# Can Remimazolam Be a New Sedative Option for Outpatients Undergoing Ambulatory Oral and Maxillofacial Surgery?

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**Purpose:** Midazolam is a classic sedative drug. The sedative effect of remimazolam has not been demonstrated in ambulatory oral and maxillofacial surgery (OMS). This study aimed to measure whether remimazolam can achieve the same sedation effects compared with midazolam, but with a faster recovery and fewer adverse reactions in outpatients undergoing ambulatory OMS.

**Materials and Methods:** This was a prospective, randomized, controlled, single-center study of 40 patients who underwent ambulatory OMS at Peking University Hospital of Stomatology, Beijing, China, between April 2021 and June 2021. The patients were randomly divided into a midazolam group (Group M) and a remimazolam group (Group R). The success rate of sedation, which was defined as completion of the operation with no rescue sedative medication, was the primary outcome. In this study, bispectral index and modified observer's assessment of alertness/sedation value, intraoperative adverse events, time to discharge, and the number of additional doses of sedative were compared. Descriptive, comparative analyses were conducted.

**Results:** Forty patients were eligible for this study, and the final sample size was 40 (including 25 males, average age was 29). The success rate of sedation in Group R was statistically significantly higher than that in Group M (Group R vs Group M: 95% [19/20] vs 70% [14/20], $P = .037$, 95% confidence interval [CI]: 0.681 to 0.913). The median number of additional doses of the medications per 5 minutes in Group R was lower than that in Group M (0.51 [0.19, 0.71] vs 0.82 [0.51, 1.25], $P = .006$, 95% CI: 0.013 to 0.583). Group R showed a higher bispectral index number (93.9 $\pm$ 4.6 vs 86.6 $\pm$ 7.2, $P = .001$, 95% CI: 3.451 to 11.149) at the end of the surgery and a higher modified observer's assessment of alertness/sedation score (4.70 $\pm$ 0.47 vs 4.05 $\pm$ 0.68, $P = .001$, 95% CI: 0.273 to 1.027) after 5 minutes at the recovery room compared with Group M.

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**Conclusions:** The success rate of remimazolam is higher than that of midazolam. The use of remimazolam is effective for sedation of patients undergoing ambulatory OMS.

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Intravenous minimal/moderate sedation has widely been used to overcome dental anxiety.[1] With the help of sedation, patients can receive dental treatment with more comfort or even psychological and physiological pleasure. Choosing an ideal anesthetic drug is vital to ensure the safety and effectiveness of minimal/moderate sedation for outpatients undergoing ambulatory oral and maxillofacial surgery (OMS).

Midazolam is widely used in OMS, and is a classic and commonly used drug in outpatient sedation,[2,3] especially for intravenous sedation. Nonetheless, its disadvantages include increased accumulation and respiratory depression, which limit the use of midazolam in sedation for ambulatory surgery.[4]

Remimazolam is a novel benzodiazepine. It has similar pharmacological effects to midazolam (mean distribution half-life of 0.5 to 2 minutes[5]), but is different to midazolam in many respects, such as rapid onset, fast metabolism, safely even in deep sedation[6]). A previous study has shown that remimazolam is effective in providing sedation for gastroscopy[7] and bronchoscopy.[6] Ambulatory surgery requires a faster recovery, so remimazolam may be an alternative to midazolam as it is metabolized more rapidly. To our knowledge, this is the first study to evaluate the sedation effects of remimazolam in ambulatory OMS relative to midazolam. The purpose of this study was to examine whether remimazolam can achieve the same sedation effects as midazolam, while evaluating recovery and adverse reactions for patients undergoing ambulatory OMS. The investigators hypothesized that remimazolam can be used for outpatients undergoing ambulatory OMS with a high successful rate. The specific aims of the study were to measure the effects of remimazolam in ambulatory OMS, compare bispectral index (BIS), modified observer's assessment of alertness/sedation (MOSS/A) score, and adverse reactions between remimazolam and midazolam.

## Materials and Methods

### STUDY DESIGN

The present study was a randomized, double-blind, controlled trial and was conducted at Peking University Hospital of Stomatology. The protocol was approved by the Institutional Research Ethics Board of Peking University Hospital of Stomatology (No. PKUSSIRB-202056103) and was registered with clinicaltrials.gov (NCT04602845). Written informed consent was obtained from each participant.

All patients enrolled in this study underwent ambulatory oral surgery at Peking University Hospital of Stomatology, Beijing, China. The need to receive surgery under sedation was evaluated by the attending surgeon. The inclusion criteria were as follows: age 18 to 60 years old; American Society of Anesthesiologists grade I to II; body mass index (BMI) 18 to 30 kg/m$^2$; and scheduled elective ambulatory oral surgery that was expected to last less than 1 hour. Local anesthesia methods included only supraperiosteal infiltration anesthesia, periodontal injection, and regional nerve block.

### SAMPLE

The exclusion criteria were allergies or contraindications to benzodiazepines, opioids, and flumazenil; history of long-term use of benzodiazepines; history of long-term use of opioid; participation in another clinical trial within 4 weeks; pregnant or breastfeeding women; or a history of substance abuse or chronic alcohol abuse (more than 14 shots/week, 1 shot = 150 ml wine or 360 ml beer or 45 ml spirits).

#### *Sample Size Calculation*

The sample size was calculated based on a previous study.[7] The sedation success rate of remimazolam and midazolam in colonoscopy was 94.0% and 45.6%, respectively. We calculated the sample size for Pearson chi-square test by SAS 9.4 (test = PCHI, $\alpha$ = 0.05, (1-$\beta$) = 0.95); the total number of cases was 34. Considering 15% data loss and loss to follow-up, the final planned sample size was 40.[8]

### VARIABLES

Patients were randomly allocated into 2 groups using a random number table. The random number was stored in an opaque envelope opened by a researcher before the trial began, and the experimental drug was prepared according to the random number. The researcher did not participate in perioperative care and follow-up.

Group M was given a 2 ml solution containing 2.5 mg of midazolam (5 mg/1 mL, Jiangsu Nhwa Pharmaceutical Co, Ltd, Jiangsu, PR China, diluted by 3 ml normal saline to 1.25 mg/ml). Group R was given a 2 ml solution containing 3 mg of remimazolam (36 mg/powder/piece, Jiangsu Hengrui Pharmaceuticals Co, Ltd, Jiangsu, PR China, diluted by 24 ml

normal saline to 1.5 mg/ml). BIS was continuously monitored.

Both groups were given 50 μg of fentanyl at the beginning of induction. The surgeon was informed of the initial sedative injection, and the additional sedative injection did not interrupt the surgeon's operation. MOSS/A was measured by calling the patient's name to see if they could follow the commands.

Group R was given preprepared drugs with the label of "initial dose," which contained 3 mg of remimazolam. Local anesthesia was started when patients reached MOAA/S score ≤ 4. An oral surgeon started treatment when the patient reached a MOAA/S score ≤ 3 (Table 1).[9] Sedation was satisfactory if the MOAA/S score in the entire diagnosis and treatment process was always less than or equal to 4. If the MOAA/S score was greater than 4, 1 ml per additional dose (remimazolam 1 mg) (36 mg/powder/piece, Jiangsu Hengrui Pharmaceuticals Co, Ltd, Jiangsu, PR China, diluted as 1 mg/ml into 5 ml syringe) was administered for deepening sedation, but only to a maximum of 3 times within 15 minutes. Sedation failure was defined as 3 top-ups of additional doses in the first 15 minutes or 5 top-ups of additional doses in any 15 minutes still not making the patient's MOAA/S score less than or equal to 4.

Group M was given preprepared drugs with the label of initial dose, which contained 2.5 mg of midazolam. Local anesthesia was started when patients reached MOAA/S score ≤ 4. An oral and maxillofacial surgeon started treatment when the patient reached a MOAA/S score ≤ 3. Sedation was satisfactory if the MOAA/S score in the whole diagnosis and treatment process was always less than or equal to 4. If the MOAA/S score was greater than 4, 1 ml per additional dose (midazolam 1 mg) (5 mg/1 mL, Jiangsu Nhwa Pharmaceutical Co, Ltd, Jiangsu, PR China, diluted as 1 mg/ml into 5 ml syringe) was administered for deepening sedation, up to a maximum of 3 times within 15 minutes. Sedation failure was defined as 1) in the first 15 minutes, 3 top-ups of additional doses or 2) after the first 15 minutes, 5 top-ups of additional doses in every 15 minutes interval still not making the patient's MOAA/S score less than or equal to 4.

**Table 1. MOAA/S SCALE**

| MOAA/S Scale | Scale | Condition |
|---|---|---|
| Responds readily to name spoken in normal tone | 5 | (alert) Minimal |
| Lethargic response to name spoken in normal tone | 4 | Moderate |
| Responds only after name is called loudly and/or repeatedly | 3 | Moderate |
| Responds only after mild prodding or shaking | 2 | Moderate |
| Responds only after painful trapezius squeeze | 1 | Deep |
| Does not respond to painful trapezius squeeze | 0 | Deep/general anesthesia |

ASA indicates American Society of Anesthesiologists; MOAA/S, modified observer's assessment of alertness and sedation.

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Patients and their families, surgeons, anesthesiologists and nurses were blinded to the group assignment.

*Outcome Variables*

The primary outcome was the success rate of sedation, which was defined as completion of the operation with no rescue sedative medication, that is, *1)* in the first 15 minutes, 3 top-ups of additional doses or *2)* after the first 15 minutes, 5 top-ups of additional doses in any 15 minutes period.

The secondary outcomes were as follows: *1)* the time required to reach MOAA/S ≤ 4, *2)* the lowest intraoperative depth of sedation and BIS, *3)* the time from the end of surgery to recovery of orientation, *4)* intraoperative doses of benzodiazepines in patients of the 2 groups, *5)* intraoperative adverse events, including hypoxemia ($SPO_2$% lower than 92%) and respiratory depression, *6)* the utilization rate of flumazenil and other antagonist, and *7)* the time to discharge after completion of surgical procedures.

## DATA COLLECTION METHODS

The collected preoperative data included gender, age, history of hypertension (yes/no), type 2 diabetes (yes/no), BMI, and results of laboratory tests. As for routine blood tests, the results obtained closest to surgery were recorded. Intraoperative data included heart rate (HR), noninvasive blood pressure (NIBP), pulse oxygen saturation ($SPO_2$), MOAA/S score, BIS value, number of pain signs, and medicine dosage. Postoperative data included time in the recovery room, visual analog scale score, complications, and time to discharge.

*Anesthetic Management*

The patients were assigned to the midazolam group (Group M) and the remimazolam group (Group R) by the investigator based on a random scale. Perioperative monitoring included continuous 5-lead electrocardiogram, $SPO_2$, NIBP, and BIS (Covidien, USA) value. All patients received peripheral venipuncture catheterization by nurses. MOAA/S was performed by the investigator. The patients received oxygen inhalation at 4 L/minutes before sedative medication until

recovery after the procedure. The investigator dispensed preformulated drugs labeled inducers to the nurse, and 2 ml of inducers and 50 μg of fentanyl were given by the instruction of anesthesiologists. An oral and maxillofacial surgeon started treatment when a patient reached a MOAA/S score ≤ 3. If required, an additional 1 ml dose was permitted to achieve satisfactory sedation. Patients were instructed to raise their hands to indicate insufficiency of analgesia, and 25 μg of fentanyl was added once for analgesia insufficiency, with an interval of at least 5 minutes. The total dose was not more than 100 μg (including the initial dose).

If a patient suffered sedation failure, remimazolam was not allowed to be added, only midazolam was allowed. If additional midazolam still failed to achieve satisfactory sedation, additional fentanyl (if the patient was already given 100ug) and propofol (which were seen as rescue sedative medication) could be added according to the judgment of the anesthesiologist and patients' requirement.

Basic vital signs, including HR, NIBP, respiratory rate (RR), and $SPO_2$, were recorded before treatment. MOAA/S scores were obtained at 1, 2, and 3 minutes after the initial dose, and then MOAA/S scores were obtained at 5-minute intervals. BIS was recorded until the patient left the clinic. The patient's HR, NIBP, RR, oxygen saturation, and other vital indicators were continuously recorded.

In the recovery room, all subjects were monitored for at least 0.5 hour and patients were monitored for HR, $SPO_2$, RR, NIBP, and MOAA/S scores. MOAA/S was evaluated every 5 minutes after the operation until the patient was fully alert and reached the discharge criteria,[10] and the recovery time was recorded. Aldrete modified score was evaluated at 15-minute intervals after admission to the recovery room. Fifty milligrams of flurbiprofen was administered once when the postoperative visual analog scale score reached 40 or above. When the patients' Aldrete modified score greater than or equal to 9, and ability to walk independently without obvious side effects such as nausea and dizziness, they were permitted to leave the recovery room. Basic vital signs were recorded at discharge.

### DATA ANALYSIS

SPSS Statistics Desktop (version 21.0.0 for Mac OS, IBM, Armonk, NY, USA) was used for statistical analysis. Mean ± standard deviation was used to express continuous data, median (interquartile range) was used to express nonnormally distributed data, and number (%) was used to express categorical data. Normally distributed continuous variables were compared using a two-tailed Student's $t$ test. The Wilcoxon rank-sum test and Mann–Whitney $U$ test were used for intergroup comparisons when continuous data were not normally distributed. $\chi^2$ testing was performed to compare categorical variables. A two-sided $P$ value lower than .05 indicated a statistically significant difference.

## Results

### BASELINE CHARACTERISTICS

A total of 81 patients underwent ambulatory OMS between April 2021 and June 2021. Thirty-two patients were less than 18 or more than 60 years old, while 49 patients were between 18 and 60 years old. Nine patients were excluded for the following reasons: 5 patients refused to sign informed consent; one patient routinely took antiepileptics; one patient had a recent history of benzodiazepine use; 2 patients were excluded due to the absence of the investigator. Forty cases were eligible for this study (Fig 1).

There were no differences between Group M and Group R in the baseline characteristics including

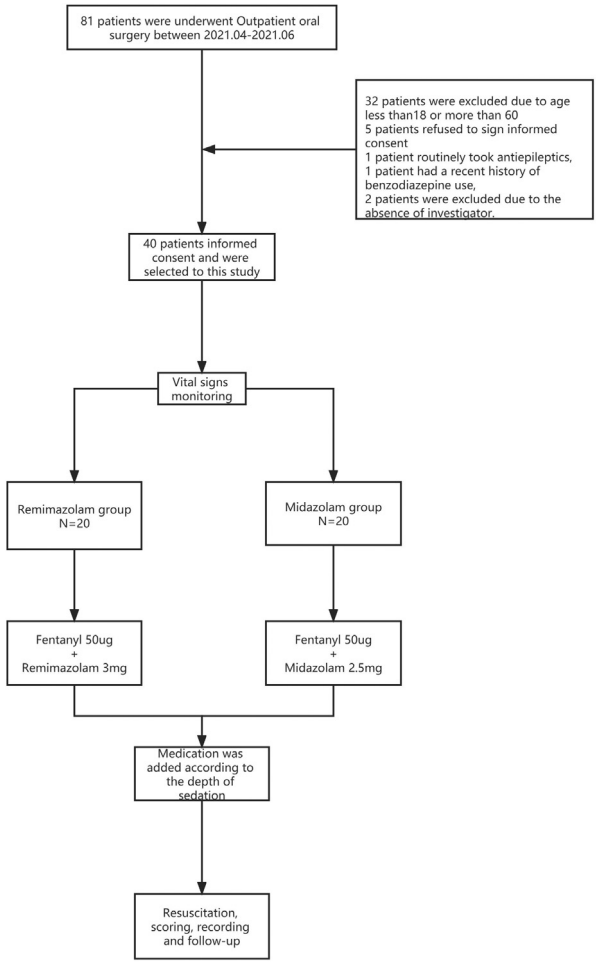


**FIGURE 1.** Patients' selection of sedation in ambulatory oral surgery between remimazolam and midazolam group.

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height, weight, preoperative systolic pressure, preoperative diastolic pressure, preoperative heart rate, alanine aminotransferase, white blood cell, hemoglobin, and red blood cell (Table 2). BIS and MOAA/S score showed a declining trend after injection in both groups (Fig 2).

### THE PRIMARY OUTCOME

A total of 40 patients were included in this study, and the total sedation success rate was 82.5%. The sedation success rate was 70% in the midazolam group and 95% in the remimazolam group ($P$ = .037) (Tables 2 and 3).

### THE SECONDARY OUTCOMES

There was a statistically significant difference in the median number of additional doses within 5 minutes between the midazolam group and the remimazolam group (0.82 vs 0.51, $P$ = .006) (Table 3).

The average MOAA/S in Group R was lower in the first and second minute compared with Group M (first minutes: 3.65 ± 0.59 vs 4.35 ± 0.75, $P$ = .002; second minutes: 3.25 ± 0.44 vs 3.75 ± 0.72, $P$ = .012). The average BIS value was lower in Group M than in Group R (86.6 ± 7.2 vs 93.9 ± 4.6, $P$ < .001). The average MOAA/S value in Group M was lower than that in Group R (4.05 ± 0.68 vs 4.70 ± 0.47, $P$ < .001) after 5 minutes in the recovery room (Table 4).

The average Aldrete score was statistically significantly higher in Group R than in Group M both at the end of the surgery (9.6 ± 0.5 vs 9.3 ± 0.5, $P$ = .025) and 5 minutes after the surgery (9.8 ± 0.4 vs 9.2 ± 0.4, $P$ < .001) (Table 4).

Additional fentanyl was used in one patient in Group R (25 ug, once) and 2 patients in Group M (both of them were 25ug, once).

All patients were able to walk to the recovery room with the help of a nurse immediately after the surgery. At the end of the surgery, orientation was fully recovered in both groups, and there was no statistically significant difference between them.

None of the patients had $SPO_2 \leq 92\%$ during the surgery. Two patients had $SPO_2 \leq 95\%$ in Group M, and none of the patients in Group R had $SPO_2 \leq 95\%$.

**Table 2. PATIENTS' DEMOGRAPHICS AND CLINICAL CHARACTERISTICS PERIOPERATIVELY IN MIDAZOLAM GROUP AND REMIMAZOLAM GROUP IN PATIENTS UNDERWENT AMBULATORY ORAL SURGERY**

| Demographics and Clinical Characteristics | M Group | R Group | *P* Value |
|---|---|---|---|
| Number, n | 20 | 20 | - |
| Baseline characteristic | | | |
| Male, n (%) | 13 (65) | 12 (50) | .744† |
| Age, years | 28.2 ± 5.5 | 29.8 ± 4.3 | .323* |
| Height, cm | 171.6 ± 7.0 | 170.8 ± 8.6 | .743* |
| Weight, kg | 66.7 ± 9.7 | 71.6 ± 13.2 | .188* |
| Preoperative systolic pressure, mmHg | 123.5 ± 13.2 | 120.5 ± 16.5 | .529* |
| Preoperative diastolic pressure, mmHg | 78.4 ± 10.5 | 18.7 ± 13.5 | .928* |
| Preoperative heart rate, times | 81.4 ± 12.6 | 82.7 ± 12.6 | .746* |
| Preoperative respiratory rate, times | 18.6 ± 2.3 | 19.2 ± 2.5 | .472* |
| ALT, U/L | 22.9 ± 7.8 | 22.5 ± 9.6 | .886* |
| WBC,$10^9$/L | 4.9 ± 1.7 | 4.9 ± 1.8 | .920* |
| Hemoglobin, g/L | 126.1 ± 14.0 | 128.0 ± 15.1 | .636* |
| RBC, $10^{12}$/L | 4.8 ± 0.4 | 4.9 ± 0.4 | .336* |
| Surgery procedures | | | |
| Tooth extraction, n (%) | 17 (85) | 16 (80) | .677† |
| Average amount of tooth, n | 1.3 ± 0.5 | 1.3 ± 0.5 | .912* |
| Impacted, n (%) | 9 (52) | 11 (69) | .353† |
| Cyst curettage, n (%) | 3 (15) | 3 (15) | 1.000† |
| Repair of maxillary sinus leakage, n (%) | 0 | 1 (5) | .584† |

Abbreviations: ALT, alanine aminotransferase; RBC, red blood cell; WBC, white blood cell.
* Independent t test.
† Pearson chi-square test or Fisher's exact test.

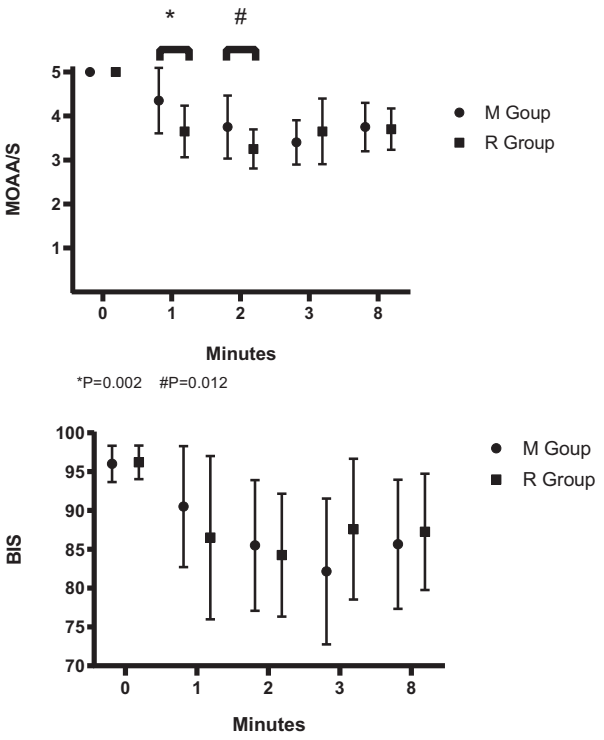


**FIGURE 2.** MOAA/S and BIS value in the first 8 minutes after sedative drug was given.

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There was no statistically significant difference in the incidence of other adverse events between the 2 groups (Table 3).

The average time spent in the recovery room was 35.5 minutes in Group M and 33.6 minutes in Group R ($P$ = .084) (Table 4).

### THE RESULTS OF PATIENTS WHO WERE SEDATION FAILURE

Seven patients were judged as sedation failure (1 in Group R and 6 in Group M) because they exceeded the upper limit (1) in the first 15 minutes, 3 top-ups of additional doses or 2) after the first 15 minutes, 5 top-ups of additional doses in any 15 minutes interval) of additional sedation drugs. In group M, 2 patients received an additional 1 mg midazolam for 2 times after the experimental drugs reached the predetermined upper limit and the MOAA/S level reached 4 points; 3 patients received an additional 1 mg midazolam after the experimental drugs reached the predetermined upper limit and the MOAA/S level reached 4; 1 patient did not receive additional drugs due to the end of the surgery. In group R, 1 patient received an additional 1 mg midazolam for 2 times after the experimental drugs reached the predetermined upper limit and the MOAA/S level recovered 4 points.

**Table 3. PRIMARY AND SECONDARY OUTCOMES AND SIDE EFFECTS IN THESE TWO GROUPS DURING THE SURGERY**

| Primary and Secondary Outcomes | M Group | R Group | *P* | 95% CI |
|---|---|---|---|---|
| Successful number of sedation, n (%)‡ | 14 (70) | 19 (95) | .037† | 0.681-0.913 |
| Successful number of surgery completion, n (%)‡ | 20 (100) | 20 (100) | 1.000† | 0.912-1.000 |
| Median operation time, min§ | 25.5 (14.3,43.0) | 32.5 (19.3,44.5) | .201† | 0.989-1.037 |
| Median number of additional dose, n§ | 5 (2,6) | 3 (1,5) | .107† | 0.639-1.064 |
| Additional dose of medication use per 5 min, n§ | 0.82 (0.51,1.25) | 0.51 (0.19,0.71) | .006† | 0.013-0.583 |
| Time of first MOAA/S ≤ 4, min‡ | 1.60 ± 0.68 | 1.05 ± 0.22 | .001* | 0.226-0.874 |
| Apnea more than 0.5 min, n (%)‖ | 0 (0) | 0 (0) | 1.000† | 0.013-0.088 |
| $SPO_2$≤92%, n (%)‖ | 0 (0) | 0 (0) | 1.000† | 0.013-0.088 |
| $SPO_2$≤95%, n (%)‖ | 2 (10) | 0 (0) | .147† | 0.014-0.165 |
| Hypotension, n (%)‖ | 0 (0) | 1 (5) | .311† | 0.004-0.129 |
| Hypertension, n (%)‖ | 0 (0) | 0 (0) | 1.000† | 0.013-0.088 |
| Tachycardia, n (%)‖ | 3 (15) | 4 (20) | .677† | 0.088-0.320 |
| Bradycardia, n (%)‖ | 1 (5) | 0 (0) | .311† | 0.004-0.129 |

* Independent t test.
† Pearson chi-square test or Fisher's exact test.
‡ Data included all patients in this group.
§ Data included only patients whose sedation was successful.
‖ Data included: (1) data of patients whose sedation was successful and (2) data before rescue sedative medication was administered of patients whose sedation was unsuccessful.

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**Table 4. PATIENTS' SEDATION DATA AT THE END OF THE SURGERY AND DATA IN THE RECOVERY ROOM**

| Sedation Data | M Group (N = 14) | R Group (N = 19) | *P* | 95% CI |
|---|---|---|---|---|
| MOAA/S end of the surgery | 4.00 ± 0.56 | 4.10 ± 0.44 | .537* | 0.223-0.543 |
| BIS end of the surgery | 86.6 ± 7.2 | 93.9 ± 4.6 | .001* | 3.451-11.149 |
| MOAA/S 5 min after surgery | 4.05 ± 0.68 | 4.70 ± 0.47 | .001* | 0.273-1.027 |
| Aldrete score end of the surgery | 9.3 ± 0.5 | 9.6 ± 0.5 | .025* | 0.046-0.654 |
| Aldrete score 5 min after surgery | 9.2 ± 0.4 | 9.8 ± 0.4 | <.001* | 0.276-0.824 |
| Time during the recovery room, minutes | 35.5 ± 3.7 | 33.6 ± 0.7 | .084* | −4.068-0.268 |

Data were included patients whose sedation was successful.
* Independent t test.

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### BIS AND MOAA/S TENDENCY IN THE TWO GROUPS

With the use of sedative drugs, the MOAA/S score in both groups showed a downward trend (Fig 2). The average MOAA/S score in the remimazolam group was statistically significantly lower than that in the midazolam group at the first minute (3.65 ± 0.59 vs 4.35 ± 0.75, $P$ = .002) and second minute (3.25 ± 0.44 vs 3.75 ± 0.12, $P$ = .012) after administration (Fig 2). In contrast to the MOAA/S score, there was no statistically significant difference in the BIS value between the 2 groups (Fig 2).

## Discussion

The study was envisaged to evaluate the sedation effects of remimazolam compared to midazolam for outpatients undergoing ambulatory OMS. We hypothesize that remimazolam can be used for outpatients undergoing ambulatory OMS with a high success rate. In our study, we have observed that the success rate of sedation in Group R was higher, BIS and the MOAA/S score at the end of the operation were statistically significantly higher than those in Group M.

For Group R, the average time spent in the recovery room was lower, and the mean number of additional sedatives in 5 minutes was lower than Group M. The BIS and MOAA/S score at the end of the operation were statistically significantly higher than those in Group M.

In our study, the initial dose of remimazolam was based on *1)* the calculation of Keith M's research[11] to compare sedation success rates, *2)* the synergistic effect of fentanyl and benzodiazepine, and *3)* risk of aspiration. The rapid action of remimazolam may be more effective in eliminating patients' dental fears, thereby leading to improved sedation success rates. The immediate metabolism of remimazolam allows patients to have higher MOAA/S score after treatment and higher Aldrete score in the recovery room, which allows them to recover faster and be ready for discharge sooner. The use of fentanyl and remimazolam in our study was different from that in other studies[6,7,12,13]: we used 50 μg fentanyl and decreased the dose of remimazolam and midazolam because there are differences between sedation in ambulatory OMS and gastroscopy. Given that oral outpatient sedation requires patients to cooperate, and there is a high risk of aspiration caused by blood and irrigation fluid, a level of sedation at the depth comparable to gastroscopy is considered dangerous for outpatient OMS. Higher doses of concomitant fentanyl with remimazolam may increase the incidence of adverse drug reactions and deep sedation events[5,14] (an MOAA/S score of 0 by fentanyl dose of 75 μg[6]).

We used both MOAA/S score and BIS to evaluate the sedation effects in these 2 groups. The remimazolam group achieved adequate sedation defined by the MOAA/S score faster, and BIS showed the same tendency as the MOAA/S score. Nevertheless, individual differences in BIS were large in both groups. Compared with the MOAA/S score, BIS was higher than expected. Another study reported that BIS was relatively high with the use of remimazolam.[15] Thus, we recommend not judging the sedation effect by BIS alone when using remimazolam and midazolam, and use MOAA/S as the primary indicator for assessing sedation. In our study, we evaluated the depth of sedation during clinical procedures. MOAA/S was evaluated not only by calling the patient's name directly but by calling the patient's name to see whether he can follow the commands. Measurement of the depth of sedation by BIS resulted in a degree of wakefulness. BIS values were generally higher than expected. MOAA/S was an important mark for evaluation of patients' sedation.

Dental anxiety is one of the biggest barriers for patients seeking treatment. A survey in the United States reported that 18% of adults would visit a dentist more often if they were given a drug that would make them

less nervous.[1] Intravenous minimal/moderate sedation by benzodiazepines is a perfect method to avoid dental anxiety[16] and overcome preoperative anxiety.[17] Intravenous minimal/moderate sedation refers to the administration of hypnotic agents or techniques to enable the effective completion of a diagnostic or therapeutic procedure, which may be otherwise painful or uncomfortable for patients.[10,18]

Both remimazolam and midazolam can be safely used in outpatient sedation, even in critical patients (American Society of Anesthesiologists III/IV patients).[13] Remimazolam provides effective procedural sedation with increased success rates and recovery profile relative to midazolam.[19] The rapid induction of sedation and short recovery time with remimazolam may be beneficial in improving patient throughput in a clinic setting. In particular, the short recovery times may result in reduced costs and decreased time in recovery rooms.[20]

Although remimazolam has been recommended for gastroscopy[7] and bronchoscopy,[6] few studies have evaluated its sedation effects in ambulatory OMS. Sedation in ambulatory OMS is generally based on midazolam. The advantages of midazolam include excellent amnesia, easy titration, and widespread acceptance of administration. Disadvantages of midazolam include greater cumulative effects because of a long-acting metabolite that causes slow recovery of neuropsychiatric function.[21]

Remimazolam is an ultra-short-acting benzodiazepine, and the sedative is produced by binding to benzodiazepine sites on gamma-aminobutyric acid receptors in the brain.[22] Remimazolam is rapidly distributed following IV administration (with a mean distribution half-life of 0.5 to 2 minutes). The terminal half-life of remimazolam in plasma is 37 to 53 minutes; its clearance (54 to 75 L/h) is not linked to body weight; and no statistically significant differences in heart rate, oxygen saturation levels, or respiration rate have been reported between groups in any of the pivotal trials.[6,7,13] Remimazolam's degradation product is CNS7054, which has very low hypnotic activity.[19] Its sedative effect can be completely reversed by flumazenil, and a previous study has shown that the sedation effect of 0.25 mg/kg of remimazolam can be completely reversed by 0.5 mg of flumazenil within 1 minute.[23]

We showed that remimazolam had a higher success rate and required fewer additional doses despite its ultra-short action. The need for fewer additional doses and the ultra-short action may be in opposition that sedatives with ultra-short action should be added more often to achieve a sustained sedative effect. However, this may be explained by the time to intraoral local anesthesia. Local anesthesia is often perceived as the most painful of the treatment,[24] study reported[25]: severe pain (13.3%) and worst pain (4.4%). Inducing a sufficient depth of sedation quickly can help patients to feel more comfortable during local anesthesia and thus increase the success rate of sedation. Furthermore, a good match of operative and sedative procedures plays an important role in improving the success rate of sedation. Besides it can also reduce the total dosage of sedative drugs by minimizing additional drugs. Due to the longer time of midazolam to act, sedative effect in a short time was always unsatisfying. So, occasional excessive irritation of operative procedure might cause more additional number of sedative uses in Group M than in Group R. However, remimazolam has its disadvantages. As with other benzodiazepines, remimazolam has the potential for misuse. In the United States, remimazolam is categorized as a Schedule IV controlled substance,[5] and its potential for abuse and dependence is also recognized in the Europe.[26] The most commonly reported adverse reactions (incidence $\geq$ 10%) in remimazolam recipients across the phase III trials are hypotension, diastolic hypertension, systolic hypertension, hypoxia, and diastolic hypotension.[7,13] In our study, tachycardia occurred frequently in both groups (15% in Group M and 20% in Group R); however, this may be a consequence of pain that patients felt during the surgery rather than related to the sedation. Two minutes earlier to discharge in Group R is not statistically significant clinically to influence the outcomes of patients in the recovery room. More options for both drugs (such as pumping), more use of different initial doses, will be the focus of our research in the next phase.

To our knowledge, this is the first study to evaluate the sedation effects of remimazolam in ambulatory OMS relative to midazolam. There are some limitations to our study. First, different types of surgical procedures may affect the sedation. However, we randomized the patients to these 2 groups, and there was no difference in the types of operations between these 2 groups. Second, there were no statistically significant differences in body weight and BMI between 2 groups. The dosage of remimazolam and midazolam administration by weight might be more accurate. There is no recommended dosage of remimazolam measured by weight in its instructions and the recommended initial dose of remimazolam was 5 mg instead of according to weight. However, we already excluded patients whose BMI was below 18 kg/m$^2$ or above 30 kg/m$^2$, and there was no statistically significant intergroup difference in weight in our study. Third, this is a single-center study with a relatively small sample, and the results need to be validated in a wider area.

In conclusion, remimazolam can be used effectively in sedation of patients undergoing ambulatory OMS. It can be a new sedative option for outpatients undergoing ambulatory OMS.

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## References

1. Dionne RA, Yagiela JA, Coté CJ, et al: Balancing efficacy and safety in the use of oral sedation in dental outpatients. J Am Dent Assoc 137:502–513, 2006
2. de Morais HH, Barbalho JC, de Holanda Vasconcellos RJ, Landim FS, da Costa Araújo FA, de Souza Dias TG: Comparative study of hemodynamic changes caused by diazepam and midazolam during third molar surgery: A randomized controlled trial. Oral Maxillofac Surg 19:267–273, 2015
3. Eriksson LB, Tegelberg Å: Safety of adjunct pre-emptive intravenous tramadol with midazolam sedation for third molar surgery. Oral Maxillofac Surg 19:353–359, 2015
4. Athanassoglou V, Cozowicz C, Zhong H, et al: Association of perioperative midazolam use and complications: A population-based analysis. Reg Anesth Pain Med 47:228–233, 2022
5. Acacia Pharma, Inc Byfavo Dosing and Administration. Acacia Pharma, Inc. 2021. Available at: https://www.byfavo.com/dosing-and-administration. Accessed October 8, 2022
6. Pastis NJ, Yarmus LB, Schippers F, et al: Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. Chest 155:137–146, 2019
7. Rex DK, Bhandari R, Desta T, et al: A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. Gastrointest Endosc 88:427–437, 2018
8. Chow SC, Shao J, Wang H, Lokhnygina Y: Sample Size Calculations in Clinical Research (3rd ed Vol. 1). London, Taylor & Francis Journals, 2017, pp 265–266
9. Pastis NJ, Hill NT, Yarmus LB, et al: Correlation of vital signs and depth of sedation by modified observer's assessment of alertness and sedation (MOAA/S) scale in bronchoscopy. J Bronchology Interv Pulmonol 29:54–61, 2022
10. Hinkelbein J, Lamperti M, Akeson J, et al: European Society of Anaesthesiology and European Board of Anaesthesiology guidelines for procedural sedation and analgesia in adults. Eur J Anaesthesiol 35:6–24, 2018
11. Borkett KM, Riff DS, Schwartz HI, et al: A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. Anesth Analg 120:771–780, 2015
12. Pambianco DJ, Borkett KM, Riff DS, et al: A phase IIb study comparing the safety and efficacy of remimazolam and midazolam in patients undergoing colonoscopy. Gastrointest Endosc 83:984–992, 2016
13. Rex DK, Bhandari R, Lorch DG, Meyers M, Schippers F, Bernstein D: Safety and efficacy of remimazolam in high risk colonoscopy: A randomized trial. Dig Liver Dis 53:94–101, 2021
14. Lee A, Shirley M: Remimazolam: A review in procedural sedation. Drugs 81:1193–1201, 2021
15. Shirozu K, Nobukuni K, Tsumura S, et al: Neurological sedative indicators during general anesthesia with remimazolam. J Anesth 36:194–200, 2022
16. De Stefano R: Psychological Factors in dental patient care: Odontophobia. Medicina (Kaunas) 55:678, 2019
17. Sebastiani FR, Dym H, Wolf J: Oral sedation in the dental Office. Dent Clin North Am 60:295–307, 2016
18. Benzoni T, Cascella M: Procedural sedation. StatPearls. Treasure Island (FL), StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., 2022
19. Sneyd JR, Rigby-Jones AE: Remimazolam for anaesthesia or sedation. Curr Opin Anaesthesiol 33:506–511, 2020
20. Helmers RA, Dilling JA, Chaffee CR, et al: Overall cost comparison of gastrointestinal endoscopic procedures with endoscopist- or anesthesia-supported sedation by activity-based costing techniques. Mayo Clin Proc Innov Qual Outcomes 1:234–241, 2017
21. Wang F, Zhou Q, Shen M, et al: Efficacy and safety of remimazolam in procedural sedation and analgesia: A protocol for systematic review and meta analysis. Medicine (Baltimore) 99:1–3, 2020
22. Kilpatrick GJ, McIntyre MS, Cox RF, et al: CNS 7056: A novel ultra-short-acting benzodiazepine. Anesthesiology 107:60–66, 2007
23. Worthington MT, Antonik LJ, Goldwater DR, et al: A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. Anesth Analg 117:1093–1100, 2013
24. Kaufman E, Epstein JB, Naveh E, Gorsky M, Gross A, Cohen G: A survey of pain, pressure, and discomfort induced by commonly used oral local anesthesia injections. Anesth Prog 52:122–127, 2005
25. Venkat Narayanan J, Gurram P, Krishnan R, Muthusubramanian V, Sadesh Kannan V: Infiltrative local anesthesia with articaine is equally as effective as inferior alveolar nerve block with lidocaine for the removal of erupted molars. Oral Maxillofac Surg 21:295–299, 2017
26. The European Medicines Agency (EMA) Byfavo (Remimazolam): EU Summary of Product Characteristics. Amsterdam: The European Medicines Agency. 2021. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/byfavo. Accessed October 8, 2022