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Efficacy and safety of remimazolam tosilate in anesthesia for short otolaryngology surgery

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Abstract

Background Remimazolam tosilate represents the novel ultrashort-acting benzodiazepine drug. This work focused on exploring whether remimazolam tosilate was effective and safe in anesthesia for short otolaryngology surgery in adults, and optimize its medication regimen, thus providing a theoretical basis for its widespread clinical application.

Methods The present unicentric, double-blind, randomized controlled study enrolled altogether 85 otolaryngology surgery patients aged 18–60 years, and they were divided as remimazolam (RM, 42 cases) or midazolam (MD, 43 cases) group. Efficacy outcomes included successful sedation time, sedation effect (Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score), bispectral index values (BIS), and postoperative recovery. The safety outcomes were patient vital signs at each time point (before induction (T0), 2 min and 5 min after trial drug treatment (T1 and T2 separately), during successful intubation (T3), at the end of surgery (T4), during extubation (T5), and at the time of exiting the room (T6)), any adverse reactions (AEs) during perioperative period, and patient satisfaction with anesthesia experience.

Results Demographics were not significantly different in both groups ($P > 0.05$). RM group had significantly decreased successful sedation time relative to MD group ($P < 0.05$), while increased successful sedation rate (100%) relative to MD group (90.70%, $P = 0.116$). RM group showed decreased MOAA/S score and BIS value compared with MD group at T1 and T2 ($P < 0.05$). The spontaneous respiration recovery time and extubation time were not significantly different in both groups ($P > 0.05$), but RM group exhibited decreased discharge time compared with MD group ($P < 0.05$). Compared with MD group, the RM group had lower blood pressure (BP) at T3 ($P < 0.05$); whereas higher heart rate (HR) and respiration rate (RR) at T1 and T2 ($P < 0.05$). Difference in AEs was not of statistical significance. Finally, RM group exhibited the increased satisfaction of anesthesia experience compared with MD group ($P < 0.05$).

Conclusion Remimazolam tosilate is effective on anesthesia for short otolaryngology surgery. Remimazolam shows the rapid onset, stable circulation, fast postoperative recovery, no increase in perioperative AEs, and high satisfaction with anesthesia experience compared with midazolam.

Trial Registration https://www.chictr.org.cn/ (ChiCTR2200067123) on 27/12/2022. This study was consistent with CONSORT guidelines.

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Keywords Remimazolam tosilate, General anesthesia, Otolaryngology surgery

Introduction

Adult otolaryngology short surgeries mostly involve throat and nose surgery, with a shorter time and faster turnover velocity. Thus, the requirement for anesthesia management is high, which requires not only appropriate sedation and rapid onset but also rapid postoperative recovery [1].

Among drugs used for general anesthesia induction, those classic hypnotic and sedative agents include benzodiazepines, among which, the representative drug is midazolam; it is also the first clinically used water-soluble sedative and hypnotic drug. It not only provides sedation, but also simultaneously acts as an auxiliary application of general anesthesia drugs, thereby reducing the dosage of other drugs. However, its disadvantages include slow onset and pharmacological activity of the metabolites, prolonging the recovery time [2, 3]. In addition, there could be an accumulation effect, resulting in residual sedation after recovery [4].

Remimazolam represents the new ultrashort-acting benzodiazepine drug, which acts on gamma-aminobutyric acid type A (GABA(A)) receptors in the central nervous system for producing anesthetic sedation. It can be rapidly hydrolyzed via a tissue nonspecific esterase in vivo, and its metabolites have no pharmacological activity with no effect on liver and kidney function [5, 6]. On January 23, 2020, Japan had first approved the use of remimazolam for general anesthesia, subsequently in November 2021, China had approved its application [7]. Previous clinical trials have proven its faster metabolism compared with midazolam, along with rapid recovery and better safety and efficacy [8–11]. Prolonged injection time or high dosage of remimazolam rarely causes accumulation or delayed recovery, and moreover, it can be antagonized by flumazenil even when excessively used [12]. Remimazolam tosilate is found to be safe during outpatient colonoscopy, upper gastrointestinal endoscopy [13], and flexible bronchoscopy with rapid recovery after surgery [14].

Compared with midazolam, remimazolam tosilate is advantageous as a sedative not only in outpatient endoscopic treatment, but also in induction of general anesthesia for short surgeries. However, currently, the application of anesthesia to induce sedation in otolaryngology surgery has not been reported. Considering the advantages of remimazolam tosilate and the short surgery conducted in the otorhinolaryngology department, the primary aim of this study was to apply remimazolam tosilate to short otolaryngology surgery in adults to explore its appropriate sedation and rapid postoperative recovery after induction of general anesthesia; the secondary aim was hemodynamic stability during the perioperative period and patient satisfaction with anesthesia experience. Finally we hope to optimize the anesthesia induction medication regimen.

Materials and methods

Study design

The present prospective, unicentric, double-blind, randomized, controlled trial was carried out between April 2022 and January 2023 in Second Affiliated Hospital of Zunyi Medical University. Our protocol gained approval from medical ethics review committee of the Second Affiliated Hospital of Zunyi Medical University(NO. KYLL-2022-027). Every patient or the legal representative provided informed consent prior to performing these procedures. This study was performed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) criteria and the Declaration of Helsinki, registered in the Chinese Clinical Trial Registry (https://www.chictr.org.cn, ChiCTR2200067123, 27/12/2022).

Patient inclusion and exclusion criteria

Otorhinolaryngological short surgery in adults who underwent general anesthesia for endotracheal intubation participated in this study. A total of 92 patients from April 2022 to January 2023 were recruited in our trial. Of these, 7 were excluded, and 85 were recruited into this work. Patients below were included: (1) adults who were to undergo an otorhinolaryngological short surgery (procedure time 10 min to 1 h) under general anesthesia with tracheal intubation, consistent with surgical indications; (2) aged 18–60 years with no sex limitation; and (3) grades I-II according to American Society of Anesthesiologists (ASA) guideline. Patients below were excluded: (1) there were contraindications to surgery and patients and the families refused to sign informed consent; (2) heart rate < 50 beats per minute; (3) incurable acute respiratory inflammation for 2 weeks; (4) those with severe metabolic diseases of heart, brain, lung, liver or kidney; (5) those who have or possessed a history of difficult airway or abnormal recovery from surgical anesthesia; (6) those with hyperkalemia, hypokalemia or other obvious electrolyte abnormalities with dysplasmic disorders; (7) those allergic to benzodiazepines; (8) preoperative usage of other sedative or analgesic drugs (injection, oral or use of relevant proprietary Chinese medicine); (9) those suspected to have sedative or narcotic analgesic abuse; and (10) patients with neuromuscular system diseases.

Randomization and blinding

We randomized all patients as remimazolam tosilate (RM) or midazolam (MD) group. The randomization was completed by an anesthesiologist blinded to these trials and responsible for drug preparation and outcome assessment with the use of sealed envelopes. Every procedure was carried out by one otolaryngologist and anesthesiologist group blinded to grouping. Before anesthesia, we randomized all patients into RM or MD group at the 1:1 ratio. All the patients had no knowledge of allocation. After completing this study, group allocation information was unblinded.

Procedures

An 8-h routine fasting from solids and a 2-h fasting of clear fluid were conducted in all patients. After entering the operating room, the patients were subjected to establishment of venous access. Standard vital signs were monitored, including electrocardiogram (ECG), noninvasive blood pressure (BP), heart rate (HR), respiration rate (RR), bispectral index (BIS), and pulse oxygen saturation (SpO_2).

Patients were sedate with the trial drugs and observed for 5 min before induction of general anesthesia. Once intubation conditions were achieved following anesthesia induction, endotracheal intubation was performed. After the operation, every patient was transferred to postanesthesia care unit (PACU). An observer recorded relevant indicators until the patients awaked. If the patient did not wake up 30 min after surgery, we considered giving the antagonist flumazenil. All patients exited the operating room once they were fully alert following adequate mask oxygen inhalation.

Postoperative follow-up: on the 2nd postoperative day, the patients were questioned regarding their satisfaction with the experience of sedation and anesthesia.

Interventions

Sedation was induced by intravenous injection with 0.3 mg/kg [15, 16] remimazolam tosilate (Jiangsu Hengrui Pharmaceutical Co. Ltd. in China) or 0.075 mg/kg [17] midazolam (Jiangsu Enhua Pharmaceutical in China) to the RM or MD groups, respectively. All patients were under observation for 5 min following administration of the sedative. Subsequently, 0.01 mg/kg penehyclidine hydrochloride, 3 ug/kg sufentanil, 0.3 mg/kg etomidate and 0.8 mg/kg rocuronium bromide were intravenously injected.

Later, 4–12 mg/kg/h propofol and 3-120 ug/kg/h remifentanil combined with sevoflurane 1-2% inhalation were used for anesthesia maintenance. If a muscle relaxant was needed, we intravenously injected rocuronium bromide (20 mg). A loading dose of sufentanil (10ug) and flurbiprofen ester (50 mg) were administered 10 min before the completion of the procedure, and sevoflurane was simultaneously discontinued. Propofol and remifentanil were withdrawn postoperatively.

Efficacy and safety evaluation

The efficacy evaluation: (1) the sedative effect of the experimental drug was observed mainly using the bispectral index (BIS: 81–100 points, waking state; 61–80 points, mild-moderate sedation; 41–60 points, moderate-severe sedation; ≤40 points, depressed state) and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score (Table 1) [18]. Sedation success [13, 19] was defined as reaching an appropriate sedation level (MOAA/$S \leq 3$) after trial drug injection. MOAA/$S \geq 4$ was defined as alert. (2) time to sedation success recorded using BIS level and MOAA/S score (from sedative drug injection to MOAA/S≤3) after administering the trial drug; (3) time of spontaneous respiration recovery (from immediately after surgery to spontaneous breathing resumption), extubation time (after procedure until tracheal extubation) and exit time (from removal of the tracheal tube until exiting the operating room); (4) recorded the Steward recovery score (Table 2) [20] 10, 15 and 30 min postoperatively and determined the level of wake fulness (Grade 0: Patient is asleep and breathing unresponsive; Grade 1: Patient falls asleep, breathing with body movement or eye opening, head and neck movement; Grade 2: Patient is awake and has grade 1 presentation with open mouth and tongue; Grade 3: Patient is awake, has grade 2 performance and can say his/her name and age; Grade 4: Patient is awake, has grade 3 performance and recognizes people in the environment or their position).

The safety evaluation: (1) at each time point (T0~T6: preinduction (T0), 2 min post-drug administration (T1), 5 min post-drug administration (T2), upon successful

Table 1 Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score [18]

Response	Score
Ready response to name spoken in a normal tone	5 (alert)
Lethargic response to name spoken in normal tone	4
Only responses to name spoken repeatedly or loudly	3
Only responses to mild prodding or shaking	2
No response to mild prodding or shaking	1
No response to noxious stimulation	0

Table 2 Steward recovery score [20]

	Level of consciousness	Degree of airway patency	Physical activity
2 points	Fully awake	Coughing according to the order	Conscious activity
1 point	Response to stimulation	Maintaining airway patency without support	Unconscious activity
0 point	No response to stimulation	Supported respiration	Non-limb activity

Patients with Steward recovery score ≥ 4 were allowed to leave the anesthesia recovery room

tracheal tube intubation (T3), at the end of the surgery (T4), upon tracheal extubation (T5), and at the time of exiting the operating room (T6)), vital signs were recorded, including BP, HR, RR and SpO_2; (2) the rate of postoperative agitation/delirium occurrence 5, 10, 15, 20 and 30 min after recovery; (3) intraoperative awareness incidence; (4) use of antagonists; and (5) adverse reactions (AEs) incidence, including hypoxia, airway obstruction and respiratory depression. The AEs severity was evaluated in line with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0, with grades 1–4 being categorized into mild, moderate, severe, and life-threatening or disabling, separately [13].

Patients' satisfaction was assessed using a five-point Likert scale [21]: 1 = Strong dissatisfaction, 2 = Dissatisfaction, 3 = Not sure, 4 = Satisfaction and 5 = Strong satisfaction. Scores > 3 were deemed as satisfaction, whereas those ≤ 3 as dissatisfaction. We conducted a telephone follow-up to question the patients' satisfaction with sedation and anesthesia on the 2nd postoperative day, with setting up the following question "On the overall, how satisfed are you with the sedation and anesthesia you have received?" with responses on a five-point Likert scale – very dissatisfed to very satisfed.

Common AEs and rescue measures during the study: hypoxia was defined as oxygen desaturation (SpO_2 < 90% for > 60 s) [14, 22]. Without hypoxia, maneuvers below were performed when needed: increased oxygen delivery, face mask, chin lift, jaw thrust, inserted oropharyngeal airway or mechanical ventilation through tracheal intubation. We deemed respiratory depression to be RR < 8 breaths/min. Once respiratory depression occurred, respiration was closely observed, and ventilation was assisted by initiating mask pressurization, with tracheal intubation being conducted when needed. Hypotension was deemed to be mean arterial pressure (MAP) decrease of > 20% compared with baseline or SBP ≤ 80 mmHg. In the case of hypotension, fluid therapy was immediately administered (130/0.4 hydroxyethyl starch and sodium chloride given through intravenous infusion). As for unsatisfactory fluid resuscitation efficacy, vasoactive agents were administered (9 mg ephedrine or 100 μg phenylephrine (a rescue IV bolus), according to HR. Hypertension was defined as MAP increased by > 20% compared with baseline or SBP ≥ 140 mmHg and managed through 10–15 mg urapidil. Besides, bradycardia was deemed to be HR < 60 beats/min or decreased by > 20% relative to baseline and managed through 0.5 mg atropine. Besides, tachycardia was deemed to be HR > 100 beats/min or increased > 20% relative to baseline and managed through 10 mg esmolol.

Sample size and statistical analysis

In this study, midazolam was used as the control, and the sedation success rate of MD and RM groups was assumed to be 95%. $\alpha = 0.05$ stood for significance, and degree of assurance was set at $1\text{-}\beta = 90\%$. The sample size of $n = 36$ persons per group was calculated using PASS software, and the shedding rate of each group was considered to be 20%. It was calculated that 45 people per group would be enrolled for analysis, and altogether 90 people would participate in this study.

SPSS software (Version 29.0, IBM Corp, Armonk, NY, USA) was employed for statistical analysis. Continuous data conforming to normal distribution were represented by mean ± standard deviation ($\bar{\chi} \pm s$) and examined by Student's t-test. Homogeneity of variance was examined by a single-factor analysis of variance (ANOVA), while heterogeneity of variance was analyzed through a non-parametric test (Wilcoxon rank sum test). Differences between groups were compared by independent sample t-tests, while those in individual groups were compared by repeated measurement univariate analysis of variance. Categorical data were represented by percentages (%) and analyzed by a chi-square test or Fisher's exact test. Rank data were analyzed by rank sum test. $P < 0.05$ stood for statistical significance.

Results

Patient demographics

There were altogether 92 patients recruited for the work and they were randomized as remimazolam tosilate (RM, $n = 46$) and midazolam (MD, $n = 46$) group. Among them seven were excluded, including four patients in the RM group whose surgery time was > 1 h, two patients in the MD group whose surgery time was > 1 h and one patient in the group MD whose surgery time was < 10 min. Finally, we recruited 85 patients, including 42 of RM whereas 43 of MD groups. The detailed study flow is shown in Fig. 1.

Table 3 displays patients' demographics. Age, sex, height, weight, BMI, and ASA classification were not significantly different in RM versus MD groups ($P > 0.05$).

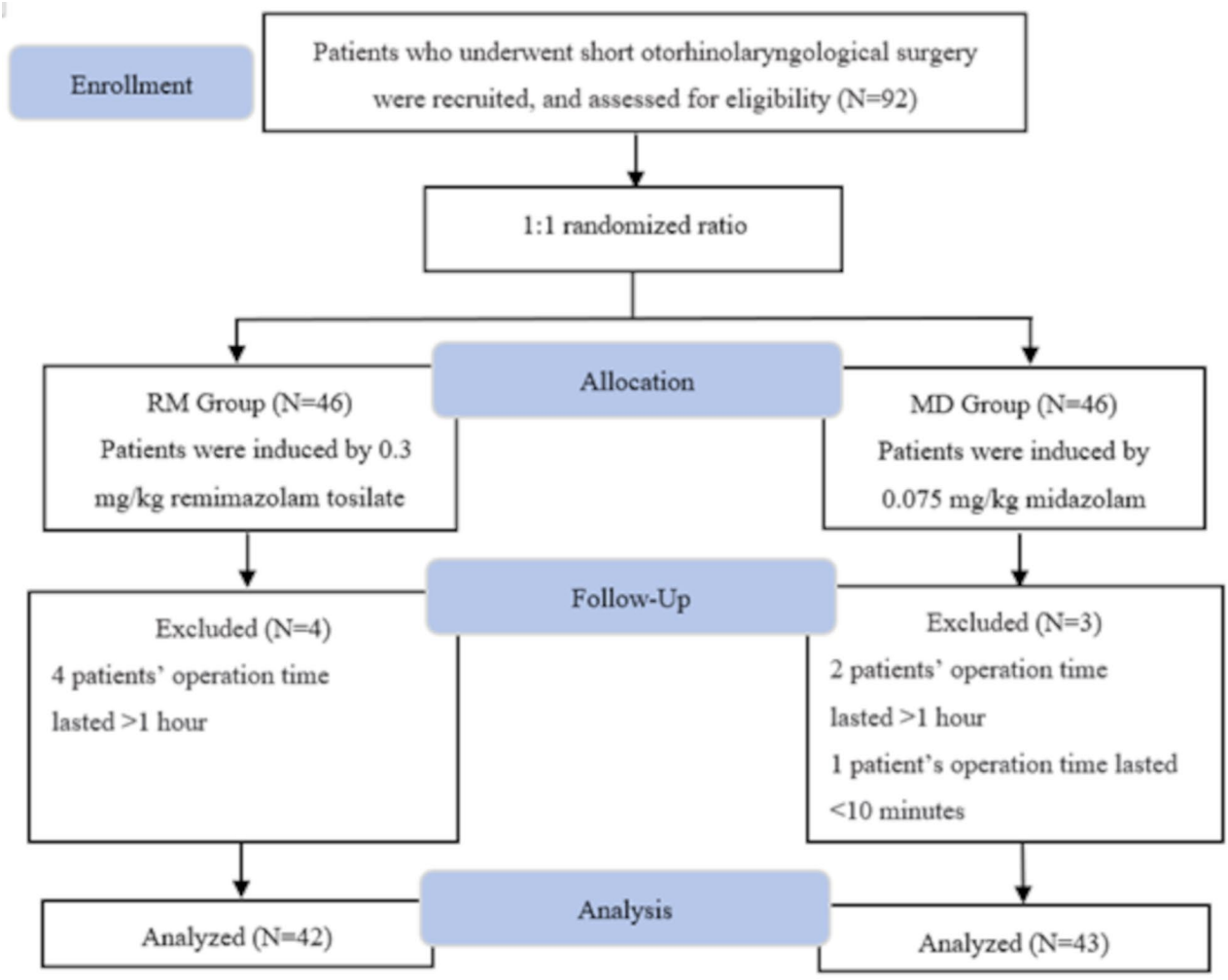

Fig. 1 CONSORT flow diagram showing of the study participants

Table 3 Demographics of both study groups

	Group RM (*N* = 42)	Group MD (*N* = 43)	t/χ^2 value	*P* value
Age (years), mean ± SD	35.55 ± 12.51	38.40 ± 12.13	1.066	0.290
Sex, n (%)			0.015	0.902
Male	24(57.14)	24(55.81)		
Female	18(42.86)	19(44.19)		
Height(cm), mean ± SD	163.86 ± 7.73	162.84 ± 7.52	-0.617	0.539
Weight(kg), mean ± SD	64.04 ± 10.50	63.60 ± 12.20	-0.174	0.862
BMI(kg/m^2),mean ± SD	23.79 ± 3.13	23.86 ± 3.59	0.098	0.922
ASA class, n.(%)			0.005	0.943
I	29(69.05)	30(69.77)		
II	13(30.95)	13(30.23)		

Data are represented by frequencies or means ± SD, SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists

Information on the operation and dosage of anesthesia

Information on the operation and anesthesia is listed in Table 4. The amount of bleeding was not recorded because the amount was small, and irrigation water was mixed. The short otorhinolaryngological operation time, infusion volume, and anesthetic use were not significantly different in both groups ($P > 0.05$).

Efficacy outcomes

The 100% and 90.70% successful sedation rates were noted in RM and MD groups, respectively. Although

Table 4 Data regarding the operation and anesthesia

	Group RM (*N* = 42)	Group MD (*N* = 43)	t value	*P* value
Duration of operation (min)	43.60 ± 12.11	38.70 ± 14.86	-1.663	0.100
Infusion volume (ml)	663.10 ± 152.64	651.16 ± 164.93	-0.346	0.730
Propofol(mg)	97.86 ± 25.71	86.74 ± 37.53	-1.589	0.116
Remifentanil(mg)	0.49 ± 0.12	0.43 ± 0.18	-1.912	0.059
Sevoflurane(ml)	25.12 ± 5.00	24.42 ± 5.90	-0.590	0.557

Data are represented as means ± SD

Table 5 Efficacy outcomes and postoperative recovery time

	Group RM (*N* = 42)	Group MD (*N* = 43)	t/χ^2 value	*P* value
Success rate of sedation (n, %)	42(100%)	39(90.70%)	4.100	0.116
Time to sedation success (s), mean ± SD	33.74 ± 6.95*	84.91 ± 42.62	10.725	0.000
Spontaneous breathing time (min), mean ± SD	19.12 ± 8.56	20.37 ± 9.32	0.645	0.520
Extubation time (min), mean ± SD	26.40 ± 10.69	27.51 ± 10.54	0.481	0.632
Exit time (min), mean ± SD	25.86 ± 7.06*	31.70 ± 12.96	2.587	0.012

*comparison with group MD, $p<0.05$

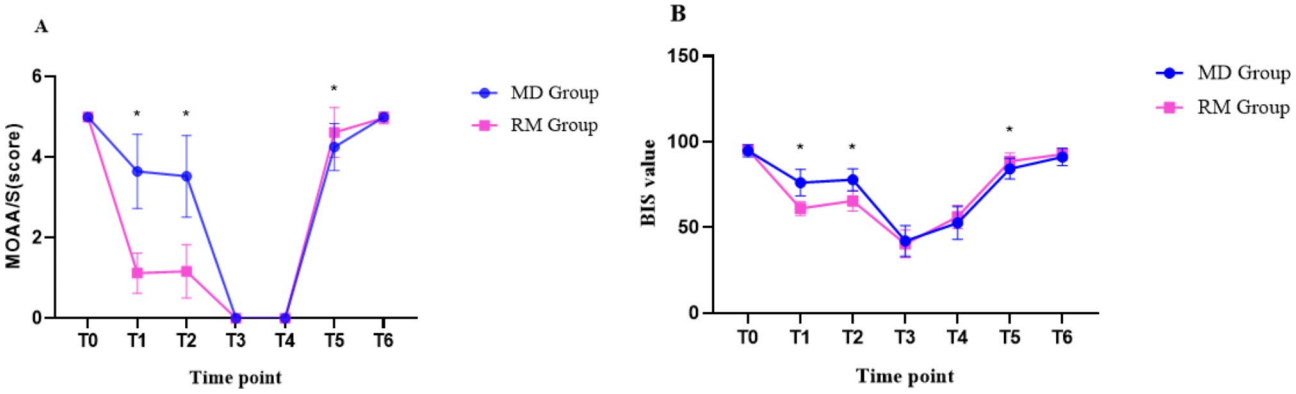

Fig. 2 MOAA/S and BIS values throughout the whole surgical process. Assessment of (**A**) MOAA/S score (**B**) BIS value at preinduction (T0), 2 min post-drug treatment (T1), 5 min post-drug treatment (T2), following successful tracheal tube intubation (T3), at the end of the surgery (T4), following tracheal catheter removal (T5), and at the time of exiting the operating room (T6). *Comparison with group MD, $p < 0.05$

sedation failed in four patients in the MD group, the successful sedation rate was not significantly different ($P>0.05$). RM group had a markedly shorter time to sedation success (33.74±6.95 s) than the MD group (84.91±42.62 s, $P<0.05$) (Table 5).

In this work, a base MOAA/S score of 5 was recorded when patients entered the operating room. When trial drugs were administered to the two groups, we observed that MOAA/S at T1 and T2 was significantly reduced in the RM group (1.12±0.50, 1.17±0.66) compared with that in the MD group (3.65±0.92, 3.53±1.01, $P<0.05$). MOAA/S=0 was maintained following anesthesia induction, for the sake of ensuring the adequate anesthesia state postoperatively. At T5, MOAA/S of RM group increased relative to MD group (4.62±0.62 vs. 4.26±0.58, $P<0.05$). Patients in both groups were alert (MOAA/$S>4$) and left the room ($P>0.05$, Fig. 2A).

We also detected the BIS value during the surgery. BIS values of RM group remarkably decreased relative to MD group at T1 and T2 (61.05±4.06 vs. 76.12±7.71; 65.45±5.93 vs. 77.76±6.39, $P<0.05$). However, at T5, the BIS value of the RM group (88.50±4.76) apparently increased relative to MD group (84.24±6.11, $P<0.05$). The rest time points were not significantly different ($P>0.05$, Fig. 2B).

The postoperative recovery time of RM group, including spontaneous respiration recovery time, extubation time, and exit time, decreased relative to MD group as shown in Table 5. Spontaneous respiration recovery time (19.12±8.56 min vs. 20.37±9.32 min, $P=0.520$) and extubation time (26.40±10.69 min vs. 27.51±10.54 min, $P=0.632$) of RM group slightly decreased relative to MD group, but no significant difference was observed. However, RM group had markedly decreased mean exit time (25.86±7.06 min) relative to MD group (31.70±12.96 min, $P<0.05$).

We recorded the Steward recovery score and level of wakefulness postoperatively at 10, 15, and 30 min. The Steward recovery score and wakefulness level of

Table 6 Steward recovery score

	Group RM (*N* = 42)	Group MD (*N* = 43)	t value	*P* value
10 min postoperation (point)	0.95 ± 1.78	0.88 ± 1.43	-0.196	0.845
15 min postoperation(point)	2.50 ± 2.09	2.33 ± 2.08	-0.386	0.700
30 min postoperation(point)	5.43 ± 1.40	5.33 ± 1.43	-0.336	0.738

Data are represented as means ± SD

Table 7 Level of wakefulness

	Group RM (*N* = 42)	Group MD (*N* = 43)	Z value	*P* value
10 min postoperation (n (%))			-0.018	0.986
Grade 0	33(78.57)	33(76.74)		
Grade 1	3(7.14)	5(11.63)		
Grade 2	3(7.14)	5(11.63)		
Grade 3	1(2.38)	0(0)		
Grade 4	2(4.76)	0(0)		
15 min postoperation			-0.358	0.720
Grade 0	17(40.48)	19(44.19)		
Grade 1	12(28.57)	11(25.58)		
Grade 2	8(19.05)	10(23.26)		
Grade 3	1(2.38)	0(0)		
Grade 4	4(9.52)	3(6.98)		
30 min postoperation			-0.965	0.334
Grade 0	3(7.14)	2(4.65)		
Grade 1	2(4.76)	1(2.33)		
Grade 2	2(4.76)	8(18.60)		
Grade 3	1(2.38)	2(4.65)		
Grade 4	34(80.95)	30(69.77)		

RM group slightly increased compared with MD group ($P > 0.05$) (Tables 6 and 7).

Safety outcomes

At each time point, vital signs, including BP, HR, and RR, were analyzed as shown in Fig. 3A ~ 3E. At T3, SBP, DBP, and MAP of RM group apparently decreased relative to MD group ($P < 0.05$); at T6, MAP of RM group markedly increased relative to MD group ($P < 0.05$). BP was not significantly different in both groups at remaining time points ($P > 0.05$, Fig. 3A ~ 3 C). After trial drug administration, SBP, DBP, and MAP gradually decreased in both the groups, particularly at T2; at T3, SBP, DBP, and MAP increased, but the amplitude of increase of RM group decreased compared with MD group; possibly due to anesthesia, BP was at the lowest level at T4; at T5, the BP increased and slightly decreased at T6, and that of RM group increased relative to MD group (Fig. 3A ~ 3 C). This indicated that BP fluctuation of RM group decreased. HR and RR in RM group evidently increased relative to MD group at T1 and T2 ($P < 0.05$); however, the remaining time points were not significantly different ($P > 0.05$, Fig. 3D and E). In the RM group, following remimazolam administration, HR and RR increased, while MD group did not show any obvious change. This trend of fluctuation of HR was similar to that of BP at T3-T6.

No intraoperative awareness or postoperative agitation/delirium was observed in either group. During the recovery phase, three patients from RM group while five from MD group received antagonist flumazenil at PACU ($P = 0.713$).

Table 8 lists the incidence of AEs. During the induction of sedation, grade 1 - grade 3 hypoxia (minimum SpO_2 76%) occurred in nine (21.43%), five (11.90%) and six (14.29%) patients, respectively in the RM group; whereas only one (2.33%) patient demonstrated grade 1 hypoxia of MD group. However, difference was of no statistical significance ($P > 0.05$). Among the six patients with grade 3 hypoxia, five received jaw thrust maneuver treatment, and one returned to normal oxygen saturation without treatment. However, after extubation at PACU, two patients showed signs of hypoxia with a minimum SpO_2 of 74%, and one patient even experienced hypoxia three times and received jaw thrust maneuver treatment. One patient experienced dyspnea after extubation in the MD group. In the RM group, upper airway obstruction occurred in 28 (66.67%) patients (18 (42.86%), 9 (21.43%), and 1 (2.38%) had grades 1, 2, and 3 AEs, respectively), and of those, three received jaw thrust maneuver treatment. In the MD group, upper airway obstruction occurred in 18 (41.86%) patients (16 (37.21%) and 2 (4.65%) had grade 1 and 2 AEs, respectively, whereas no patient had grade 3 AEs). In our study, the change in HR manifested as tachycardia, and six (14.29%) patients in the RM group (five (11.90%) had grade 1 AEs, and one (2.38%) had grade 2 AEs) had tachycardia, whereas one

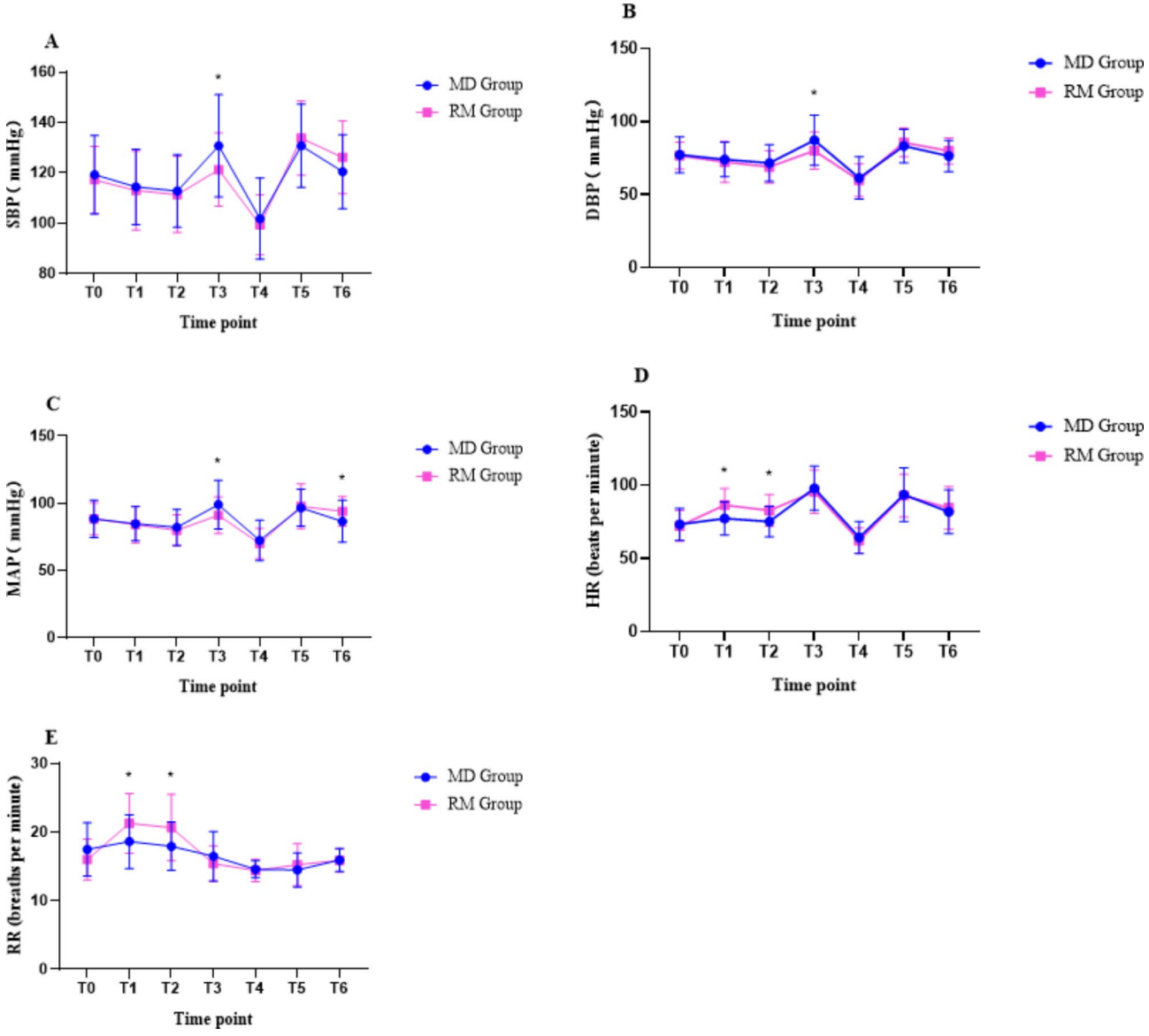

Fig. 3 Vital signs in the whole operation process. Assessment of (**A**) SBP, (**B**) DBP, (**C**) MAP, (**D**) HR and (**E**) RR at preinduction (T0), 2 min post-drug treatment (T1), 5 min post-drug treatment (T2), following successful tracheal tube intubation (T3), at the end of the surgery (T4), following tracheal catheter removal (T5), and at the time of exiting the operating room (T6). *comparison with group MD, $p<0.05$

(2.33%) had grade 1 tachycardia of MD group, but no significant difference was observed ($P>0.05$). In addition, one respective patient from two groups developed hypotension during surgery and were treated with 6 mg ephedrine IV.

Patient satisfaction with anesthesia

All patients' satisfaction scores were >3. The satisfaction score of the RM group (4.71±0.46) remarkably increased relative to MD group (4.40±0.49, $P=0.006$).

Discussion

The present work is the first to apply remimazolam tosilate for anesthesia during otolaryngology surgery for evaluating their effectiveness and safety compared with midazolam. This prospective, double-blind, randomized controlled trial analyzed 85 patients. The observations of this study are as follows: (1) the onset of action of remimazolam tosilate was faster than that of midazolam, the successful sedation rate increased, and sedation was deeper in patients undergoing short otolaryngology surgery. Although not statistically significant, the postoperative recovery time after remimazolam administration was slightly faster than that after midazolam administration;

Table 8 Incidence of adverse reactions

Variable, *n* (%)	Group RM (*N* = 42)	Group MD (*N* = 43)	Z/χ^2 value	*P* value
Hypoxia			-0.981	0.327
Grade 1	9(21.43)	1(2.33)		
Grade 2	5(11.90)	0(0)		
Grade 3	6(14.29)	0(0)		
Hypoxia after extubation	0(0)	2(4.65)	2.001	0.494
Dyspnea after extubation	0(0)	1(2.33)	0.988	1.000
Upper airway obstruction			-1.857	0.063
Grade 1	18(42.86)	16(37.21)		
Grade 2	9(21.43)	2(4.65)		
Grade 3	1(2.38)	0(0)		
Change in heart rate			-0.408	0.683
Grade 1	5(11.90)	1(2.33)		
Grade 2	1(2.38)	0(0)		

but the final discharge time with remimazolam was significantly shorter than that with midazolam. (2) BP slightly decreased after remimazolam induction, but no hypotension was noted. At the time of intubation, BP, HR and RR increased, but the increases in amplitude were smaller than those with midazolam. (3) Compared with midazolam, remimazolam did not significantly increase perioperative AEs. (4) Finally, patients who received remimazolam had a more satisfactory anesthesia experience than those who received midazolam.

Otorhinolaryngology surgery is mostly a short surgery with fast turnover velocity. Appropriate sedation is crucial during the perioperative period. Remimazolam salts include benzene sulfonate and tosylate salt. Tosylate salt has higher optical purity and lower toxicity, and its clinical application has better safety [23]. It was manufactured in Jiangsu Hengrui Pharmaceutical Co. Ltd. in China and approved for sedation in 2020 [24].

The results of our trial are consistent with the characteristics of remimazolam. We found that remimazolam had a significantly faster onset than that of midazolam, with a mean of 33.74 s in the RM group vs. 84.91 s of MD group; the successful sedation rates were 100% and 90.70% of RM and MD groups, separately. These findings conform to those reported by Nicholas J.et al. suggesting the shortened onset and accelerated neuropsychiatric recovery compared with midazolam during flexible bronchoscopy [25]. In addition, BIS and MOAA/S were adopted for determining sedation depth, with MOAA/S≤3 or BIS value≤80 defining successful sedation. In our study, at T1 and T2, we observed decreased BIS and MOAA/S scores in RM relative to MD groups. Besides, Steward recovery score and level of wakefulness in RM group slightly increased relative to MD group at PACU, and the exit time in RM group (25.86±7.06 min) was shorter than MD group (31.70±12.96 min), conforming to prior reports. Remimazolam provides satisfactory anesthetic effects for surgery, with faster recovery and a shorter PACU stay time [26]. Another study reported that patients administered remimazolam had fast neuropsychiatric functional recovery, and early discharge compared with those administered midazolam [9, 23]. This may be related to the pharmacological properties of remimazolam [5, 6].

Some changes in vital signs were observed after remimazolam administration, such as a slightly lower BP, higher HR, and faster RR. Although the decline in BP was similar in the two groups, the magnitude of the increase in HR and RR of RM group increased relative to MD group. Such result aligns with that reported by Zhu X, et al. who suggesting the weak impacts on inhibiting circulation and respiration compared with midazolam [27]. At T3, both BP and HR were increased, the mean MAP was 91.19 mmHg vs. 99.00mmHg and HR was 95.67 beats per min vs. 97.98 beats per min in the RM and MD group respectively. These results demonstrate that the group RM had less stress response stimulation and more stable hemodynamics [16].

AEs such as hypoxia are common during the perioperative period. Only a few patients experienced a transient decrease in SpO_2 after induction (minimum SpO_2 76%). When a patient appeared hypoxic, a jaw thrust maneuver was performed to raise SpO_2. The hypoxia rate of RM group increased compared with MD group. Upper airway obstruction, primarily manifesting as snoring, occurred in both the groups. However, not all patients with upper airway obstruction developed hypoxia. Nevertheless, the occurrence of hypoxia and dyspnea after extubation in the MD group received timely treatment. Therefore, remimazolam administration requires an anesthesiologist with clinical experience, and professional equipment for anesthesia machines and oxygen supply. Other AEs, such as the change of HR, primarily manifested as tachycardia, but not bradycardia. Overall, the AEs of RM group was not increased relative to MD group. This finding fits previous studies that revealed remimazolam is the sedative with high tolerance and low AEs such as

respiratory and circulation depression in patients undergoing endoscopy [10, 25].

Previous studies have demonstrated comparable or superior patient satisfaction with remimazolam sedation relative to other sedatives, such as propofol or dexmedetomidine [14, 26]. In our trial, patients in the RM group reported higher satisfaction scores than those in the MD group, indicating that patients who received remimazolam experienced a more satisfactory anesthetic outcome.

Limitations

Certain limitations should be noted in our trial. Firstly, this was an unicentric investigation that had a small sample size. Secondly, we selected patients aged 18–60 years according to the instructions with ASA classification I-II, and we did not consider various populations, such as elderly and younger individuals with higher ASA classification. Thus, more large-scale studies are needed for validating our findings.

Conclusions

To sum up, remimazolam tosilate is effective on the anesthesia for short otolaryngology surgery. Relative to midazolam, remimazolam shows a faster onset, rapider postoperative recovery, more stable circulation, higher satisfaction with anesthesia experience, and no increase in perioperative adverse reactions.

Abbreviations

MOAA/S	Modified alertness/sedation
BIS	Bispectral index values
ASA	American Society of Anesthesiologists
ECG	Electrocardiogram
BP	Noninvasive blood pressure
SBP	Systolic pressure
DBP	Diastolic pressure
MAP	Mean arterial pressure
HR	Heart rate
RR	Respiration rate
SpO_2	Pulse oxygen saturation
AE	Adverse event
PACU	Postanesthesia care unit
BMI	Body mass index
GABAA	Gamma-aminobutyric acid type A

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Author contributions

W.C. contributed to study design and manuscript drafting; Y.C. recruited patients and performed the study; H.H. performed statistical processing; D.Z. completed the postoperative observation and follow-up; J.W. prepared the figures and reviewed the tables; Y.Z. was responsible for study directing and manuscript revising; Z.W. was in charge of study directing and supervising. Our authors have read and agreed to the final version for submission.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was permitted by the medical ethics review committee of the Second Affiliated Hospital of Zunyi Medical University (NO. KYLL-2022-027) and registered in the Chinese Clinical Trial Registry (ChiCTR2200067123). Every patient or the legal representative provided informed consent prior to performing these procedures. This study was performed in accordance with the CONSORT criteria and Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Figures' authenticity

The figures presented are plotted by our authors, who verify the image originality without any duplication or previous publication.

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