluctuations during endotracheal intubation under general anesthesia is the contact of the laryngoscope blade with the tongue base and epiglottis, which stimulates the sympathetic adrenergic system and leads to increased catecholamine release, resulting in elevated heart rate and blood pressure [16]. These hemodynamic changes can disrupt the balance between myocardial oxygen demand and supply, causing severe myocardial ischemia and even cardiac arrest [17]. Therefore, it is essential to select appropriate perioperative anesthetic drugs to attenuate these stress responses and avoid any intraoperative adverse events. In this study, neither the remimazolam tosylate group nor the propofol group experienced serious adverse events. The main adverse reaction of propofol is dose-dependent cardiorespiratory depression; the lower impact of remimazolam tosylate on cardiorespiratory depression may be related to its mild effect on the sympathetic nervous system [15]. When

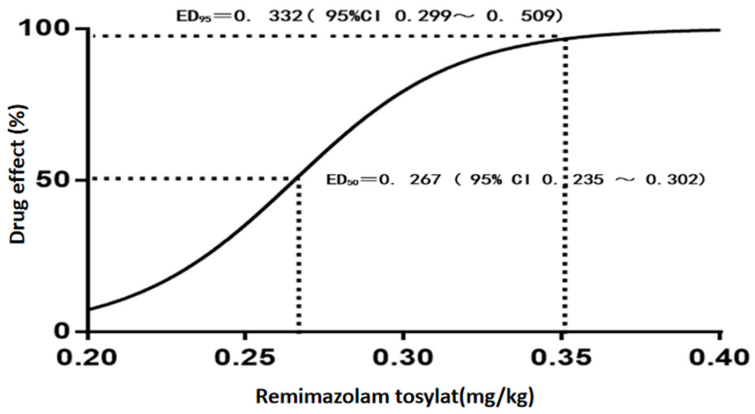

Figure 4. Dose-response relationship of remimazolam tosylate in suppressing endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement.

used for inducing general anesthesia in patients undergoing peritoneal dialysis catheter placement, remimazolam tosylate exhibited more stable hemodynamics compared to propofol, with HR remaining stable at various time points without significant differences and a slight decrease in MAP, along with stable SpO_2 levels. Remimazolam tosylate has a minor impact on heart rate, that may be influenced by complex physiologic feedback mechanisms [18]. The inhibitory effect of remimazolam tosylate on the sympathetic nervous system leads to vasodilation and a reduction in MAP [19, 20]. The incidence of hypotension in the remimazolam tosylate group was lower than that of the propofol group, and the incidence of injection pain was also lower. Studies suggest that remimazolam tosylate may alleviate injection pain by blocking the release of kinin signals [21]. The incidence of injection pain with remimazolam tosylate was reported to be approximately 2.4% [22, 23]; however, in this study, the incidence of injection pain in the remimazolam tosylate group was higher than in previous studies, possibly due to higher local vascular stimulation caused by the high pressure of remimazolam tosylate administration during intravenous push. According to reports [21, 24], there is a weak positive correlation between the dose of remimazolam tosylate administered and the occurrence of hiccups. In this study, we speculate that the occurrence of hiccups may be related to the dose and speed of intravenous remimazolam tosylate administration. In addition, within 24 hours after surgery, follow-up patients in both groups did not experience postoperative nausea and vomiting, awareness during surgery, or other adverse reactions, with good recovery quality.

Both remimazolam tosylate and propofol are effective in suppressing endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement. Pernerstorfer and colleagues found that adrenaline levels slightly decreased after anesthesia induction and remained unchanged after intubation [22, 25]; however, noradrenaline levels significantly increased post-intubation [5, 23, 26]. In this study, both the propofol group and the remimazolam tosylate group showed a significant decrease in adrenaline and noradrenaline levels before and after endotracheal intubation, indicating that both agents could effectively reduce the stress response during endotracheal intubation procedures. The success rates of sedation in the two groups in this study showed no significant difference, consistent with findings from other similar research [7, 27].

Studies [25, 28, 29] have shown that the pharmacokinetics of remimazolam tosylate are not affected by age, gender, weight, race, or chronic kidney disease. Research indicated [17, 30] that the ED95 of remimazolam tosylate for inhibiting double-lumen endobronchial intubation reaction was 0.344 mg/kg. Another study of us showed that the ED95 of remimazolam tosylate for inhibiting endotracheal intubation reactions in frail elderly patients was 0.331 mg/kg [23]. In this study, the 95% effective dose of remimazolam tosylate for suppressing endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement was 0.332 mg/kg (95% CI 0.299-0.509 mg/kg), which is consistent with the results of the aforementioned studies, supporting previous basic research conclusions.

In conclusion, our study suggests that remimazolam tosylate can effectively suppress endotracheal intubation reactions in patients undergoing peritoneal dialysis catheter placement,

while demonstrating a lower incidence of hypotension and injection pain compared to propofol induction. The ED95 of remimazolam tosylate for inhibiting endotracheal intubation reactions in this patient population was found to be 0.332 mg/kg.

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The patients/participants provided their written informed consent to participate in this study.

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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