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Comparative study of the efficacy and safety of remimazolam and midazolam for general anesthesia in elderly patients: a randomized controlled trial

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Abstract

Background Elderly patients are a vulnerable group with high perioperative risks. Thus, reducing the duration of anesthesia is important. Remimazolam is a benzodiazepine sedative commonly used for the induction and maintenance of general anesthesia given its rapid induction and rapid recovery. Most reports have focused on nonelderly patients.

Aim To compare the time to loss of consciousness, length of PACU stay and incidence of adverse events in patients older than 65 years who received remimazolam for general anesthesia with those of patients who received midazolam.

Methods This study was conducted at a university hospital between February 2022 and March 2023. We included 100 patients aged 65 years or older who were scheduled for surgery under general anesthesia. Patients were divided into 2 groups, namely, the midazolam group and the remimazolam group, with 50 patients in each group. The primary outcome was the time to loss of consciousness. The secondary outcomes included the time to extubation and length of PACU stay. We also recorded the percentage of flumazenil used and incidence of adverse events.

Results Clinical data from 96 patients who were scheduled for surgery under general anesthesia were included in the final analysis, with 46 patients in the remimazolam group and 50 patients in the midazolam group. The time to loss of consciousness was 304 (222, 330) s in the remimazolam group and 95 (67, 25) s in the midazolam group, and the difference was significant ($p=0.000$). The time to extubation was 24.93 ± 11.617 min in the remimazolam group and 34.88 ± 19.740 min in the midazolam group, revealing a significant difference ($p=0.003$). The length of PACU stay was 55 (48, 64) min in the remimazolam group and 65 (55, 85) min in the midazolam group, and the difference was significant ($p=0.001$). The percentage of flumazenil used was 6% in the remimazolam group and 20% in the midazolam group, and the difference was significant ($p=0.003$).

Conclusion General anesthesia with remimazolam has been shown to be effective and safe for surgery in elderly patients. The time to extubation was significantly shorter, length of PACU stay was shorter, and percentage of flumazenil used was lower in the remimazolam group than in the midazolam group.

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Keywords Remimazolam, Elderly patients, Midazolam

Introduction

Remimazolam is a new and ultrashort-acting sedative used for procedural sedation, general anesthesia, and in intensive care units. Although its structure is similar to that of midazolam, remimazolam has an ester-linked side chain to the diazepine ring, making it an ultrashort-acting intravenous drug that is metabolized rapidly, mainly by liver tissue esterases (Oka et al. 2021). There are currently many related studies on the use of remimazolam in young patients, but very few of them have focused on senile patients. Elderly patients, as a special group, have low body resistance and are often comorbid with multiple underlying diseases, thus resulting in high perioperative anesthesia requirements (Bantie et al. 2020; Pu and Sun 2019). The same should be true for the use of remimazolam. Midazolam is traditionally used for induction and maintenance of general anesthesia. Compared with remimazolam, midazolam has a longer drug half-life. As elderly patients age, their hepatic and renal functions gradually decline, and their ability to metabolize anesthetic drugs is reduced, which can easily lead to drug accumulation in the body, potentially causing delayed recovery from anesthesia and subsequently increasing the risk of perioperative complications. Although existing studies have shown that remimazolam has a lesser impact on the hemodynamics of elderly patients, its pharmacokinetic characteristics (such as clearance rate and half-life) and long-term safety still require further verification. Moreover, when remimazolam is used in combination with opioids (such as fentanyl and remifentanil), the additive effects on respiratory depression and circulatory depression, as well as the mechanism of interaction, have not been fully elucidated. This randomized controlled trial compared remimazolam and midazolam for general anesthesia in elderly patients (aged >65).The goal was to evaluate remimazolam's efficacy and safety versus midazolam in elderly surgical patients and offer clinical insights.

Materials and methods

The study was approved by the ethics committee of The Second Affiliated Hospital of Xi'an Medical University (XZY202219) and conducted in accordance with the Helsinki Declaration. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2400082156) and conducted according to the Consolidated Standards of Reporting Trials statement. Each participant provided written informed consent. We provided participants with detailed information about the study aims, procedures, and risks before enrolling them in the study.

Study design and patients

This study was a randomized controlled trial. Since the sample size calculated using the primary research outcome of the time to loss of consciousness was too small, we opted to use the secondary research outcome of the time to extubation for sample size calculation. The sample size was determined based on a pilot study. In this pilot study, the mean ± standard deviation for the time to extubation was 21.88 ± 8.63 min in the remimazolam group and 31.68 ± 18.71 min in the midazolam group. Under the conditions of setting the significance level at 0.05 (two-tailed) and the test power at 0.9, and based on the calculated effect size of 0.72, each group requires at least 41 participants. From February 2022 to March 2023, 100 patients who were older than 65 years and underwent surgery under general anesthesia at the Department of Anesthesiology, The Second Affiliated Hospital of Xi'an Medical University, Xi'an, China, were included. All patients underwent laparoscopic surgery under general anesthesia, including laparoscopic cholecystectomy, laparoscopic total hysterectomy with bilateral adnexectomy, and laparoscopic hernia repair. The inclusion criteria were as follows: patients over 65 years who underwent elective surgery under general anesthesia, regardless of sex; were classified as having an American Society of Anesthesiologists (ASA) status I–III and who had a body mass index lower than 30 kg/m^2; patients or authorized family members who provided their consent in writing; and patients who were willing and able to comply with the research requirements and underwent follow-up on the 7 th day after surgery. The exclusion criteria were as follows: patients who were allergic to benzodiazepines, nicotinamides, opioids or flumazenil; had a history of cerebral hemorrhage or cerebral infarction; were receiving long-term treatment with benzodiazepines for anxiety or insomnia; had a history of long-term use of opioids; were using illicit drugs regularly; had a history of drug abuse; had a positive drug screening test; had a history of alcohol or substance abuse in the past 2 years; had used the investigational drug within 30 days prior to screening or within seven half-lives of the agent, whichever is longer; patients who had participated in remimazolam clinical trials; and patients who were unable to communicate and those who the investigator considered unsuitable for the study.

Randomization and grouping

Patients were divided into 2 groups using a random number table: the midazolam group (M group) and the remimazolam group (R group), with 50 patients in each group. First, the random number table method was used to ensure equal distribution in the two groups (the remimazolam group and the midazolam group). A nurse anesthetist, who was not involved in anesthetisizing the patients, was responsible for randomization. The nurse anesthetist opened the sealed envelope just before entry into the operating room. She or he then prepared the medications and recorded the data according to the instructions inside the envelope and put the recorded data back in the envelope to reseal. The anesthesiologist induced anesthesia according to the instructions in the envelope. Finally, after the data of all the enrolled patients were collected, envelopes were opened only by good clinical practice (GCP) monitoring and by the investigators. Thus, all patients, data collectors, and data analysts were blinded to the group allocation.

Anesthesia induction and maintenance

All patients were evaluated prior to surgery to ensure the patient's understanding and cooperation. Total intravenous anesthesia was used for the induction and maintenance of anesthesia.

As soon as the patient entered the operating room, the electrocardiograph (ECG), noninvasive blood pressure, and pulse oximetry were routinely monitored, and peripheral venous access was established. Following at least 5 min of rest, the baseline data were recorded.

Anesthesia induction: A constant infusion of 1 mg/kg/h remimazolam (Renfu Pharmaceutical Co. Ltd., approval number: 30 T06081) was performed in Group R (Bantie et al. 2020) until consciousness disappeared. According to the product instructions, midazolam (Jiangsu Enhua Pharmaceutical Co. Ltd., approval number: TMZ23D03) 0.1 mg/kg was administered intravenously for 20–30 s in Group M. After the patient lost consciousness, intravenous treatment began in the two groups via the sequential administration of 0.15 mg/kg etomidate (Jiangsu Enhua Pharmaceutical Co. Ltd., approval number: TMZ23D03 TYT23B45), 0.5 μg/kg sufentanil (Renfu Pharmaceutical Co. Ltd., approval number: 31 A021812), and 0.6 mg/kg rocuronium bromide (Hainan Sida Pharmaceutical Co. Ltd., approval number: 2306040 A), and after 60 s, tracheal intubation was performed.

Anesthesia maintenance: During anesthesia maintenance, the remimazolam group was maintained by pumping remimazolam at 0.1–0.2 mg/kg/h until the end of the procedure. The half-life of midazolam is approximately 90–150 min. If the total time exceeds 150 min measured from the induction of anesthesia to the completion of the procedure, a 25% induction dose of midazolam was given via an intravenous bolus in Group M. After tracheal intubation, anesthesia was maintained by a continuous infusion of 2–4 mg/kg/h propofol and 0.25–2 μg/kg/min remifentanil during surgery. If necessary, additional single increments of 0.5–1.0 μg/kg remifentanil were given when appropriate, or with additional single increments of 25–50 mg propofol when appropriate. When the time-to-recovery of muscle function was 25% (TOF 25), a 0.15 mg/kg rocuronium bromide intravenous bolus was administered. At the end of surgery, 2–4 mg/kg sugammadex was given to reverse the effects of the muscle relaxant. During surgery, hemodynamics were carefully maintained by adjusting the fluid infusion volume and using anesthetic drugs and/or vasoactive drugs. The BIS value was maintained between 40 and 60, the mean arterial pressure (MAP) was maintained between 70 and 100 mmHg, and the HR was maintained between 50 and 100 beats per minute (bpm). Propofol, remimazolam, and remifentanil infusion was discontinued at the end of surgery.

Outcome measures

General data, including sex, age, height, weight and body mass index (BMI), were recorded

The values of MAP, HR and SpO_2 were recorded at baseline (5 min after arrival at the operating room (T0)), immediately after the test drug injection (T1), before intubation (T2), immediately after intubation (T3), 1 min after intubation (T4), after all drug withdrawal (T5), before extubation (T6), immediately after extubation (T7), 3 min after extubation (T8), 6 min after extubation (T9), and at the PACU discharge criteria (T10).

The primary outcome was the time to loss of consciousness

The secondary outcomes included the time to extubation and length of PACU stay. The time to loss of consciousness (time from the induction of anesthesia until the disappearance of the eyelash-conditioned reflex), total anesthesia time (time from the induction of anesthesia to the discontinuation of all drugs), time to extubation (the time from the discontinuation of anesthetics to extubation), and length of PACU stay (the time when the patient arrived at the PACU to the time of PACU discharge of the two groups of patients) were recorded and compared. For anesthesia induction and anesthesia maintenance, the total dosage of the experimental drug administered to the two groups was recorded, and the total time of anesthesia and the total dosages of propofol and remifentanil were recorded. During the first 30 min of the procedure, if no eye opening was observed, patients were given a 0.3 mg intravenous bolus of flumazenil, and the number of cases was counted and recorded.

With the exception of the BIS recorded, patients who showed signs of movement or arousal (including changes in heart rate or blood pressure, lacrimation, and sweating) during the procedure were monitored and recorded

Intraoperative awareness was assessed via modified Brice interviews. When patients were fully awake (defined as 3 consecutive modified observer assessment of alertness/sedation (MOAA/S) scores of 5), their recall ability was evaluated via the Brice questionnaire before discharge from the PACU. Intraoperative recall or awareness was assessed with a modified Brice structured interview on the first postoperative day and at the 1-week postoperative assessment, and the factors possibly related to the intraoperative awareness of patients were counted and recorded.

At the end of discharge from the PACU

The anesthesia effects were evaluated by trained clinical staff (supervised by the principal investigator) using a three-point scale (Excellent = 1, Good = 2, Poor = 3).

The occurrence of any adverse events was recorded

Adverse events were defined as any untoward medical event that occurred during the hospital stay but was not necessarily related to medication use. Adverse events were defined as an intraoperative systolic blood pressure exceeding ± 20% from the baseline value on two successive occasions or a heart rate greater than ± 20% above the baseline. If severe adverse events occurred, then vasoactive drugs (atropine or ephedrine, noradrenaline or phenylephrine) were administered, and the name and dosage of the drug were recorded in detail.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 statistical software. Quantitative measurement data were presented as the mean ± standard deviation. For nonparametric data, the median (interquartile range) was employed to describe the central tendency and variability. Qualitative data were described through frequency distributions (expressed as percentages).The normality of the data was tested via the Kolmogorov–Smirnov test. The data that conformed to a normal distribution were analyzed via Student's t test, and those that did not adhere to a normal distribution were analyzed via the Mann–Whitney U test. Between-group comparisons were performed via one-way ANOVA. The counting data were compared via the χ^2 test, and $P < 0.05$ indicated that the difference was statistically significant.

Results

Baseline characteristics of the study participants

We included 100 patients according to the inclusion and exclusion criteria: 50 patients were in the M group (midazolam group), 46 patients were in the R group (remimazolam group) (Fig. 1), and 4 patients in the remimazolam group were not successfully followed up via telephone at 1 week postoperative. There were no significant differences in sex, age, or BMI between the 2 groups (Table 1).

Outcomes

The primary outcome was the time to loss of consciousness. The secondary outcomes included the time to extubation and length of PACU stay.

The time to loss of consciousness was 304 (222, 330) s in the remimazolam group and 95 (67, 25) s in the midazolam group, and the difference was significant ($p =$ 0.000; Table 2). The time to extubation was 24.93 ± 11.617 min in the remimazolam group and 34.88 ± 19.740 min in the midazolam group; the difference was significance ($p =$ 0.003; Table 2). The length of PACU stay was 55 (48, 64) min in the remimazolam group and 65 (55, 85) min in the midazolam group, and the difference was significant ($p =$ 0.001; Table 2). The percentage of flumazenil used was 6% in the remimazolam group and 20% in the midazolam group, and the difference was significant ($p =$ 0.003; Table 3). The total dosages of remimazolam were 6.30 ± 1.996 mg and 14.00 ± 9.033 mg, and the total dosages of midazolam were 6.06 ± 0.925 mg and 0.63 ± 0.800 mg, respectively (Table 4). There were no significant differences between the two groups in terms of the total anesthesia time, intraoperative awareness rate, anesthesia effects, and total dosage of atropine, ephedrine, noradrenaline, phenylephrine, propofol, or remifentanil (Tables 2, 4, 5). The percentage of patients with intraoperative awareness was 8.7% in the remimazolam group and 16% in the midazolam group, and the difference was not significant between the two groups ($p =$ 0.280; Table 5).

There was no significant difference in HR between the remimazolam and midazolam groups (For detailed results, please refer to Tables 6 and 7.) MAP was significantly greater in the remimazolam group than in the midazolam group immediately after extubation (T7) ($p =$ 0.048; Table 8). The SpO_2 was significantly lower in the remimazolam group than in the midazolam group immediately after extubation (T7) ($p =$ 0.004; Table 8) and at PACU discharge (T10) (p = 0.041; Table 8). For detailed results, please refer to Tables 9, 10, and 11.

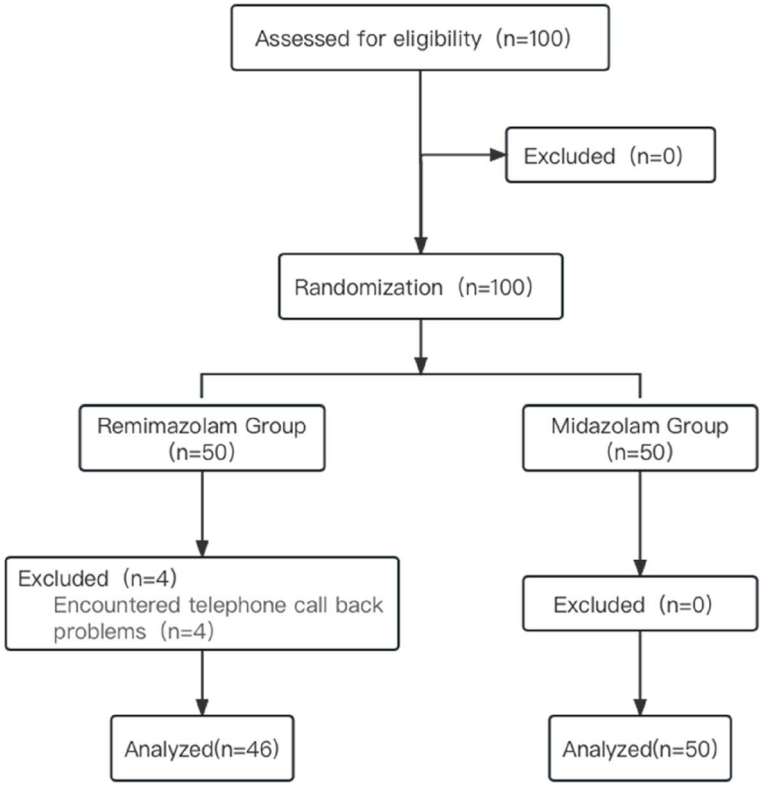

Fig. 1 Consort flow diagram of patients

Table 1 Baseline characteristics of the study participants

Group	Male/female (*n*)	Age (years)	BMI (kg/m^2)
Remimazolam	20/26	69 (67, 74)	23 (21.2, 24.9)
Midazolam	29/21	70 (66, 75)	24 (22, 25)
Z	− 0.411	− 0.754	− 0.396
p value	0.681	0.451	0.692

Discussion

Remimazolam mainly acts on the GABA-A receptor and has the advantages of rapid induction, rapid recovery, stable hemodynamics, and mild respiratory inhibition (Keam 2020; Wesolowski et al. 2016a). This is provided by the binding of the benzodiazepine molecule, which causes a conformational change in the chloride ion channel to cause hyperpolarization and thus inhibition of the central nervous system (Noor et al. 2021). It is an

Table 2 Primary and secondary outcomes (s/min/point)

Group	Loc (s)	AT (min)	ET (min)	PT (min)	AE (point)
Remimazolam	304 (222, 330)	133 (87, 180)	24.93 ± 11.617	55 (48, 64)	1 (1, 2)
Midazolam	95 (67, 25)	117.5 (67, 189)	34.88 ± 19.740	65 (55, 85)	1 (1, 2)
Z	− 7.555	− 0.367	-	− 3.235	− 1.075
p value	0.000	0.714	0.003	0.001	0.282

Abbreviations: Loc Lost consciousness time, *AT* Anesthesia time, *ET* Extubation time, *PT* PACU stay time, *AE* Anesthesia effects

Table 3 Flumazenil use statistics

Group	Total, *n*	Yes, *n* (%)	No, *n* (%)	Difference and 95% CI (%)	χ^2	*p* value
Remimazolam	46	6 (13)	40 (87)	27 (62.9–81.5)	8.816	0.003
Midazolam	50	20 (40)	30 (60)			

Table 4 Intraoperative medication use statistics (mg/μg)

Group	Induction (mg)	Maintenance (mg)	Total dosage (mg)	Propofol (mg)	Remifentanil (mg)	EP (mg)	NE (mg)	PE (μg)	AP (mg)
Remimazolam	6.30 ± 1.996	14.00 ± 9.033	20.30 ± 9.217	315 (230, 700)	1.43 (1, 2)	6.57 ± 0.929	1.74 ± 1.216	5.22 ± 3.648	0.022 ± 0.015
Midazolam	6.06 ± 0.925	0.63 ± 0.800	6.69 ± 1.418	324 (300, 600)	1.7 (1, 2.5)	5.00 ± 0.906	0.00 ± 0.000	6.67 ± 3.639	0.083 ± 0.040
Z	-	-	-	− 0.415	− 0.661	-	-	-	-
p value	-	-	-	0.678	0.509	0.110	0.138	0.484	0.159

Abbreviations: AP Atropine, *EP* Ephedrine, *NE* Noradrenaline, *PE* Phenylephrine

Table 5 Intraoperative awareness

Group	Total, *n*	PA, *n* (%)	NA, *n* (%)	Difference and 95% CI (%)	χ^2	*p* value
Remimazolam	46	4 (8.7)	42 (91.3)	7.3 (79.2–93.4)	1.169	0.280
Midazolam	50	8 (16)	42 (84)			

Abbreviations: PA Possibly related to intraoperative awareness, *NA* No intraoperative awareness

Table 6 Fluctuations in heart rate (HR) among the study participants (beats/minute)

Group	T0	T1	T2	T4	T6	T7	T10
Remimazolam	75.80 ± 12.81	74.74 ± 11.32	67.89 ± 11.84	72.74 ± 10.21	81.89 ± 11.46	88.20 ± 13.20	79.98 ± 9.34
Midazolam	77.02 ± 11.19	76.78 ± 10.15	71.34 ± 12.52	72.62 ± 12.02	85.12 ± 16.64	85.44 ± 15.08	80.22 ± 10.78
p value	0.621	0.354	0.170	0.959	0.268	0.345	0.907

Data are presented as the mean ± SD

ultrashort-acting novel benzodiazepine, similar to midazolam and remifentanil in terms of their complementary advantages (Tanious et al. 2017). One study revealed that the pharmacokinetic half-life of remimazolam is approximately one-fifth that of midazolam after 3 h of constant-rate infusion (Masui 2020). A study also revealed that when remimazolam was used, there were no significant changes in Lac or Glu values before or after endotracheal intubation, which indicated that no hypoxia or excessive stress led to in tissue perfusion dysfunction (Liu et al. 2021). Additionally, remimazolam does not affect liver or kidney function, and it does not accumulate after long-term infusion (Liu et al. 2021).

This study was a randomized controlled trial in which we compared the time of loss of consciousness, length of PACU stay, percentage of flumazenil used and incidence of adverse events in patients who were older than 65 years who received remimazolam for general anesthesia with those of patients who received midazolam. We found that the time to loss of consciousness was significantly shorter with midazolam than with remimazolam, and the time to extubation was shorter, length of PACU stay was shorter, and percentage of flumazenil used was significantly lower with remimazolam than with midazolam for elderly patients.

In our study, the time to loss of consciousness was 304 (222, 330) s in the remimazolam group and 95 (67, 25) s in the midazolam group, and the difference was significant ($p = 0.000$). One study of remimazolam revealed that the time from drug administration to optimal sedation was shorter for remimazolam (approximately 1.5–6.4 min) than for midazolam (Lee and Shirley 2021), which

Table 7 Fluctuations in heart rate (HR) among the study participants (beats/minute)

Group	T3	T5	T8	T9
Remimazolam	81 (69, 91)	69 (62, 80)	81 (77, 85)	79.5 (76, 85)
Midazolam	81 (66, 93)	68 (60, 75)	80.5 (72, 86)	76 (73, 85)
Z	− 0.573	− 0.672	− 0.893	− 1.458
p value	0.567	0.502	0.372	0.145

Table 8 Fluctuations in MAP (mmHg) and SpO_2 (%) among the study participants

Group	T7 (MAP)	T7 (SpO_2)	T10 (SpO_2)
Remimazolam	115.3 ± 13.56	96.52 ± 2.934	96.96 ± 2.241
Midazolam	109.84 ± 13.20	98.02 ± 1.813	97.98 ± 2.564
p value	0.048	0.004	0.041

Table 9 Fluctuations in mean arterial pressure (MAP) among the study participants (mmHg)

Group	T1	T7	T8	T9	T10
Remimazolam	89.61 ± 12.78	115.3 ± 13.56	110.65 ± 12.23	105.67 ± 10.78	103.98 ± 8.40
Midazolam	94.34 ± 14.54	109.84 ± 13.20	108.22 ± 11.95	107.00 ± 12.65	103.58 ± 10.73
p value	0.095	0.048	0.372	0.583	0.841

Data are presented as the mean ± SD

Table 10 Fluctuations in mean arterial pressure (MAP) among the study participants (mmHg)

Group	T0	T2	T3	T4	T5	T6
Remimazolam	100 (93, 109)	77 (68, 86)	94.5 (76, 104)	88 (72, 94)	84 (75, 93)	108.5 (99, 118)
Midazolam	102.5 (89, 111)	79 (73, 86)	87.5 (78, 96)	81 (72, 94)	83 (77, 86)	105.5 (98, 114)
Z	− 1.046	− 0.543	− 1.549	− 0.819	− 0.925	− 0.665
p value	0.296	0.587	0.121	0.413	0.355	0.056

is consistent with our results concerning the time to loss of consciousness; however, in our study, the time to loss of consciousness in the remimazolam group was longer than that in the midazolam group. A possible reason for this difference is that remimazolam was administered as a continuous intravenous infusion rather than a bolus dose, whereas midazolam was administered as a bolus dose. A study of older patients revealed that the time to loss of consciousness was 80 (69, 86) s and that the time to tracheal intubation was 322 (292, 346) s after the remimazolam infusion was started at 6 mg/kg/h (Nakanishi et al. 2021). In our study, the time to loss of consciousness was 304 (222, 330) s because the remimazolam infusion was started at 1 mg/kg/h. A previous study revealed that when the infusion rate of remimazolam is faster, it is easier to achieve a deeper level of sedation (Schüttler et al. 2020), which could explain why our results differ from those of previous studies investigating the time to loss of consciousness.

In our study, the length of PACU stay was significantly shorter in the remimazolam group than in the midazolam group ($p = 0.001$), the time to extubation was significantly shorter in the remimazolam group than in the midazolam group ($p = 0.003$), and the percentage of flumazenil used was significantly lower in the remimazolam group than in the midazolam group ($p = 0.003$), mainly because the half-life of remimazolam was very short. In a study comparing remimazolam with midazolam, lower-dose, on-label midazolam had similar recovery characteristics to remimazolam but a significantly longer time to produce adequate initial sedation, whereas higher-dose, real-world midazolam produced a similar rapid onset of sedation to remimazolam but significantly longer recovery times (Dao et al. 2022), which is consistent with our research results.

Elderly patients with reduced reserves of various physiological functions have poor anesthesia tolerance, and the risk of anesthesia increases to some extent (Evered et al. 2017). However, in most reports, remimazolam was used to induce general anesthesia in nonelderly patients (Sheng et al. 2020; Doi et al. 2020). Even though the effects of age and ASA class were small in terms of the time to extubation following awakening form remimazolam anesthesia, lower doses of remimazolam are recommended for some fragile elderly patients. Therefore, anesthesia was induced with a 1 mg/kg/h infusion of remimazolam, and the anesthesia induction process was peaceful. In our study, there was no significant difference

Table 11 Fluctuations in SpO_2 among the study participants (%)

Group	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Remimazolam	97.48 ± 1.859	99.43 ± 0.729	99.61 ± 0.649	99.61 ± 0.774	99.61 ± 0.774	99.57 ± 0.981	97.87 ± 2.754	96.52 ± 2.934	97.91 ± 2.169	98.22 ± 2.107	96.96 ± 2.241
Midazolam	98.02 ± 1.491	99.10 ± 1.261	99.74 ± 0.443	99.74 ± 0.527	99.74 ± 0.527	99.24 ± 2.404	98.64 ± 2.456	98.02 ± 1.813	98.24 ± 1.956	98.48 ± 2.112	97.98 ± 2.564
p value	0.121	0.109	0.254	0.338	0.338	0.395	0.151	0.004	0.440	0.544	0.041

Data are presented as the mean ± SD

between the remimazolam and midazolam groups in terms of HR or MAP during anesthesia induction, indicating that the anesthesia induction process was peaceful. The time to loss of consciousness was significantly shorter in the midazolam group than in the remimazolam group ($p = 0.000$), possibly because during anesthesia induction, remimazolam is administered as a continuous intravenous infusion rather than a bolus dose, whereas midazolam is administered as a bolus dose.

One study on remimazolam revealed that involuntary movement was the most notable adverse event during infusion (Schüttler et al. 2020). However, in our study, we did not observe this adverse event, because of the muscle relaxant used in our study, and there were no significant differences between the two groups in terms of the total dose of atropine, ephedrine, noradrenaline, phenylephrine, propofol, or remifentanil. The MAP was significantly greater in the remimazolam group than in the midazolam group immediately after extubation ($p = 0.048$). These findings indicated that the effect of remimazolam on circulatory dynamics was comparable to that of midazolam. Therefore, remimazolam is safe for anesthesia induction and maintenance in elderly patients. Remimazolam undergoes rapid metabolism via abundantly available plasma and tissue esterases, organ-independent metabolism, and a first-order pharmacokinetic profile independent of body weight and elimination clearance while maintaining a similar safety profile to that of midazolam (Wesolowski et al. 2016b; Pambianco et al. 2016), which is consistent with our research results. In our study, although SpO_2 was significantly lower in the remimazolam group than in the midazolam group at the time of extubation ($p = 0.004$), and at the time of PACU discharge ($p = 0.041$), it was still well within the ranges considered safe.

With respect to the dose of remimazolam, one study revealed that the initial dose of remimazolam to induce adequate sedation was 0.04–0.2 mg/kg by a single iv over 1 min or 5 mg by a single bolus iv (Lee and Shirley 2021). Therefore, to induce anesthesia, remimazolam was infused at a rate of 1 mg/kg/h. We observed that during anesthesia induction, the total dose of remimazolam was 6.30 ± 1.996 mg, which was greater than 5 mg. One study revealed that the remimazolam ED95 was 0.118 mg/kg (95% CI 0.103–0.649) and 0.090 mg/kg (95% CI 0.075–0.199) in elderly patients aged 60–69 and 70–85 years, respectively (Liu et al. 2022). More studies are needed to determine the optimal dose of remimazolam for older patients. In our study, the percentage of intraoperative awareness was 8.7% in the remimazolam group and 16% in the midazolam group. Although there were no significant differences between the two groups, we believe that remimazolam may have some advantages in reducing the incidence of intraoperative awareness. This point has not been addressed in previous studies. More studies are needed to confirm this point.

Conclusion

In conclusion, the time to loss of consciousness was significantly shorter with midazolam than with remimazolam. Compared with the patients who received midazolam, those who received remimazolam had a significantly shorter time to extubation, shorter length of PACU stay, and lower percentage of flumazenil used. No severe adverse events associated with remimazolam sedation were observed. General anesthesia with remimazolam has been shown to be effective and safe in elderly patients undergoing surgery.

Limitations

In this study, midazolam and remimazolam were administered through different methods. The administration methods we chose were commonly used in clinical practice, with midazolam administered via intravenous bolus injection and remimazolam via intravenous infusion pump. These two different administration methods may have a certain impact on the study results. However, the study still holds certain value. It is recommended that future studies consider using a consistent administration method.

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Authors' contributions

All authors have contributed significantly to all aspects of the work, including the conceptualization, design, methodology, analysis, and writing. YWJ. GZL. GYY and CCY wrote the main manuscript text .All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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