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Effect of Remimazolam vs Midazolam on Early Postoperative Cognitive Recovery in Elderly Patients Undergoing Dental Extraction: A Prospective Randomized Controlled Study

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Purpose: Elderly patients undergoing dental extraction are particularly susceptible to delayed cognitive recovery after sedation. This study aimed to compare the effects of remimazolam and midazolam on early postoperative cognitive recovery in elderly patients undergoing dental extraction.

Patients and Methods: This was a single-centre randomized controlled study with elderly patients scheduled for receiving dental extraction under sedation of remimazolam (Group R) or midazolam (Group M). The primary outcome was postoperative cognitive recovery, as measured by the Montreal cognitive assessment 5-minute (MoCA 5-minute) 30 min postoperatively (T_{30}). Secondary outcomes included MoCA 5-minute score 1 h postoperatively (T_{1h}), incidence of post-extraction bleeding, intraoperative adverse events, success rate of sedation, time to discharge, and complications.

Results: 106 patients (53 in each group) were eligible for the study. At T_{30}, MoCA 5-minute score was 25 (IQR 23.5, 27) in Group R, significantly higher than that of 23 (IQR 21, 25) in Group M ($P < 0.001$). This difference persisted at T_{1h} [27 (IQR 26, 28) vs 26 (IQR 25, 27), $P = 0.003$]. Group R also exhibited better hemostasis, with a lower post-extraction bleeding rate at T_1 (5.67% vs 33.96%, $\chi^2 = 13.36$, $P < 0.001$). Group R showed significantly shorter times to peak sedation after the first dose of medication, awake time, and time to discharge compared to Group M ($P < 0.001$, $P < 0.001$, $P < 0.001$).

Conclusion: Remimazolam sedation significantly improves early postoperative cognitive recovery, leading to expedited hemostasis and a shorter discharge time.

Keywords: remimazolam, midazolam, elderly patients, cognitive recovery, sedation, dental extraction

Introduction

The global increase in the aging population has led to a growing number of elderly individuals seeking dental treatment.[1,2] Dental extraction is often the initial step in their treatment, addressing issues like residual roots and periodontitis. However, the vulnerability of elderly patients to adverse events, particularly cardiovascular incidents resulting from stress during dental procedures, has prompted the widespread use of intravenous sedation to mitigate these risks.[3–5]

Midazolam, renowned for its sedative, anxiolytic, and amnestic properties, is a common choice for dental sedation in the elderly.[6] Despite its efficacy, the biological activity of midazolam metabolites, with an elimination half-life of 1.8–6.4 hours, can lead to prolonged recovery time for patients undergoing dental extraction.[7,8] This heightened susceptibility to delayed cognitive recovery not only extends the discharge time but also compromises patient compliance and increases the risk of post-extraction bleeding.

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Remimazolam, a novel benzodiazepine medication, serves as an ultra-short-acting γ-aminobutyric acid sub-type A (GABAA) receptor agonist and an analog of midazolam. By modulating the central GABAA receptor, it hyperpolarizes the nerve cell membrane, increases chloride ion influx, and inhibits neuronal activity, thereby inducing sedative and amnestic effects.[9,10] Notably, remimazolam's sedative effects dissipate rapidly, leading to a shorter recovery time, as it undergoes swift conversion to inactive metabolites by tissue esterases in the body.[11,12] Furthermore, its primary excretion through the kidneys sets it apart from midazolam, which is metabolized by liver metabolism.[13]

Despite remimazolam's increasing use in elderly patients for various procedures, such as gastrointestinal endoscopy, bronchoscopy, and general anesthesia, its application in elderly patients undergoing dental procedures remains relatively underexplored in existing literature.[14] Therefore, this study aims to investigate and compare the impact of remimazolam and midazolam on early postoperative cognitive recovery in elderly patients following tooth extraction.

Materials and Methods

Trial Design

The trial was carried out at the School of Stomatology, Fourth Military Medical University, from June 2022 to June 2023. The study was approved by the Institutional Review Board of the School of Stomatology, Fourth Military Medical University (approval number: IRB-REV-2021091, approval date: 22 October 2021) and registered on the Chinese Clinical Trial Registry (ChiCTR2200062344; principle investigator: Bing Liu; registration date: 02 August 2022). The trial adhered strictly to the principles outlined in the Declaration of Helsinki and CONSORT guidelines. The first research participant was recruited into the study on 10 August, 2022 and all participants provided written informed consent.

Patients

The participants comprised elderly individuals aged 60–80 years undergoing tooth extraction, with American Society Anesthesiologists (ASA) grades 1–3 and BMI 18–30 kg/m^2. Patients were excluded if they had a history of neurological disorders (cognitive impairment, dementia, brain damage, etc), severe cardiovascular and cerebrovascular diseases, ASA grade above 3, liver dysfunction, chronic or acute liver failure, renal insufficiency, chronic or acute kidney failure, myasthenia gravis, known allergies to benzodiazepines or local anesthetics, refusal to undergo sedation, a history of alcohol or drug abuse, dental extraction in an emergency period, and participation in other clinical trials within the past three months.

Randomization and Masking

All eligible patients were randomly assigned to either the remimazolam group (Group R) or the midazolam group (Group M). Randomization was generated with a 1:1 allocation ratio from the web (https://www.random.org/) by an investigator with no clinical involvement in the trial. The allocation, sealed in an envelope by an independent investigator, was provided to the attending anesthesiologist before entering the operation room. Remimazolam and midazolam were prepared in accordance with the random number and both drugs were prepared at 1mg/mL. The anesthesiologists administering the sedation were not blinded to group allocation but were not involved in perioperative care or follow-up. Both patients and outcome assessors were blinded to treatment allocation. The outcome assessors were research assistants who had been trained in the assessment prior to the study.

Sedation Procedure

Prior to sedation, patients were assessed using the Montreal Cognitive Assessment (MoCA) 5-minute and the Modified Dental Anxiety Scale (MDAS). Experienced anesthesiologists and dentists were responsible for sedation and tooth extraction. Patients were positioned in a dentist chair and received supplemental oxygen (2 L/min) via nasal cannula. Vital signs, including heart rate (HR), noninvasive blood pressure (NIBP), ECG, and respiration rate, were monitored automatically. Based on randomized allocation, remimazolam or midazolam was administered. Remimazolam (Yichang Humanwell Pharmaceutical CO. Ltd., China) was given at an initial dose of 2 mg and an additional dose of 1 mg, while midazolam (Jiangsu Nhwa Pharmaceutical CO. Ltd., China) was given at an initial dose of 1 mg with an additional dose of 0.5 mg. Local anesthesia was administered when the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale was at 3–4. If MOAA/S was above 4, a 1 mg bolus of remimazolam or a 0.5 mg bolus of midazolam was administered, respectively. No

systematic opioids or anesthetics were used during the procedure. The Frankl Treatment Compliance Scale, ranging from 1 to 4 points, was used to assess patient cooperation during sedation, with a higher score indicating better cooperation.[15]

After the procedure, patients were transferred to the recovery room, where HR, NIBP, and MOAA/S were monitored. When reaching at least 9 in evaluation using the Post-Anesthetic Discharge Scoring System (PADSS), patients were discharged. Perioperative side effects were recorded during sedation.

Outcome Evaluation

The cognitive recovery of patients was assessed using the 30 points of MoCA 5-minute scale.[16,17] This scale encompasses four sections: attention, memory, executive functions/language, and orientation. Studies have indicated that the scale exhibits strong reliability, validity, and user-friendliness. The baseline score was measured before sedation, and subsequent assessments were conducted 30 min and an hour after sedation. All assessments were conducted by a trained medical professional. MoCA 5-minute score at 30 min postoperatively (T_{30}) was considered the primary outcome.

The secondary outcomes of the study were as follows: (1) The MoCA 5-minute score at 1 h postoperatively (T_{1h}). (2) Post-extraction bleeding: if the compressed cotton swab is removed and there is still visible bleeding half an hour after the tooth extraction. (3) Success of sedation: completion of the procedure, no use of rescue medication and less than 3 doses of medication within 15 minutes. (4) Time to peak sedation: the lowest level of sedation following the initial dose of medication. (5) Sedation time: initial dose of medication to fully alert. (6) Procedure time: time from start of dental extraction to end of the procedure. (7) Awake time: the first three MOAA/S scores to reach 5 after dental procedure. (8) Time to discharge: time from last dose to PADSS score≥9. (9) The fluctuations included HR, SP (systolic pressure), DP (diastolic pressure) and MOAA/S score at baseline (T1), 2min post induction (T2), start of procedure (T3), end of procedure (T4) and awakening (T5). (10) Intraoperative adverse events and complications: bradycardia, hypertension, hypotension, hypoxemia and cough defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0. Sedation delay was defined as MOAA/S <4 for a duration exceeding 60 minutes following the administration of the final dose, and respiratory deceleration was defined as <8 breaths/min.

Statistical Analysis

The sample size was determined using a two-sided Student's *t*-test based on the preliminary findings from an institution's pilot study. The MoCA 5-min score at T_{30} was 26.5 in Group R and 24.5 in Group M. With an alpha error of 0.05 and a power of 90%, the required sample size was calculated to be 49 per group. Assuming the anticipated dropout rate was 8%, 53 patients were required in each group.

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables were presented as the mean (standard deviation) if normally distributed and as the median (interquartile range) if not normally distributed. The comparison of these variables was conducted using the Mann–Whitney *U*-test. Categorical variables were expressed as the number of patients (%) and compared using the Chi-squared test.

The generalized linear regression model was used to examine the association between baseline patient characters and MoCA 5-min scores. A two-sided *P*-value < 0.05 was considered statistically significant. All analyses were carried out using SPSS 25.0 (IBM Corp., Chicago, IL, USA) and GraphPad Prism 9.4.1 (GraphPad Software, Boston, MA, USA).

Results

Out of the 110 individuals assessed for eligibility, 106 met the inclusion criteria and were randomly assigned to either Group R (n = 53) or Group M (n = 53). All participants received their designated treatments and were included in the intention-to-treat (ITT) analyses. Figure 1 shows the CONSORT diagram.

Both groups exhibited similar baseline characteristics (Table 1) and were well-matched with a median age of 70 (IQR 65 to 74) in Group R and 68 (IQR 63 to 72) in Group M ($P = 0.09$). Over 90% of the patients had comorbidities and were classified as ASA II. The number of teeth extracted was 2 (IQR 1, 2) and 2 (IQR 1, 3) in the two groups ($P = 0.94$).

The time to peak sedation after the first dose of medication was significantly shorter in Group R than in Group M [2 (IQR 3, 3) vs 3 (IQR 3, 4), $P < 0.001$] (Table 2). Additionally, patients receiving remimazolam sedation exhibited higher frankl scores [4 (IQR 3, 4) vs 3 (IQR 3, 4), $P = 0.01$]. No significant differences were observed in the sedation time and procedure

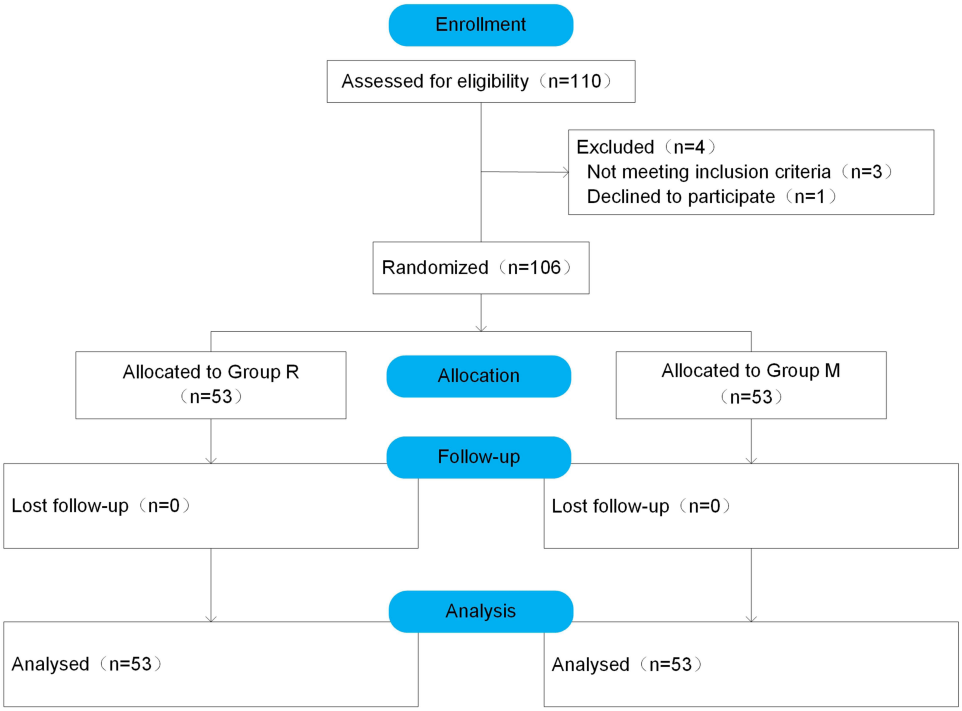

Figure 1 The CONSORT diagram.

time ($P = 0.80$, $P = 0.09$). However, the awake time and time to discharge were significantly shorter in Group R than in Group M ($P < 0.001$).

In the ITT analysis, the MoCA 5-min score at T_{30} was 25 (IQR 23.5, 27) in Group R and 23 (IQR 21, 25) in Group M (Table 3). The difference also existed at T_{1h} [27 (IQR 26, 28) vs 26 (IQR 25, 27), $P < 0.01$]. The two groups had a significant

Table 1 Demographics and Clinical Characteristics of the Two Groups

Variables	Group R (n = 53)	Group M (n = 53)	*P* value
Gender, n (%)			1.00
Male	23 (43.40)	23 (43.40)	
Female	30 (56.60)	30 (56.60)	
Age, median (IQR)	70 (65,74)	68 (63,72)	0.09
BMI, kg/m^2	24.38 ± 3.51	23.86 ± 2.56	0.39
ASA physical status			0.84
I, n (%)	1 (1.89)	2 (3.78)	
II, n (%)	50 (94.34)	49 (92.45)	
III, n (%)	2 (3.77)	2 (3.77)	
Mallampati score			0.49
Class 1, n (%)	42 (79.25)	39 (73.58)	
Class 2, n (%)	11 (20.75)	14 (26.42)	

(*Continued*)

Table 1 (Continued).

Variables	Group R (n = 53)	Group M (n = 53)	*P* value
Comorbidities			0.44
Cardiovascular diseases, n (%)	42 (79.25)	43 (81.13)	
Cerebrovascular diseases, n (%)	1 (1.89)	1 (1.89)	
Diabetes, n (%)	2 (3.77)	4 (7.55)	
Digesting system diseases, n (%)	2 (3.77)	0	
MDAS score, median (IQR)	10 (5, 10)	10 (5, 10)	0.19
Number of teeth extracted, median (IQR)	2 (1, 2)	2 (1, 3)	0.94

Abbreviations: ASA, American Society Anesthesiologists; Group M, midazolam group; Group R, remimazolam group; MDAS, Modified Dental Anxiety Scale.

Table 2 Procedure and Sedation-Related Outcomes

Variables	Group R (n = 53)	Group M (n = 53)	*P* value
Time to peak sedation after first dose of medication, min	2 (2, 3)	3 (3, 4)	< 0.001
Remimazolam dose (mg), median (IQR)	3 (3, 4)	–	–
Midazolam dose (mg), median (IQR)	–	1.5 (1, 2)	–
Frankl score	4 (3, 4)	3 (3, 4)	0.01
Local anesthetic (articaine)	65 (57, 74)	64 (53, 64)	0.33
Sedation time, min	16 (15, 18)	16 (15, 17)	0.80
Procedure time, min	10 (5, 12)	8 (3.5, 11.5)	0.09
Awake time, min	12 (12, 13)	15 (14, 16)	< 0.001
Time to discharge, min	17 (17, 18)	20 (19, 21)	< 0.001

Abbreviations: Group M, midazolam group; Group R, remimazolam group; MDAS, Modified Dental Anxiety Scale.

Table 3 Primary and Secondary Outcomes Between the Two Groups

Primary and Secondary Outcomes	Group R (n = 53)	Group M (n = 53)	*P* value
MoCA 5-min score before sedation, median (IQR)	27 (26, 28)	27 (26, 28)	0.24
MoCA 5-min score at T_{30}, median (IQR)	25 (23.5, 27)	23 (21, 25)	< 0.001
MoCA 5-min score return to baseline at T_{30}, n (%)	33 (62.26)	16 (30.19)	0.001
MoCA5-min score at T_{1h}, median (IQR)	27 (26, 28)	26 (25, 27)	< 0.01
MoCA 5-min score return to baseline at T_{1h}, n (%)	46 (86.79)	38 (71.70)	0.06
Successful number of sedation, n (%)	52 (98.11)	51 (96.23)	1.00
Post-extraction bleeding at T_{30}, n (%)	3 (5.67)	18 (33.96)	< 0.001

Abbreviations: Group M, midazolam group; Group R, remimazolam group; MoCA, Montreal Cognitive Assessment; T1h, 1 h postoperatively; T30, 30 min postoperatively.

difference in the rate of MoCA 5-min score return to baseline at T_{30} (62.26% vs 30.19%, $P = 0.001$). Almost all patients returned to baseline MoCA 5-min score at 24 hours postoperatively. The two groups also did not differ in the rate of successful sedation (98.11% vs 96.23%, $P = 1.00$). The remimazolam group had a lower rate of post-extraction bleeding at T_{30} (5.67% vs 33.96%, $P < 0.001$). Figure 2 depicts the association between the MoCA 5-min score and the baseline characteristics of patients, as well as their vital signs during sedation. The main factors influencing the difference between MoCA score at T_{30} and baseline were found to be SP of baseline, number of teeth extracted, the dosage of articaine and anesthetic regimen.

Figure 3 illustrates the changes in the vital signs recorded over the course of sedation. The two groups did not differ in HR, systolic pressure, and diastolic pressure during sedation. Patients in the remimazolam group had a lower MOAA/S score at T2, and no significant differences were observed at other time points.

The two groups did not differ in the rate of any adverse event during sedation, with 1 patient in Group R and 2 patients in Group M experiencing hypotension after receiving medication, and 2 patients in Group R and 3 patients in Group M with cough reflex during the procedure (5.66% vs 9.43%, $P = 0.71$) (Table 4). The two groups also did not differ in the rate of complications after sedation (3.77% vs 5.66%, $P = 1.00$).

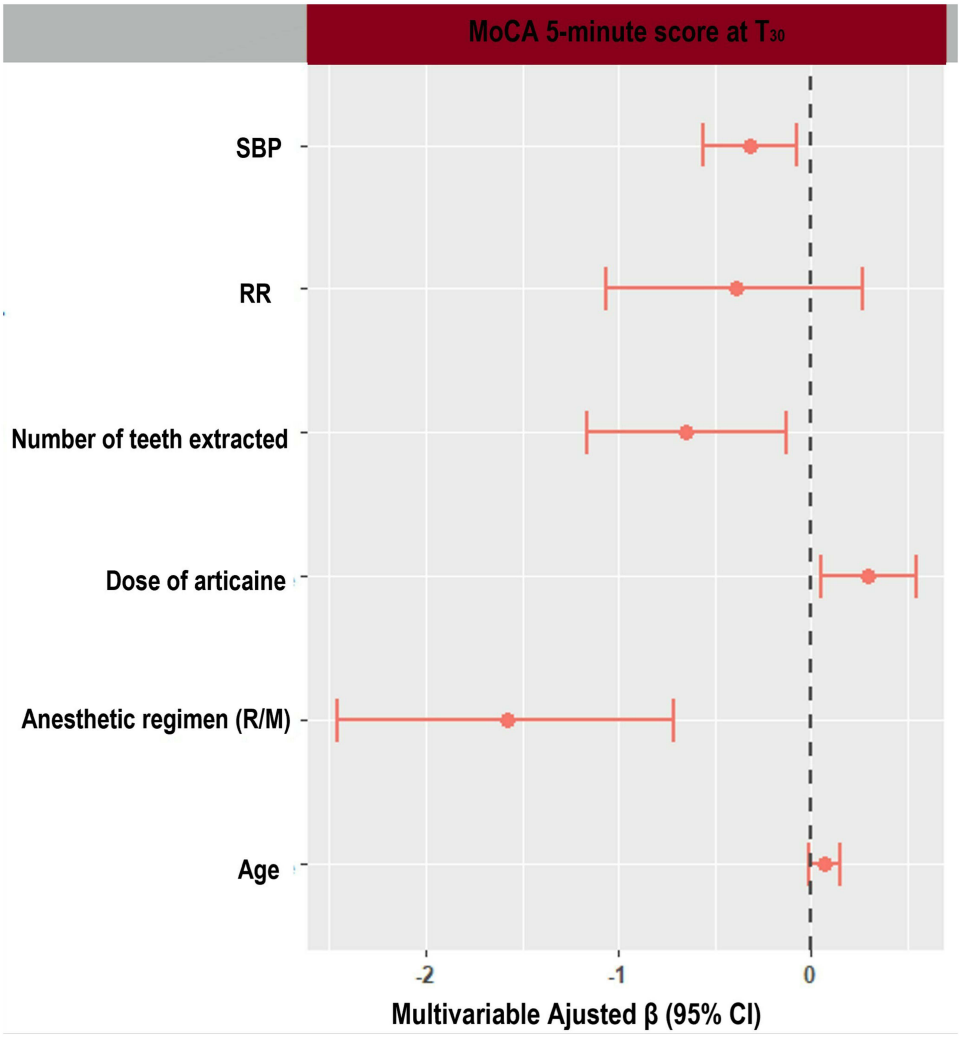

Figure 2 The association between the MoCA 5-min score and the characteristics of patients.
Abbreviation: MoCA, Montreal Cognitive Assessment.

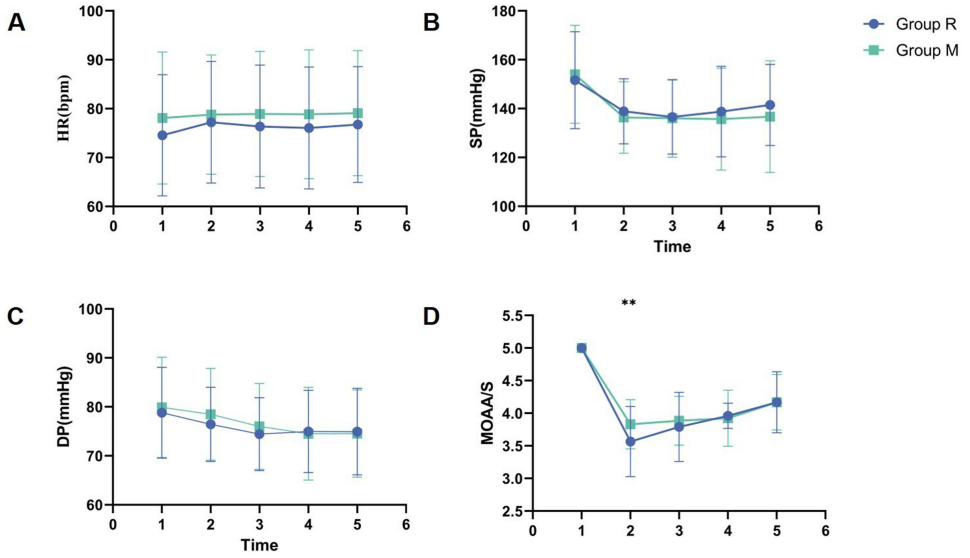

Figure 3 Changes in the vital signs including (**A**) heart rate (HR), (**B**) systolic pressure (SP), (**C**) diastolic pressure (DP), and (**D**) modified observer's assessment of alertness/sedaion (MOAA/S) scale recorded over the course of sedation.
Notes: **Statistical significance (*P*<0.01). T1: baseline, T2: 2min post induction, T3: start of procedure, T4: end of procedure, T5: awakening.

Discussion

This randomized clinical trial investigated the effectiveness and safety profile of remimazolam sedation in elderly patients undergoing dental extraction. The study revealed that remimazolam led to a faster recovery of cognitive function compared to midazolam sedation.

Midazolam, a commonly used sedative in dental procedures, is known for its anxiolytic and amnesic effects, with a lower risk of respiratory and circulatory depression compared to other sedative drugs, like propofol and dexmedetomidine.[18] However, its longer metabolism and elimination times result in delayed recovery and have been associated with delirium and postoperative cognitive dysfunction in elderly patients.[19–22] In contrast, remimazolam, a novel ultra-short-acting benzodiazepine, offers rapid onset, short recovery time, and stable hemodynamics.[23,24] A previous randomized controlled trial comparing remimazolam to midazolam found higher success rates for the procedure with remimazolam.[25,26] While limited research exists on the use of remimazolam for sedation in elderly patients during dental procedures, studies in adults have reported lower adverse events and shorter recovery and discharge times.[27,28] Several studies have indicated that midazolam administration may result in delirium and postoperative cognitive dysfunction. However, other investigations have suggested that the use of midazolam in elderly patients could lead to delayed recovery of early postoperative cognitive function, which may gradually improve over time.[29–31]

Early cognitive function recovery is particularly significant in dental extraction, as it not only reduces hospitalization duration but also enhances patient compliance. This, in turn, facilitates effective cooperation in procedures such as occlusal hemostasis and minimizing post-extraction bleeding and cough reflex. Gauze bite is the main method of hemostasis after tooth

Table 4 Summary of Adverse Events

Variables	Group R (n = 53)	Group M (n = 53)	*P* value
Patients with any adverse event, n (%)	3 (5.66)	5 (9.43)	0.71
Patients with any AESI, n (%)	0	0	–
Complications after sedation, n (%)	2 (3.77)	3 (5.66)	1.00

Abbreviations: AESI, adverse events of special interest; Group M, midazolam group; Group R, remimazolam group.

extraction. No statistical differences were observed in the history of cardiovascular disease, history of blood system disease, and number of tooth extractions between the two groups. The difference in bleeding 30 minutes after tooth extraction was more due to the delayed recovery of cognitive function caused by sedation and the failure to cooperate with the gauze bite, which led to bleeding. To assess early postoperative cognitive function, we employed the MoCA 5-min scale based on several factors. Firstly, the study concentrated on patients aged 60 to 80 years, and we opted for a less complex scale to ensure optimal patient compliance, avoiding potential impacts on research outcomes. Secondly, patients met the discharge criteria approximately 30 min after the operation. Thus, follow-up assessments within 24 hours post-procedure were only feasible via telephone. Previous research has demonstrated that the MoCA scale not only exhibits strong reliability and validity for evaluating cognitive function but also yields favorable outcomes when administered through telephone follow-ups.[32]

In our investigation, we observed that the remimazolam group exhibited superior cognitive function recovery at 30 min post-procedure compared to the midazolam group, with over half of the patients returning to their baseline levels. Previous research has indicated that variables such as intraoperative hypotension and anesthesia type may impact the delayed recovery of postoperative cognitive function.[33,34] However, our study observed a brief surgical duration and a low occurrence of intraoperative hypotension, diverging from the findings of previous studies. This investigation delves into the influence of sedative medication, articaine dosage, number of teeth extracted, the dosage of articaine and preoperative systolic blood pressure on postoperative cognitive function scores, highlighting the necessity for further research in this area. In this study, both groups achieved sedation success rates exceeding 95%. In our study, we found that the remimazolam group had a better recovery of cognitive function, time to peak sedation and awaken time than the midazolam group. However, the differences between the two groups were relatively small compared to their use in other settings. In the phase IIb study of remimazolam in colonoscopy, the mean time to fully alert was 13.3(7.21) minutes for remimazolam 5.0/3.0mg and 15.2 (7.43) minutes for midazolam 2.5/1.0mg, which was similar to our study.[24] There are few articles on the use of remimazolam in elderly patients undergoing dental extraction. The small differences observed in our study may be due to the short extraction time and low dose of both drugs. The incidence of post-extraction bleeding 30 min after the procedure was significantly lower in the remimazolam group compared to the midazolam group. Furthermore, the effects of remimazolam sedation on patients' blood pressure, HR, and oxygen saturation were minimal, with no need for intervention in respiratory or circulatory issues. Benzodiazepines, having both peripheral and central muscle relaxant effects, reduce muscle tone in the upper airway.[35,36] Consequently, dental procedures during benzodiazepine sedation may require consideration of aspiration risk due to water administration in the oral cavity. In our study, during the dental procedures, two patients in the remimazolam group and three patients in the midazolam group experienced a cough reflex due to water or saliva entering the respiratory tract from their oral cavity.

As the understanding of remimazolam deepened, more studies employed continuous intravenous administration.[37–39] However, for elderly patients undergoing dental extraction, most procedures are relatively brief. Therefore, we achieved sedation through titration. Despite the growing use of continuous administration, there are limited reports on dental sedation in elderly patients using a single-dose approach. For dental procedures, a mild to moderate level of sedation allowing for some degree of consciousness is generally considered appropriate.[40,41] In our study, we chose to titrate the medication. For safety, the initial dose was 2 mg with an additional dose of 1 mg for remimazolam, while for midazolam, the initial dose was 1 mg with an additional dose of 0.5 mg. The level of sedation was assessed using the MOAA/S score. Moderate sedation, where patients can respond purposefully to verbal commands, is often the desired level in dental procedures. Therefore, remimazolam dosing was adjusted to achieve a MOAA/S score of 3–4.

Our trial showed that remimazolam resulted in a quicker postoperative cognitive recovery, enhancing hemostasis and minimizing discharge time compared to midazolam during dental extraction. However, the study has several limitations. First, being a single-center study, further multi-institutional, prospective research is necessary for broader generalizability. Second, to ensure patient safety during sedation, anesthesiologists were not blinded to the group assignment, although patients and research staff responsible for assessments were unaware of it. Third, our study did not provide information on long-term sedation with continuous remimazolam administration in elderly patients, necessitating further research in this area. Finally, the study did not include data on sedation levels obtained using monitoring devices, but the MOAA/S score was used for scoring and all scorers were trained during the preparation phase.

Conclusion

Our study revealed two significant findings. First, remimazolam resulted in a rapid recovery of cognitive function. Second, this rapid cognitive recovery improves patient compliance and lowers the risk of post-extraction bleeding. Therefore, for elderly patients undergoing tooth extraction, remimazolam sedation proves to be highly beneficial in improving early postoperative cognitive recovery. This rapid recovery enhances hemostasis and minimizes discharge time.

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Disclosure

The author(s) report no conflicts of interest in this work.

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