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Efficacy and Safety of Remimazolam Tosilate for General Anesthesia Induction and Maintenance in Elderly Patients: A Randomized, Controlled Study

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ABSTRACT

Purpose: To evaluate the efficacy and safety of Remimazolam Tosilate (RT) for general anesthesia in elderly patients.

Methods: 66 patients aged 60 years to 80 years who were scheduled to undergo surgery were randomized into three groups: Group A (RT 6 mg/kg/h), group B (RT 12 mg/kg/h), or group C (propofol 2.0 mg/kg-2.5 mg/kg). Primary efficacy indicators (success rate of anesthesia sedation), secondary efficacy indicators (BIS value, anesthesia induction time, anesthesia awakening time), safety efficacy indicators (incidence of anesthetic hypotension; incidence of anesthetic hypoxemia, etc.) and Adverse Events (AEs) were routinely monitored.

Results: The success rate of anesthesia sedation was 95.45% in the 6 mg/kg/h RT group, and 100% in the 12 mg/kg/h RT and propofol groups. RT was noninferior to propofpl group (difference in rate -4.55%, 95% con idence interval (CI, -0.12; 0.03), meeting criteria for noninferiority). There were no significant differences i n t he time o f a nesthesia induction o r i ncidence o f b radycardia and hypotension among the three groups. However, compared with the propofol group, the awakening time in the RT groups was significantly shorter (P<0.05), less impact on heart rate, no injection pain, and significantly less norepinephrine usage (P<0.05). The intraoperative BIS values of the three groups were all maintained at 40-72, and no intraoperative awareness was found.

Conclusion: RT (6 mg kg/h and 12 mg kg/h) was well tolerated and noninferior to propofol with regard to efficacy in inducing general anesthesia in elderly patients. And there were no significant difference in the induction and maintenance of anesthesia between different doses of RT. A preprint has previou sly been published [1].

Keywords: Remimazolam tosilate; Propofol; General anesthesia; Elderly patients

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INTRODUCTION

With the transformation of disease patterns and the aging population, the demand for surgical operations has greatly increased [2]. The proportion of surgeries performed in elderly patients has also increased yearly [3]. Because elderly patients have reduced cardiovascular regulation and reduced stress capacity for external injury, often in combination with cardiovascular and cerebrovascular system diseases [4], they are prone to severe hemodynamic fluctuations and even cardiovascular and cerebrovascular events during the induction of anesthesia and intubation [5]. Such age-related physiological and pharmacokinetic changes, as well as the presence of comorbidities and polypharmacy, complicate drug therapy in elderly individuals, thereby greatly increasing the risk of anesthesia [6]. Therefore, rational selection and appropriate application of anesthesia-inducing drugs are crucial for elderly patients who require general anesthesia for surgery.

Commonly used drugs for the induction of intravenous anesthesia in clinical practice are propofol, which has a rapid onset of action and a short duration of action [7,8]. It is often associated with injection site pain [9], especially severe cardiovascular and respiratory depression, and may even lead to cardiac arrest; its use is limited to a certain extent for elderly patients [10,12]. Therefore, preventing or reducing the occurrence of sedation-related complications is the best approach. The most important finding was that, although both RT and propofol caused transient cardiovascular and respiratory depression, the incidences of hypotension, treatment related hypotension, and respiratory depression were lower in the RT group than in the propofol group [13,14] and could be rapidly reversed by flumazenil [15].

RT (HR7056) is the toluene sulfonate of remimazolam, a new type of water soluble ultrashort-acting benzodiazepine that mainly acts on aminobutyric acid A (GABAA) receptors, inhibits neuronal action, decreases neuronal excitability, and causes decreased body activity, sedation, and amnesia [16,18]. Previous studies have shown equivalent anesthetic effects for remimazolam and propofol in patients undergoing colonoscopy and in elderly patients undergoing hip replacement, with the former being significantly safer [19,20]. In addition, phase II/III clinical trials in Japan have shown that remimazolam not only induces and maintains sedation during general anesthesia but is also noninferior to propofol in terms of efficacy [21]. Studies have shown the efficacy and safety of remimazolam for inducing general anesthesia in ASA class III elderly patients [22,23]. Even though age and ASA class have little effect on remimazolam anesthesia extubation time, for some frail elderly patients, it was suggested to use a lower dose of remimazolam [24]. Nevertheless, the efficacy and safety of RT for general anesthesia induction in elderly patients remain unclear. With the characteristics of rapid onset of action, short maintenance and recovery time, no accumulation, metabolism not dependent on liver and kidney function [25] and no serious side effects, RT may become an ideal drug for the induction and maintenance of anesthesia in elderly patients.

Thus, we performed a single center, randomized, control trial to compare the efficacy and safety of RT versus propofol for general anesthesia induction in elderly patients to provide clinical experience and a theoretical basis for RT for general anesthesia induction in elderly patients

MATERIALS AND METHODS

Participants

Elderly patients aged 60 years-80 years, who required general anesthesia with tracheal intubation for elective surgery at affiliated Dongguan hospital, Southern medical university (Dongguan people's hospital) were enrolled in this study. Exclusion criteria included hypersensitivity to or dependence on anesthetic components that may be used in the study, combined craniocerebral injury and intracranial hypertension, history of allergies, history of psychiatric disorders, bradycardia (heart rate<50 beats/min), foreseeable difficult intubation, or other conditions judged to be unsuitable for participation in the clinical trial.

The criteria for exiting the trial were as follows: the subject developed a condition that met the exclusion criteria during the study or a clinical adverse event that jeopardized the safety of the subject, an abnormal laboratory test, or other medical condition that resulted in the possibility that the benefit to the subject from continued medication was less than the risk; investigators considered other anesthetic factors that prevented the subject from continuing the trial.

Randomization and Blinding

Numbering was based on the time of surgery. Random numbers were generated by SPSS 25.0 software, and the 66 patients were randomly divided into groups A (RT 6 mg/kg/h), B (RT 12 mg/kg/h), or C (propofol induction period loading dose of 2.0 mg/kg-2.5 mg/kg), with equal sample sizes. We applied a single-blind design because the administration dosage and dosage form of RT and propofol are different. The anesthesiologist who performed the sedation was aware of the treatment assignment of each participant. Throughout the trial, neither the outcome assessors nor participants were aware of the treatment assignment.

Study Protocol

This was a randomized controlled-group study comparing the efficacy and safety of different doses of RT relative to propofol. Sixty-six elderly patients requiring general anesthesia with tracheal intubation for elective surgery were recruited and included in the study based on inclusion and exclusion criteria, and the trial participants were randomized into three groups: RT 6 mg/kg/h (group A), RT 12 mg/kg/h (group B), and propofol (group C), with a sample size ratio of 1:1:1 in each group. We used RT with a specification of 36 mg/vial as the research drug, and 36 ml of 0.9% compound sodium chloride injection was added to each vial, resulting in

36 ml of 1 mg/ml injection, w hich was u sed to draw the required dose with a syringe.

The night before surgery, the anesthesiologist will perform a preanesthesia assessment, with the consent of the patient and his or her family, and the patient will sign the informed consent form. All patients fasted before surgery, and assured anesthesiologists that unnecessary premedication, such as benzodiazepines and alcohol, was not taken. After admission to the operating room, the Electro Cardiogram (ECG), Heart Rate (HR), Oxygen Saturation (SpO_2), the mean arterial pre ssure (MAP) and BIS were routinely monitored. Peripheral venous access was opened and an intravenous drip of 500 ml of 0.9% compound sodium chloride was administered. All patients inhaled oxygen (oxygen flow rate 5 L/min) through an inflatable disposable anesthetic face mask for 3 min before induction.

After recording the baseline vital signs, 6 mg/kg/h or 12 mg/kg/h of intravenous RT infusion, or (2.0 mg/kg-2.5 mg/kg) of propofol (Beijing Fresenius Kabi pharmaceutical co., ltd., China) intravenous injection was started, and this time was defined as the start of anesthesia induction. When the BIS ≤ 60, the intravenous infusion of cisatracurium besilate at 0.2 mg/kg-0.3 mg/kg and sufentanil at 0.4 μg/kg-0.6 μg/kg was started. The time from the start of the RT or propofol infusion to Loss of Consciousness (LoC was recorded. We de ined LoC as the time when the patient became unresponsive to the shaking of their shoulders (MOAA/S ≤ 1) [20]. A ter confirming LoC, the anesthesia maintenance starting dose of RT was adjusted to 0.5 mg/kg/h, and then adjust the RT infusion rate according to the BIS value to not exceed 0.2 mg/kg/h each time. In the propofol group, the anesthesia maintenance dose was 3 mg/kg/h-8 mg/kg/h. Intraoperative analgesia and muscle relaxation were maintained by intravenous pumping of remifentanil at 0.25 ug/kg/min-0.5 ug/kg/min and cisatracurium besilate at 0.06 mg/kg/h-0.12 mg/kg/h. Sufentanil 5 μg and tropisetron 2 mg-5 mg were slowly injected intravenously at 30 min to 1 h before the end of the operation. The time from the withdrawal of RT/ propofol to the extubation of the patient was recorded as the recovery time from anesthesia (**Table 1**).

Table 1: The Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale.

Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

The intraoperative BIS was maintained at 40-60 to ensure the depth of anesthesia. During the operation, the infusion rate of RT (0.05 mg/kg/h-2 mg/kg/h) or propofol (4 mg/kg/h-10 mg/kg/h) was adjusted according to the BIS value. If the BIS still rises to>60 with the maximum infusion volume of RT, RT 0.05 mg/kg can be intravenously injected each time until the BIS value is lower than 60, and the interval between the two doses cannot be less than 1 minute. If during the induction and maintenance of the process, the required depth of anesthesia was not achieved after more than 3 supplemental doses, it was determined to have failed on sedation, and RT, the anesthesia drug, was changed to propofol, and recorded in the analysis.

Differences in the primary efficacy index, secondary efficacy index and safety evaluation index between the three groups were compared and analyzed according to the intention-to-treat principle, and the occurrence of AEs during the trial period was recorded.

Measurements

Treatment plan for AEs during anesthesia. (i) Hypertension (an increase in MAP exceeding 20% of the baseline value), intravenous injection of urapidil (Xi'an Lijun pharmaceutical co., ltd., China) 5 mg/time, depending on the blood pressure. (ii) Hypotension (a decrease in MAP exceeding 20% of the baseline value), intravenous infusion of norepinephrine (Grand pharmaceuticals co., ltd., Wuhan province, China) 0.03 μg/kg/min-0.2 μg/kg/min, depending on the blood pressure. (iii) Bradycardia (HR<50 beats/min), intravenous injection of atropine 0.2 mg/time-0.3 mg/time. (iv) Tachycardia (HR>120 beats/min), the investigators implemented treatment according to clinical experience, with intravenous injection of esmolol 20 mg/time if necessary. (v) For hypoxemia (SpO_2<90%) after anesthesia and resuscitation, the patient's head and chin was raised, and the face mask was pressurized to assist with breathing if necessary.

The primary efficacy endpoint was the success rate of sedation (the percentage of patients successfully completing the procedure), as defined as follows: (i) Completion of the entire surgical procedure; (ii) No need for replacement and/or rescue sedation. Secondary efficacy endpoints included the following: (i) Change in BIS value over time (time from induction of anesthesia until BIS value ≤ 60, value before tracheal intubation, intraoperative maintenance of BIS value); (ii) Time to induction of anesthesia; (iii) Time to awaken from

anesthesia, as defined a s t he time from discontinuation of study drug to extubation (MOAA/S score ≥ 4).

Safety assessment indicators: (i) Incidence of hypotension; (ii) Incidence of hypertension; (iii) Incidence of hypoxemia; (iv) Intraoperative awareness (after general anesthesia, the patient can recall what happened during the operation); (vi) Incidence of bradycardia.

Sample Size and Statistics

This study had a non-inferiority design, and the primary efficacy endpoint was the success rate of general anesthesia sedation in elderly patients. We did not calculate the sample size for incorporating patients because we could not estimate the effect size of RT due to the lack of previous data and our own limited experience with the drug. We decided to enroll 66 patients for this study to investigate the efficacy and safety of RT.

Statistical analysis was performed using SPSSS Statistics, version 25. Shapiro wilk and levene tests were used to assess the data distribution and homogeneity of variance, respectively. Quantitative data are presented as the means ± Standard Deviations (SDs) or medians with interquartile ranges, as appropriate. Numbers (percentage) were used to describe categorical data (such as gender and MOAA/s scores). Continuous variables were analyzed using one-way Analysis Of Variance (ANOVA) or Welch ANOVA based on the homogeneity of variance test and kruskal wallis test and then followed by Bonferroni's post hoc test or Games Howell's post hoc test to compare differences among Group Categorical variables were compared using Pearson's *chi-square* test or Fisher's exact test, followed by Bonferroni's post hoc test. A p value< 0.05 was considered to indicate statistical significance.

RESULTS

Patient Characteristics

A total of 66 eligible patients were enrolled in this study and randomized into three groups (22 in each group). One patient in group A after 3 remedial doses was failed sedation due to persistent intraoperative hypertension, and 1 patient in group C was excluded, primarily because of EEG monitoring malfunction. There were no significant differences in demographic characteristics among the three groups. At baseline examination, the demographic and baseline characteristics of the patients in the three groups were well balanced in terms of age, BMI, MAP, SpO_2, and other demographic characteristics. Most patients had comorbidities, including hypertension and diabetes. Group A consisted of 11 males and 11 females, with a mean age of 69.23 (± 5.40) years. Group B consisted of 10 males and 12 females, with a mean age of 67.05 (± 4.55) years. Group C included 7 males and 15 females, with a mean age of 68.73 (± 5.68) years. The overall mean age was 68 years, and male patients accounted for 42.42% (**Table 2 and Figure 1**).

Table 2: Demographic characteristics of patients.

Characteristic	6 mg/kg/h RT	12 mg/kg/h RT	Propofol	Total	P-value
		Age, y			
Mean ± SD	69.2 ± 5.40	67.05 ±4.55	68.73 ± 5.68	68.73 ± 5.68	0.176
Median	68	67	68.4	68.4	
(IQR)	(65.00,73.25)	(62.75,71.25)	(63.00,74.25)	(63.75,72.25)	
		Sex, No. (%)			
	11 (50.00)	10 (45.45)	7 (31.82)	28 (42.42)	
Male					0.545
Female	11 (50.00)	12 (54.55)	15 (68.18)	38 (57.58)	
		BMI, kg/m^2			
Mean ± SD	24.23 ± 4.42	21.74 ± 2.43	23.59 ± 3.81	23.59 ± 3.81	0.071
Median	24.12	22.09	23.62	23.62	
(IQR)	(21.38.26.88)	(19.84,24.01)	(20.93,26.78)	(20.85,25.19)	
		Past medical history			
Yes	6 (27.3)	7 (31.8)	8 (36.4)	21 (31.8)	0.944
No	16 (72.7)	15 (68.2)	14 (63.6)	45 (68.2)	

			MAP (mmHg)		
Mean ± SD	96.97 ± 10.93	98.70 ± 10.00	92.00 ± 9.20	92.00 ± 9.20	0.08
Median	101.67	99.5	90.5	90.5	
(IQR)	(88.08,106.33)	(92.75,106.83)	(86.83,99.33)	(89.17,104.17)	
			SpO_2 (%)		
Mean ± SD	97.95 ± 0.95	98.32 ± 0.88	97.77 ± 1.41	97.77 ± 1.41	0.169
Median	98	98	98	98	
(IQR)	(97.00,98.25)	(98.00,99.00)	(97.00,99.00)	(98.00,99.00)	
			HR (beats/min)		
Mean ± SD	75.05 ± 13.09	75.41 ±12.40	74.23 ± 9.90	74.23 ± 9.90	0.944
Median	72.67	77	72	72	
(IQR)	(64.75,84.75)	(65.00,85.50)	(67.75,79.25)	(66.75,84.00)	

Notes: Data were presented as Mean ±SD, Median (Interquartile Range) or Number (Percentage). BMI, Body Mass Index; ASA, American Society of Anesthesiologists; SD, StandardDeviation. IQR, Interquarti le Range.

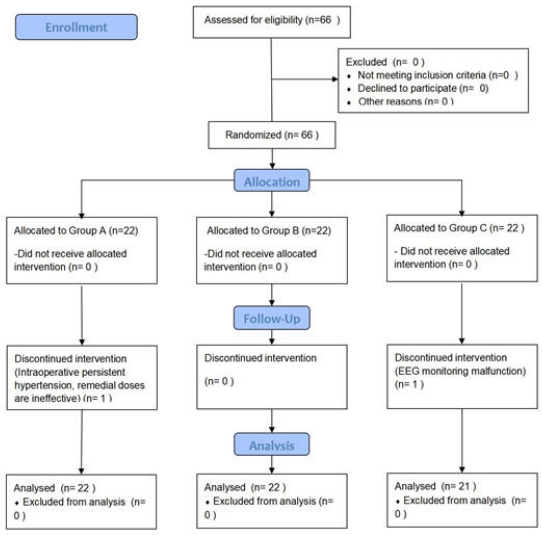

Figure 1: Consort flow chart of the procedures for elderly patients undergoing general anesthesia.

Primary Outcome

The success rate of anesthetic sedation was 95.45% (21/22) in the RT 6 kg/kg/h group and 100% (22/22) in the RT 12 kg/kg/h and propofol groups [difference in rate-4.55%; 95% CI,-0.12; 0.03), meeting criteria for non-inferiority]. There was no significant difference in the success rate of anesthetic sedation among the three groups (P>0.05).

Secondary Outcomes

MOAA/S scores ≤ 1 and BIS values<60 during anesthesia induction were observed in groups A and B, confirming the effectiveness of anesthesia induction with RT. During maintenance of anesthesia, the BIS values of the three groups were maintained at 40-72 (**Table 3**). The mean time of loc was 2.07 min in group a, 1.53 min in group B, and 1.92 min in group C after induction of anesthesia. There was no significant difference in anesthesia induction time when comparing all three groups (P=0.223). The average time to awaken from anesthesia was 17.33 (± 2.87) minutes in group A, 17.23 (± 2.31) minutes in group B, and 26.62 (± 5.60) minutes in group C. The results showed a significant difference between the RT groups (A and B) and the propofol group (P<0.05). We confirmed that the sedative effect of RT was similar to that of propofol, even though the recovery time from anesthesia was decreased in the RT groups compared to the propofol group (**Figures 2 and 3**).

Table 3: Characteristics o f surgical intervention an d RT efficacy parameters.

Item	Treatment	RT (mg/kg/h)		Propofol (mg/kg)
		6	**12**	**2.0-2.5**
All subjects		22	22	22
ASA classification	II	22 (100)	22 (100)	22 (100)
Surgical time (min)	Mean ± SD	187.14 ± 80.87	192.64 ± 66.90	188.39 ± 73.87

Efficacy rate	N (%)	21 (95.45)	22 (100.0)	21 (100.0)
BIS during maintenance	Range	40-72	40-63	40-69

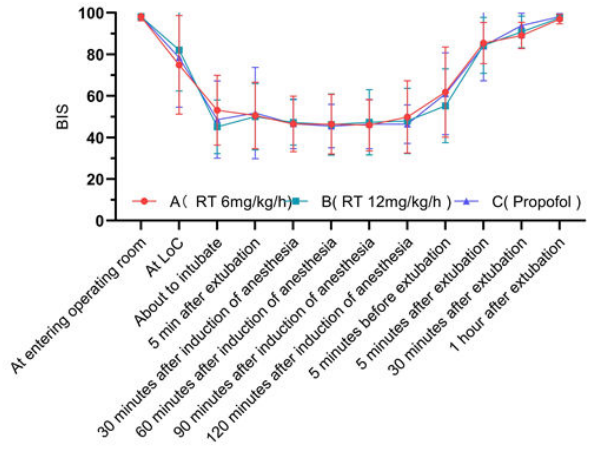

Figure 2: Change in Bispectral Index (BIS) over time (mean ± standard deviation).

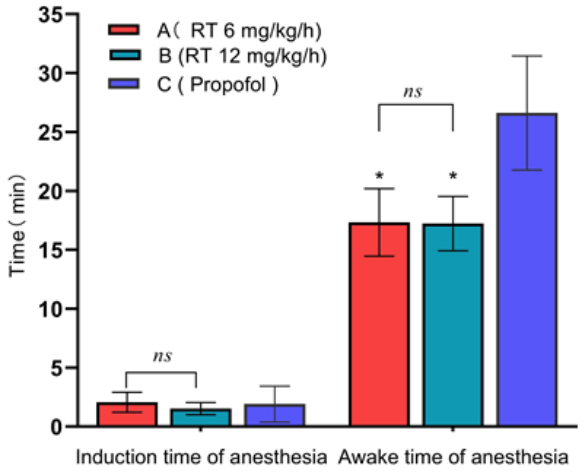

Figure 3: Comparison of induction time an d awake time of anesthesia in three groups of patients. Notes: Compared with G roup B, ns Indicates That the Difference is not Significant; Comp ared with Group C, *P<0.05.

As shown in **Figure 4**, before anesthesia induction (T0), there was no significant difference in HR among the three groups (P=0.302). However, HR was statistically significant after induction of anesthesia (T1) and 5 min after tracheal intubation (T2) (P<0.05). At T1, the mean heart rates of groups A, B, and C were 75.23 (± 11.82) beats/min, 71.41 (± 9.30) beats/min, and 56.52 (± 5.79) beats/min, respectively. Compared with group C, group A and group B had significant differences (P<0.0001), and there were no significant differences between groups A and B at T1 (P=0.541). At T2, both group B (70.95 ± 9.18 beats/min) and group C (65.24 ± 11.66 beats/min) had lower mean heart rates than group a (76.14 ± 10.37 beats/min). There was no significant difference between the A and B groups (P = 0.314), or the B and C groups (P= 0.232). However, there was a significant difference between group A and group C (P= 0.003). There was no significant difference in MAP among the three groups of patients at different time points (**Figure 5**). There was a statistically significant difference in MAP a ter the induction of anesthesia (P<0.05); MAP in the RT groups was higher than that in the propofol group, with a statistically significant difference (both P<0.05).

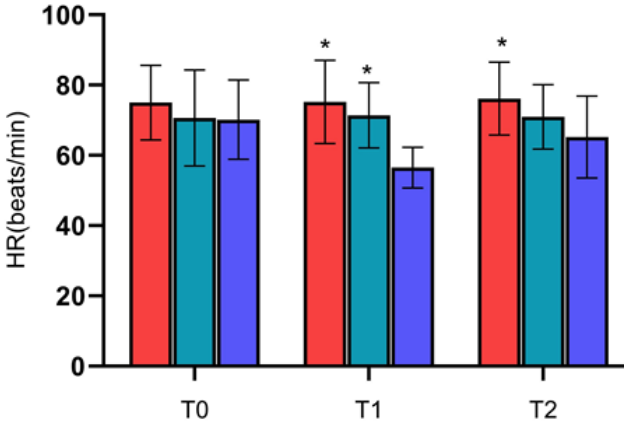

Figure 4: Changes in HR of three groups of patients at different time points. Notes: T0: Before Induction of Anesthesia; T1: Loc; T2: 5 min A fter Tracheal Intubation. *P<0.05 vs. Group C. Abbreviations: HR, Heart Rate.

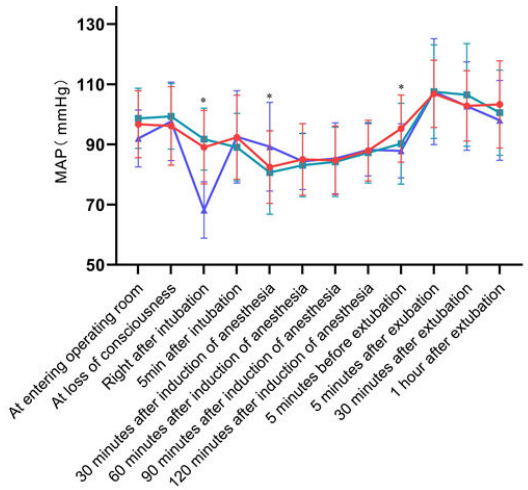

Figure 5: Change in map over time (mean ± standard deviation).

Safety Analysis

There were significant differences in the incidence of hypotension and bradycardia among the three groups (P<0.05), the incidence of bradycardia in the propofol group was 38.10%, and the incidence of hypotension was 85.71%. Overall, 8 patients (38.10%) in the propofol group developed bradycardia after the induction of anesthesia, in contrast to none in the RT group. In the different doses of RT groups, 4 and 2 subjects, respectively, developed hypotension after the

initial infusion of the study drug; 18 (85.71%) in the propofol group developed hypotension.

Adverse Outcomes

The most frequently recorded AEs included blood pressure drop, intravenous pain, nausea, vomiting, and intraoperative awareness. In total, 19.05% and 13.64% of patients in the 6 mg/kg/h RT group and the 12 mg/kg/h RT group had AEs, respectively, compared with 100% of the patients who received propofol. The overall difference between the three groups was statistically significant (P<0.05). In addition, the incidence of intravenous pain was 0% in the RT groups of the two different doses and 100% in the propofol group, with a significant difference (P<0.05). There was no significant difference in the incidence of hypotension between the 6 mg/kg/h and 12 mg/kg/h RT groups (P>0.05, 18.18% *vs.* 9.09%). No subjects in either group developed bradycardia after the induction of anesthesia (Table 4).

Table 4: Safety assessment in full analysis population (N=65).

	RT (6 mg/kg/h)	RT (12 mg/kg/h,)	Propofol	P-value
All AEs (%)	4 (19.05)	3 (13.64)	21 (100)	0
Incidence of hypertension (%)	1 (4.55)	1 (4.55)	0 (0)	1
Incidence of hypotension (%)	4 (18.18)	2 (9.09)	18 (85.71)	0
Incidence of bradycardia (%)	0 (0)	0 (0)	8 (38.10)	0
Incidence of nausea and vomiting (%)	0 (0)	0 (0)	1(4.76)	0.351
Incidence of intravenous pain (%)	0 (0)	0 (0)	21 (100)	0
Total number of additional sedatives (%)	1 (4.76)	2 (9.09)	0 (0)	0.767

Notes: The Number in () Shows %; Compared to Group C, *P<0.05

There was a statistically significant difference in the amount of vasoactive drugs used in the three groups (P=0.003). There was no significant difference in the RT 6 mg/kg/h group and RT 12 mg/kg/h group. The two groups of patients received norepinephrine at doses of 0.19 (± 0.15) mg and 0.23 (± 0.16) mg, respectively, during the entire surgical procedure. The RT 6 mg/kg/h and RT 12 mg/kg/h groups, compared with the propofol group (0.42 ± 0.31 mg), were significantly different (both P≤0.001), and the use of vasoactive drugs during surgery was significantly reduced. Neither group A nor group B was antagonized with flumazenil during anesthesia resuscitation. There were 2 postoperative adverse reactions in the propofol group, including postoperative nausea and vomiting in 1 patient, and postoperative chills in the other. One patient in the low-dose RT group required more than three rescue doses, and after switching to propofol to maintain anesthesia, the BIS value were less than 60. Both patients in the high-dose RT group required a rescue dose of RT, which was effective. In the RT group with different doses, 1 patient developed hypertension after tracheal extubation and was injected with urapidil 5 mg/time, and their vital signs returned to normal when they left the operating room. There was no hypoxemia or intraoperative awareness in the three groups of patients during anesthesia (Figure 6).

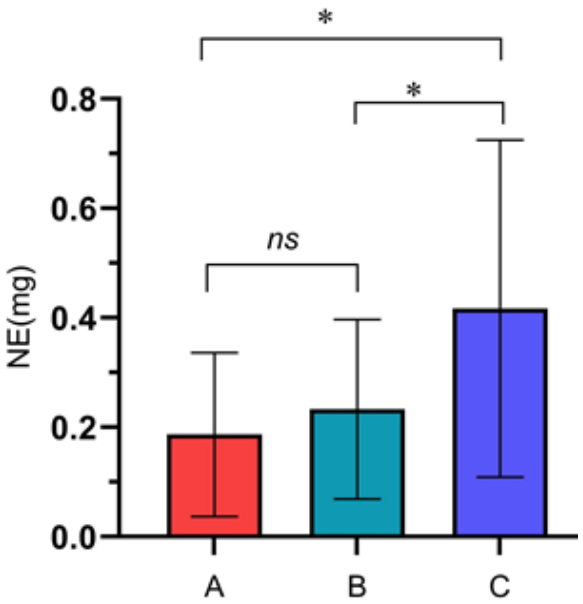

Figure 6: Comparison of the dose of Norepinephrine (NE) in three groups of elderly patients. Notes:nsIndicates Non-significant Difference, *IndicatesP<0.05

In this clinical trial, the MOAA/S scores of three groups of elderly patients during general anesthesia showed that the depth of anesthesia was adequate and effective (Figure 7). In the three groups of elderly patients, the MOAA/S scores were all ≤1, and there was no intraoperative awareness.

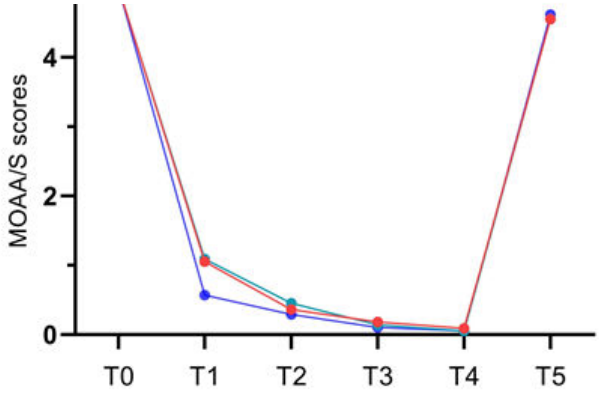

Figure 7: MOAA/S-time graph.

Notes:nsIndicates Non-significant Difference, *IndicatesP<0.05

DISCUSSION

The results showed that compared with propofol, RT has excellent characteristics of hemodynamic stability and fewer adverse reactions when used for anesthesia induction in elderly patients. Propofol combined with opioids is the most commonly used sedative in surgery worldwide [26]. However, each drug has advantages and disadvantages. The disadvantages of propofol are injection pain, cardiovascular and respiratory depression, and propofol infusion syndrome [27]. Most of the elderly patients with a variety of diseases, such as hypertension, diabetes, coronary heart disease, etc., their organ function is relatively young patients decline, there are also multiple drug use and other possible, resulting in clinical medication in elderly patients and young patients are different [28]. Therefore, anesthesiologists should use drugs rationally according to the physiological characteristics of different populations when choosing anesthetic drugs.

Remimazolam besylate is designed for fast onset of a short, predictable duration of sedative action, with more rapid recovery than currently available drugs such as propofol [29]. This pharmacodynamics profile is achieved by rapid hydrolysis of the drug's ester group by nonspecific tissue esterases to its pharmacologically inactive metabolite CNS 7054 [30]. Despite an increase in HR at 2 minutes after remimazolam administration, vital signs remain stable [31]. Pharmacokinetic modeling has shown that remimazolam has a high clearance rate, which is largely independent of body weight, and a small volume of distribution [32]. Its maximum half-life is less than 1 hour and remains unchanged when infused over 3 hours. RT is a new type of ultrashort-acting benzodiazepine that acts on Gamma-Aminobutyric Acid (GABA) receptors and was developed by Hengrui Medicine Co., Ltd, China. It was approved by the China Food and Drug Administration (CFDA) to start clinical development in March 2013. It inhibits neuronal action, reduces neuronal excitability and causes decreased body activity, sedation and amnesia [18] . Studies [33,35] have shown that RT is safe and effective for endoscopic sedation in elderly patients.

In this randomized trial, the two induction doses of RT (612 mg/kg/h and 12 mg/kg/h) showed noninferiority to propofol (2.0 mg/kg-2.5 mg/kg) in terms of efficacy when used as a sedative for general anesthesia. In fact, the success rate of anesthesia sedation was 95.45% in the 6 mg/kg/h RT group and 100% in the 12 mg/kg/h RT and propofol groups. Noninferiority of RT was observed (difference in rate-4.55%, 95% CI (-0.12; 0.03), meeting criteria for non-inferiority). During induction, both doses of RT resulted in a rapid LoC, indicating the compound's ability to induce anesthesia.

Maintenance was ensured by continuous intravenousinfusion. The mean BIS values for all three groups were in the range of 40-72, indicating a similar and adequate depth of anesthesia. Although the time to induction of anesthesia was not significantly different between the RT and propofol groups, the recovery time from anesthesia was longer in the latter group. The time to awaken from anesthesia was 17.33 ± 2.87 min, 17.23 ± 2.31 min, and 26.62 ± 4.84 min for patients in the 6 mg/kg/h RT, 12 mg/kg/h RT and propofol groups,respectively (P<0.05). This is a potential advantage of RT overpropofol. On the one hand, this advantage is attributed to themolecular design of RT, the ultrashort-acting nature of whichleads to its rapid breakdown into inactive metabolites bypopular tissue esterases [11]. On the other hand, this advantage may be attributed to the lower depth of sedation induced by RT. As shown by the sedation curve, propofol induced earlier and deeper sedation (MOAA/S=1) compared to RT (MOAA/S=3), which resulted in a longer recovery time.Therefore, RT decreases the time to recovery from anesthesia.In terms of anesthesia recovery, the time of the RT group was significantly shorter than that of the propofol group (P<0.05). Moreover, the RT groups had a shorter time to extubation[36]. Inaddition, this trial was similar to the results reported. The effect of remimazolam on HR was not obvious. The incidence of bradycardia was significantly lower in the RT groups than in the propofol group. The time of anesthesia induction and resuscitation was not significantly different between the RT 6mg/kg/h and RT 12 mg/kg/h groups, and both RT 6 mg/kg/h and RT 12 mg/kg/h also had little effect on the patient's hemodynamics (P>0.05). None of the patients in the RT 6mg/kg/h, RT 12 mg/kg/h, or propofol group experienced intraoperative awareness .

All treatment regimens were very safe, with no deaths duringthe trial and no patients with severe AEs. Overall, a greaterproportion of patients experienced AEs with propofol (100%)than with RT (16.28%). Of these, the most common AE wasinjection site pain, which occurred in all patients in thepropofol group (100%) but not in all patients who received RT.In this trial, a greater proportion of patients in the propofolgroup (100%) than in the different-dose RT groups (76.2% *vs.*86.4%) required vasoactive drugs, and the intraoperativenorepinephrine dose in the propofol group was 0.42 (± 0.31)mg. The elderly patients in the RT groups had a lowerincidence of hypotensive events than those in the propofolgroup. There was no significant difference in the incidence ofintraoperative hypotension (19.05% *vs.* 9.09%) or dosage ofvasoactive drugs (76.19% *vs.* 86.36%) between the 6 mg/kg/hand 12 mg/kg/h RT groups. Additionally, 1 patient in the propofol group experienced nausea and vomiting postoperatively.

CONCLUSION

This disparity in favor of RT deserves special attention due to the growing evidence of an impact of intraoperativehypo tension on postoperative cognitive function in elderlypatie nts. Nevertheless, the trial was not fully standardized interm s of concomitant medications and their potential impacton h emodynamics or general fluid management.

There aresome limitations of this trial. First, it was a single-b lind study,with no confidentiality among the investigators.Sec ond, there is an overall lack of multicenter, large-scale clinical data, and most anesthesiologists adjust theirmedic ation based on clinical parameters, such as bloodpressur e and heart rate, and similar parameters are used toassess the efficacy of anesthetics. This trial is no exception,and bi ases in the results may exist. Third, only relatively healt hy patients (ASA II) wererecruited in this study, and older patients with ASA III andabove and those with recent acu te high-risk diseases wereexcluded. Last, studies on BIS moni toring have shown that thecorrelation between BIS and benz odiazepines was not ideal [37].Therefore, excessive attention to BIS monitoring results may make the depth of anesthesi a in elderly patients using RT anesthesia too deep or too sh allow. Further in-depth research is needed to study the corr elation between RT and BIS.

In summary, the results of this clinical trial study showed that RTcombined with remifentanil and cisatracurium was n on-inferior to propofol in terms of sedation success rate for in duction and maintenance of general anesthesia in elderly pati ents. There was no significant difference between the two ane sthesia induction doses ofRT6 mg/kg/h and 12 mg/kg/h in ter ms of anesthesia induction time and anesthesia recovery time. As a novel sedative hypnotic, RT had a superior safety profile t o propofol in terms of hypotension and injection pain. The fo rmer is not only associated with accelerating recovery from an esthesia, but also has little effect on body heart rate, and can reduce the use of vasoactive drugs, indicating that RT may be a suitable alternative sedative agent for elderly patients than p ropofol.

ETHICS AND REGISTRATION

This study was approved by the clinical trials ethics committee of Dongguan people's hospital (KYKT2020-054), The study p rotocol was registered at Clinical Trials.gov (ChiCTR210004727 4) on 11/06/2021. And registered at this study protocol was performed at affiliated Dongguan hospital, southern medic al university (Dongguanpeople's hospital) in China, betwee n March 2021 and April 2022. This study was conducted in accordance with the principles of the declaration of Helsinki, and the protocol followed the consort guidelines.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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