Original Article

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Recovery of sedation and psychomotor and equilibrium functions following remimazolam anesthesia with or without flumazenil: a randomized, double-blind, controlled trial

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Background: Prompt awakening and sufficient recovery of psychomotor and equilibrium functions are important for day surgery. Flumazenil accelerates recovery of consciousness after remimazolam anesthesia, but its effects on psychomotor and equilibrium functions are not well known. The purpose of this study was to determine whether flumazenil improves time to recovery, psychomotor, and equilibrium functions in subjects undergoing remimazolam anesthesia.

Methods: The design was a single-center, double-blind, randomized, controlled trial. Inclusion criteria were patients aged 18–64 years scheduled for oral surgery under remimazolam anesthesia, with American Society of Anesthesiologists physical status I or II. The predictor variable was the use of a reversal agent (flumazenil group) versus placebo (non-flumazenil group). The primary outcome variable was recovery from sedation measured using the Modified Observer's Alertness/Sedation (MOAA/S) scale for wakefulness. Secondary outcome variables were psychomotor function measured using the Trieger Dot Test (number of dots missed [NDM], maximum distance of dots missed [MDDM]), and the digit symbol substitution test (DSST), as well as equilibrium function measured using the timed up and go test (TUG), and gravimetric area and speed. Statistical analyses were performed using the Mann-Whitney U test, χ^2 test, Student's t-test, two-way ANOVA, and Bonferroni correction. P-values < 0.05 were considered significant.

Results: Sixty-eight subjects were included (male: 33, female: 35). The mean time from extubation to an MOAA/S score of 5 (minutes) was 6.5 (1.5–10.5) in the flumazenil group and 13.5 (6.8–19.3) in the non-flumazenil group ($P = 0.01$). There was no significant difference in the recovery of psychomotor and balance functions between the two groups. However, the following measurements were significantly increased compared to baseline: NDM ($P < 0.001$) and DSST ($P < 0.001$) at 30 minutes, MDDM ($P < 0.001$), TUG ($P < 0.001$), and gravimetric speed ($P < 0.001$) at 60 minutes, and gravimetric area ($P = 0.03$) at 90 minutes.

Conclusion: Administration of flumazenil after remimazolam anesthesia resulted in faster recovery of consciousness, but it did not affect the recovery of psychomotor and equilibrium functions. The time until patients were safe to return home was 120 minutes. Flumazenil did not improve the time until it was safe for patients to return home.

Keywords: Equilibrium Function; Flumazenil, Psychomotor Function; Remimazolam; Sedation.

INTRODUCTION

In dental treatment, ambulatory general anesthesia is often used for patients from whom cooperation or treatment cannot be easily obtained, such as those with mental and physical disabilities or children. Patients undergoing general anesthesia are typically hospitalized after surgery

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to receive thorough postoperative management. Conversely, patients undergoing ambulatory general anesthesia return home after surgery, and unlike hospitalized patients, they do not receive sufficient postoperative management. Therefore, prompt awakening after general anesthesia and sufficient recovery of psychomotor and equilibrium functions are critical to ensuring postoperative safety.

In the United States, ambulatory surgeries account for up to 87% [1-2] of all surgical procedures, and this rate is expected to rise further. However, Mark [3] stated that patients often have not fully regained all preoperative functions at discharge, leading to potential unforeseen events. To address these concerns, the Guidelines for Day-Case Surgery 2019 [4] emphasize that the key to quality day surgery outcomes is the careful selection of short-acting anesthetic agents.

Although general anesthesia has conventionally been performed using propofol, which induces prompt awakening, remimazolam has recently been introduced as a new intravenous anesthetic. Remimazolam has a short elimination half-life [5] and, like propofol, is expected to induce prompt awakening. Additionally, while there is no antagonist for propofol, remimazolam has an antagonist called flumazenil [5]. Thus, the administration of flumazenil in ambulatory general anesthesia with remimazolam is expected to induce more rapid awakening. Previous studies [6-7] have reported that using flumazenil after intravenous sedation with midazolam, a benzodiazepines like remimazolam, results in prompt recovery of cognitive function, while recovery of equilibrium function is relatively slow.

The present study aimed to determine whether flumazenil improves time to recovery, psychomotor, and equilibrium functions in subjects undergoing remimazolam anesthesia. We hypothesized that the use of flumazenil under remimazolam anesthesia may not achieve sufficient recovery of equilibrium function, despite prompt awakening. The specific aims were:

1) To measure the time required to obtain an MOAA/S score of 5,
2) To measure the time to recover psychomotor function.
3) To measure the time to recover equilibrium function.

METHODS

1. Study design/sample

This double-blind, randomized, controlled trial was approved by the Ethics Review Committee of Tokyo Dental College (Approval Number: 1064). The purpose and contents of this study were explained to the target patients prior to anesthesia, and written informed consent was obtained. The trial was registered before patient enrollment in the University Hospital Medical Information Network Clinical Trials Registry (registration no: UMIN000045905, principal investigator: Dr. Kyotaro Koshika, date of registration: October 28, 2021), and participants were enrolled from October 2022 to March 2023. This study was conducted at Tokyo Dental College Suidobashi Hospital. This article adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines.

This study targeted patients aged 18–64 years scheduled for oral surgery under general anesthesia with American Society of Anesthesiologists physical status (ASA-PS) I or II.

Excluded cases were patients expected to have difficulty with intubation and ventilation due to micrognathia or restricted mouth opening; patients undergoing emergency surgery without sufficient preparation time; surgeries requiring inpatient management; surgeries scheduled to last more than 3 hours; cases in which patient or guardian consent was not obtained; patients with musculoskeletal disorders preventing accurate equilibrium function measurement; patients with intellectual disabilities or autism; patients with a body mass index (BMI) of 35 or more; and patients taking benzodiazepines for anxiety.

2. Variables

The predictor variables were the use of a reversal agent

(flumazenil group) versus placebo (non-flumazenil group). The primary outcome variable was the consciousness level, evaluated on a 6-point scale from 0 to 5 using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score, as follows:

0 – no response to strong pinching of the trapezius muscle;
1 – response to strong pinching of the trapezius muscle;
2 – response to mild stimulation or shaking;
3 – response only to loudly and/or repeatedly calling the patient's name;
4 – listless response when the patient's name was spoken at a normal volume;
5 – readily delivered response when the patient's name was spoken normally (i.e., wakefulness).

The time from extubation to an MOAA/S score of 5 was measured every minute. The time from study drug administration to extubation and to an MOAA/S score of 5 was also measured.

The secondary outcome variables were psychomotor and equilibrium functions. These were evaluated before the start of general anesthesia and at 30, 60, 90, and 120 minutes after extubation. The Trieger Dot Test (TDT) and Digit Symbol Substitution Test (DSST) were used to evaluate psychomotor function.

The TDT required subjects to connect 47 geometrically arranged dots with a line for 60 seconds. The number of dots missed (NDM) and the maximum distance of dots missed (MDDM) by the line were recorded. The DSST involved substituting randomly arranged numbers with corresponding pre-assigned symbols for 90 seconds, after which the number of correct answers was recorded. A new test was prepared for each testing period to prevent participants from memorizing the correct answers [8]. Psychomotor function testing was performed in the sitting position.

The Timed Up and Go test (TUG) was used to evaluate dynamic balance. In this test, the time required for the participant to stand up from a chair, walk 3 meters back and forth, and return to the chair was measured with a stopwatch. Maximum walking speed was used to ensure consistent performance.

Stabilometry was used to evaluate static balance with a stabilometer (Gravicoder GW-5000, ANIMA, Japan). Gravimetric area (outer peripheral area) and gravimetric speed (gravimetric distance per second) were assessed. The stabilometer was placed 1 meter from the wall. Participants were instructed to stand with legs closed on the stabilometer, and measurements were taken with eyes open for 60 seconds. A mark was placed on the wall directly in front of the patient to help maintain an upright posture.

Several covariates were recorded: age, sex, ASA-PS, BMI, surgery time, anesthesia time, and surgery details. Surgical procedures included tooth extraction, plate removal, caries treatment, tumor/cyst resection, and other procedures (mandibular torus removal and sialolithotomy). Sex and ASA-PS were treated as binary variables. The categories for sex were male and female, and for ASA-PS, they were I or II. Age, surgery time, anesthesia time, BMI, and surgery type were treated as continuous variables.

3. Randomization and blinding

Randomization was performed using simple randomization in Microsoft Excel® 2019. Random numbers corresponding to the numbers 1–40 were generated in Microsoft Excel®. These random numbers were sorted in increasing order, with odd numbers assigned to the flumazenil group and even numbers to the non-flumazenil group. Allocation was done sequentially based on the order of arrival at the hospital on the day of measurement, and group assignments were sealed in opaque envelopes. The allocations of subjects who could not be measured were erased and overwritten.

Patients were randomized to either the flumazenil or non-flumazenil group for both primary and secondary outcome measurements. The personnel involved in this study included:

(1) Personnel dispensing the allocated drugs. Although both test drugs were clear and colorless, the syringes were

covered with tape to conceal their contents and were handed over to the anesthesia provider before the completion of oral surgery.

(2) Person in charge of the person responsible for maintaining the allocation list and directing which drugs were dispensed.

(3) Anesthesiologists in charge of general anesthesia.

(4) A person responsible for evaluating the postoperative outcomes, who was adequately trained for measurement and evaluation.

(5) The person analyzing the study results (author).

These individuals were not involved in any other research procedures. The subjects were also not informed of which drug they had received.

Patients were randomly assigned to the flumazenil administration group (flumazenil group) or the normal saline administration group (non-flumazenil group).

Bias

Selection Bias

Since remimazolam is a novel drug and no reports of gender or age effects were available during the study period, this study employed simple randomization without considering gender or age.

Allocation Bias

Patients were randomly assigned according to an allocation table on the day of the treatment intervention. We believe that randomization minimized allocation bias, as the likelihood of bias in the distribution of any variable between groups was small.

Assessment Bias

This study was double-blind, ensuring the absence of a placebo effect. Therefore, evaluation bias was eliminated.

4. Data collection methods

The sedation score was measured in patients scheduled for minor surgery in the operating room, while psychomotor and equilibrium functions were measured in outpatients scheduled for minor surgery.

General anesthesia, preparation of flumazenil and saline, and measurement of tests were conducted by a dental anesthesiologist uninvolved in the study, with no overlap in responsibilities. Subject characteristics were extracted from anesthesia records. Anesthetic management was standardized for all subjects. Monitoring included a non-invasive automatic sphygmomanometer, pulse oximeter, bispectral index (BIS) monitor, electrocardiographic monitor, and muscle relaxant monitor.

After securing a peripheral intravenous line, anesthesia was induced with remimazolam at 12 mg/kg/h and remifentanil at 0.5 μg/kg/min. Nasotracheal intubation was performed after administering 0.6 mg/kg of rocuronium. General anesthesia was maintained with remimazolam at 1 mg/kg/h, remifentanil at 1 μg/kg/min, and rocuronium at 7 μg/kg/min. The remimazolam rate was increased by 1 mg/kg/h if the intraoperative BIS value exceeded 65. Additionally, if blood pressure changed by 20% or more from the baseline value measured 5 minutes earlier, the remifentanil rate was adjusted by 0.5 μg/kg/min. The muscle relaxant effect was monitored using a train-of-four (TOF) monitor, and 10 mg of rocuronium was administered if the fourth stimulus was detected. All anesthetics were discontinued at the end of surgery.

After administering 4 mg/kg of sugammadex, the recovery of the TOF ratio to 90% or higher was confirmed. A total of 2 mg (2 ml) of flumazenil or 2 ml of normal saline was administered as the study drug 5 minutes after surgery. No stimulation was given to patients until spontaneous awakening occurred. Upon awakening, the patient's ability to respond to commands and breathe spontaneously was confirmed before extubation.

Arousal was assessed using the MOAA/S every minute after extubation until a score of 5 was recorded three consecutive times. Psychomotor and equilibrium functions were measured at 30, 60, 90, and 120 minutes after extubation in the following order: TDT, DSST, TUG, and gravity sway test. If postoperative vomiting prevented continuation, the test was discontinued. The equilibrium function test was marked as missing if it was deemed unsafe and discontinued.

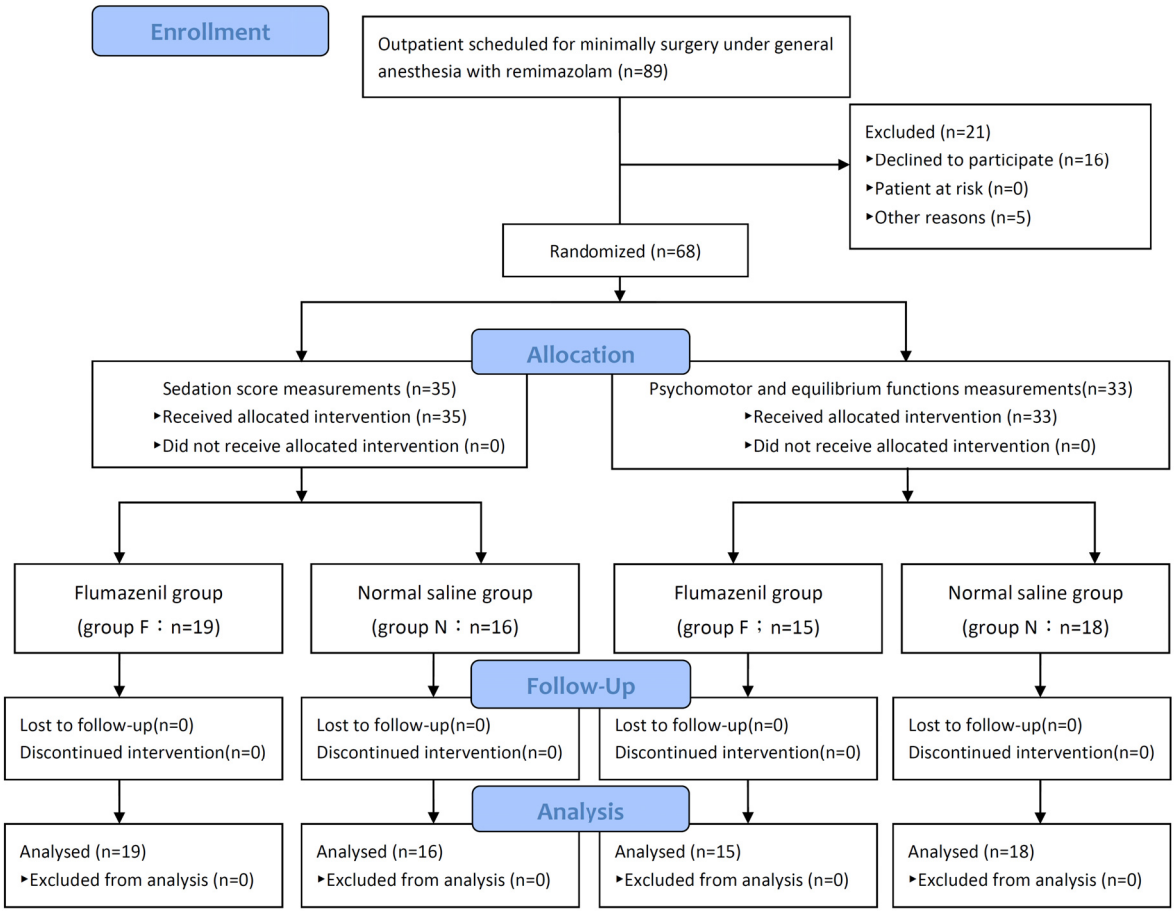

Fig. 1. Flow diagram of the study. A total of 89 patients were included in the study. However, 16 patients were excluded because they declined to participate. Two patients complained of nausea, and three patients were excluded because they could not stand up and refused to continue the study. There were no patients at risk. As a result, a total of 68 subjects were included in the study. Thirty-five subjects were included in the group for sedation score measurements, with 19 patients in the flumazenil group and 16 in the saline group (non-flumazenil group). Thirty-three subjects were included in the psychomotor and equilibrium function measurements, with 15 patients in the flumazenil group and 18 in the saline group. n, number.

5. Data analysis

Normality was tested using the Shapiro-Wilk test. Categorical data were expressed as numbers and percentages, while continuous data were presented as means and standard deviations (SD) for normally distributed data, and as medians and interquartile ranges for nonparametric data. Categorical variables (sex, ASA-PS, surgery type) were analyzed using the Chi-square test. Parametric data (duration of anesthesia and surgery) were analyzed using the independent t-test, while nonparametric data (age, BMI, the time from study drug administration to extubation and to MOAA/S score of 5) were analyzed using the Mann–Whitney U test.

Comparisons of arousal, psychomotor, and equilibrium functions between the flumazenil and non-flumazenil groups, as well as changes in psychomotor and equilibrium functions at 30, 60, 90, and 120 minutes after extubation relative to baseline, were analyzed using two-way analysis of variance with Bonferroni correction. Data were analyzed using SPSS version 27 (IBM Corp, NY), with statistical significance set at $P < 0.05$.

As remimazolam is a new intravenous anesthetic, no prior studies were available for reference. Therefore, a post-hoc power analysis was conducted using G*Power version 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf, Germany, 2020) to determine the sample size. The post-hoc analysis maintained an α error of 0.05, a β error of 0.2, and an effect size of 0.87, yielding a study power of 0.8.

Table 1. Sample characteristics

	Wakefulness	Psychomotor & equilibrium function	P value
Sample size	35	33	
Age (year)†	33 (28 – 43)	30 (24 – 42.5)	0.41
Sex			0.47
Male	16	18	
Female	19	15	
BMI (kg/m^2)†	21.64 (18.7 – 22.9)	21.88 (19.6 – 23.6)	0.33
ASA PS			0.15
Ⅰ	26	19	
Ⅱ	9	14	
Duration of anesthesia (min)††	76.9 ± 28.4	81.3 ± 28.6	0.49
Duration of operation(min)††	123.4 ± 36.2	128.4 ± 32.6	0.51
Surgical details			1.27
Tooth extraction	7	24	
Plate removal	18	0	
Cavity treatment	7	5	
Tumor/cyst resection	2	2	
Other	1	2	

Abbreviations: ASA PS, American Society of Anesthesiologists physical status classification system's classification of patients; BMI, body mass index; min, minites.
††Indicates the presented statistics are medians with interquartile ranges (25% - 75%).
†Indicates the presented statistics are mean and standard deviation (SD).

Table 2. Bivariate analyses of covariates vs. remimazolam with or without antagonist (Wakefulness)

	Wakefulness		
	Flumazil group	Non-flumazenil group	PValue
Sample size	16	19	0.42
Age (year)††	33 (24 – 46)	28.5 (23.5 – 40.3)	0.24
Sex			0.2
Male	10	8	
Female	5	10	
BMI (kg/m^2)††	21.4 (18.8 – 22.8)	22.6 (20.6 – 24.2)	0.54
ASA PS			0.8
Ⅰ	9	10	
Ⅱ	6	8	
Duration of anesthesia (min)†	122.3 ± 31.0	135.6 ± 34.0	0.24
Duration of operation (min)†	79.5 ± 29.4	83.3 ± 28.5	0.32
Surgical details			0.62
Tooth extraction	10	14	
Plate removal	0	0	
Cavity treatment	2	3	
Tumor/cyst resection	1	1	
other	2	0	

Abbreviations: flumazenil group, remimazolam with flumazenil; non-flumazenil group, remimazoram with normal saline; ASA PS, American Society of Anesthesiologists physical status classification system's classification of patients; BMI, body mass index;
†Indicates the presented statistics are mean and standard deviation (SD)
††Indicates the presented statistics are medians with interquartile ranges (25% - 75%).
*P values were obtained by the Mann-Whitney U test for continuous variables and by the chisquared test for binary variables.

The final sample size was 68 patients, reduced from an initial 89. Exclusions included 16 patients who could not provide informed consent, 3 patients who withdrew due to postoperative nausea, and 2 patients who refused measurements (Fig. 1).

An intention-to-treat analysis was not conducted

Table 3. Bivariate analyses of covariates vs. remimazolam with or without antagonist (Psychomotor & Equilibrium Function)

	Psychomotor & equilibrium function		
	Flumazil group	Non-flumazenil group	P value
Sample size	15	18	0.42
Age (year)††	33 (29.5 – 54)	30.5 (26.5 – 42)	0.24
Sex			0.2
Male	10	8	
Female	5	10	
BMI (kg/m^2)††	21.45 (19.8 – 22.3)	21.9 (18.3 – 23.3)	0.54
ASA PS			0.8
I	9	10	
II	6	8	
Duration of anesthesia (min)†	118.6 ± 33.2	127.3 ± 39.1	0.54
Duration of operation (min)†	79.5 ± 29.4	83.5 ± 28.5	0.42
Surgical details			0.62
Tooth extraction	10	14	
Plate removal	0	0	
Cavity treatment	2	3	
Tumor/cyst resection	1	1	
other	2	0	

Abbreviations: flumazenil group, remimazolam with flumazenil; non-flumazenil group, remimazoram with nrmal saline; ASA PS, American Society of Anesthesiologists physical status classification system's classification of patients; BMI, body mass index;
†Indicates the presented statistics are mean and standard deviation (SD)
††Indicates the presented statistics are medians with interquartile ranges (25% - 75%).
*P values were obtained by the Mann-Whitney U test for continuous variables and by the chisquared test for binary variables.

Table 4. Bivariate analysis of wakefulness time between the flumazenil and non-flumazenil groups

Variables	Flumazenil group	Non-flumazenil group	P value
The time from administration of study drug to MOAA/S score (min)	12.1 (5.5 - 17.5)	21.9 (14.5 - 28.3)	0.01
The time from extubation to MOAA/S score 5 (min)	6.5 (1.5 - 10.5)	13.5 (6.8 - 19.3)	0.01
The time from the administration of the study drug to extubation (min)	5.8 (2.5 - 8.5)	8.4 (6 - 10.8)	0.05

Abbreviations: MOAA/S, Modified Observer's Alertness/Sedation scale; flumazenil group, remimazolam with flumazenil; non-flumazenil group, remimazoram with normal saline; min, minutes.
Indicates the presented statistics are medians with interquartile ranges (25% - 75%).
*P values were obtained by the Mann-Whitney U test.

because one patient reported being unable to continue due to postoperative nausea and vomiting. Considering patient safety and willingness, the study could not be forcibly continued. Without outcome data, it was not possible to include these subjects in the intention-to-treat analysis.

RESULTS

A total of 89 patients were enrolled, but 16 patients could not provide informed consent, and 3 patients were excluded due to postoperative vomiting. There were no patients at risk. When MOAA/S scores were measured for 35 patients, the statistical power reached 0.8, and data collection ended. Psychomotor function was measured in 38 patients, with the following power values: NDM, 0.2; MDDM, 0.05; DSST, 0.05; TUG, 0.4; area, 0.2; speed, 0.1.

Table 1 summarizes the background characteristics of the subjects. Tables 2 and 3 present the bivariate analysis of covariates versus the outcome variables. There were no statistically significant differences between the groups for any of the covariates. Additionally, there were no significant differences in background characteristics between participants in the sedation measurements and those in the psychomotor and equilibrium function measurements.

Table 4 displays the bivariate analyses of wakefulness

Table 5. Independent variable vs. primary outcomes (Psychomotor Function)

	Baseline	30min	60min	90min	120min
	P	P	P	P	P
NDM	0.55	0.26	0.55	0.55	0.47
Flumazil group	0	4.6 (0 - 7)	0.6 (0 - 1)	0.3 (0 - 0)	0.4 (0 - 0)
Non-flumazenil group	0	1.7 (0 - 2)	0.9 (0 - 0.8)	0.2 (0 - 0)	0.1 (0 - 0)
MDDM	0.54	0.52	0.54	0.55	0.56
Flumazil group	0	1.1 (0 - 2)	0.3 (0 - 0)	0.2 (0 - 0)	0.1 (0 - 0)
Non-flumazenil group	0	0.9 (0 - 1)	0.4 (0 - 1)	0.2 (0 - 0)	0.1 (0 - 0)
DSST	0.43	0.55	0.51	0.55	0.53
Flumazil group	52.8 (44 - 61.5)	41.6 (27.3 - 55.8)	59.5 (36.7 - 65.5)	53.4 (45 - 61)	61.2 (48.5 - 71.5)
Non-flumazenil group	49.5 (40 - 59)	42.1 (32.3 - 50.5)	49.3 (41.5 - 60)	53.2 (44.3 - 62)	58.2 (49.3 - 70)

Abbreviations: flumazenil group, remimazolam with flumazenil; non-flumazenil group, remimazoram with normal saline; min, minutes; NMD, Number of dots missed; MDDM, Maximum distance of dots missed; DSST, Digit Symbol Substitution Test; P, P value.
Indicates the presented statistics are medians with interquartile ranges (25% - 75%).
P value was obtained by two-way analysis of variance and Bonferroni correction.

Table 6. Independent variable vs. primary outcomes (Equilibrium Function)

	Baseline	30min	60min	90min	120min
	P	P	P	P	P
TUG	0.52	0.16	0.14	0.36	0.42
Flumazil group	6.9 (6.2 - 8)	10.7 (8.7 - 12.2)	8.7 (7.5 - 9.6)	7.5 (6.8 - 8.1)	6.9 (6.1 - 7.5)
Non-flumazenil group	6.7 (6.2 - 7.4)	9.1 (8.2 - 10.1)	7.8 (6.9 - 8.9)	7.5 (6.2 - 8.1)	6.7 (5.8 - 7.3)
Gravimetric area	0.55	0.45	0.46	0.53	0.24
Flumazil group	3.2 (2.7 - 3.9)	15.1 (9.8 - 18.6)	10.3 (7.5 - 11.1)	7.8 (5.3 - 11.0)	5.1 (3.4 - 6.0)
Non-flumazenil group	3.4 (2.3 - 3.1)	20.2 (11.3 - 23.0)	11.8 (6.1 - 11.1)	7.5 (4.1 - 11.0)	4.5 (2.7 - 5.2)
Gravimetric speed	0.51	0.52	0.52	0.55	0.43
Flumazil group	76.7 (60.0 - 82.5)	119.4 (93.0 - 139)	97.7 (84 - 115.8)	87.1 (64.2 - 106.0)	76.2 (59.8 - 88.1)
Non-flumazenil group	70.7 (-)	129.4 (92.4 - 153.6)	96.1 (77.1 - 107.8)	85.2 (64.8 - 101.8)	69.7 (51.2 - 83)

Abbreviations: flumazenil group, remimazolam with flumazenil; non-flumazenil group, remimazoram with normal saline; min, minutes; TUG, timed up and go test; P, P value.
Indicates the presented statistics are medians with interquartile ranges (25% - 75%).
P value was obtained by two-way analysis of variance and Bonferroni correction.

time between the flumazenil group and the non-flumazenil group. The time to reach an MOAA/S score of 5 after the administration of the study drug ($P = 0.01$), the time from extubation to an MOAA/S score of 5 ($P = 0.01$), and the time from the administration of the study drug to extubation ($P = 0.05$) were all significantly shorter in the flumazenil group compared to the non-flumazenil group. Thus, the flumazenil group awoke faster than the non-flumazenil group.

Tables 5 and 6 show the measured values of psychomotor and balance functions after extubation. Two-way analysis of variance with mixed models revealed no interaction and no significant difference between the flumazenil and non-flumazenil groups in measures of psychomotor and equilibrium function. Compared to baseline, NDM and DSST showed a significant functional decline at 30 minutes after extubation (NDM: $P < 0.001$; DSST: $P < 0.001$). MDDM, TUG, and gravimetric speed showed a significant decline at 60 minutes after extubation (MDDM: $P < 0.001$; TUG: $P < 0.001$; gravimetric speed: $P < 0.001$), and gravimetric area showed a significant decline at 90 minutes after extubation ($P = 0.03$).

DISCUSSION

The aim of this study was to determine the effect of flumazenil following general anesthesia with remimazolam on expediting the recovery of

consciousness, psychomotor, and equilibrium functions. Specifically, we investigated the time required to obtain a MOAA/S score of 5 and the time required to recover psychomotor and equilibrium functions. The time from extubation to a MOAA/S score of 5 was 12.1 (5.5–17.5) minutes in the flumazenil group, which was significantly shorter than in the non-flumazenil group, while the groups exhibited no significant differences in the speed of recovery for psychomotor and equilibrium functions. Administration of flumazenil after remimazolam anesthesia did not result in faster recovery of psychomotor and equilibrium functions despite faster recovery of consciousness. Thus, hospital stay was not affected.

In this study, the time to awakening, the time to extubation, and the time to a MOAA/S score of 5 were all significantly shorter when flumazenil was administered. This result is consistent with the findings reported by Yoshida et al. [9], who noted that the administration of flumazenil resulted in faster recovery of consciousness. Therefore, flumazenil is shown to antagonize sedative effects. Psychomotor function exhibited faster recovery in NDM and DSST than in MDDM. The NDM task simply requires connecting dots; however, the DSST is a complex test that requires the full use of multiple functions (informational input, processing, and output). The slowest recovery was observed for MDDM, likely because it requires finer finger movements in addition to attention. Shimizu et al. [10] investigated psychomotor function in remimazolam anesthesia with antagonists and propofol anesthesia. This study also noted that recovery of psychomotor function was slower with remimazolam anesthesia compared to the speed of awakening, consistent with our results. However, that study was a comparison with propofol and involved a different subject group. This is the first study to examine temporal changes from baseline for anesthesia with remimazolam.

Recovery was slower for gravimetric area than for gravimetric speed, and completion time was longest for the gravimetric test compared with other tests. Maeda et al. reported that the administration of 0.5 mg of flumazenil after intravenous administration of midazolam resulted in the functional recovery of gravimetric speed immediately after flumazenil administration. However, under deep sedation, a functional decline in gravimetric area was observed up to 120 minutes after flumazenil administration [11-12]. This was consistent with the present result, likely indicating that small sway required a longer recovery time than large sway. These results also suggest that tests performed in a standing position with the legs closed may be best for examining postoperative recovery of equilibrium function. Recovery of consciousness was faster with flumazenil; however, there was no difference in the recovery of psychomotor and equilibrium functions. These differences may be attributable to the partial binding of flumazenil to benzodiazepine binding sites on GABAA receptors. The $\alpha 1\beta 2\gamma 2$ subtype has been found to be involved in sedation, anterograde amnesia, and anticonvulsant effects, whereas $\alpha 2,3\beta\gamma 2$ receptors are involved in muscle relaxation and coordinated movements, and $\alpha 5\beta\gamma 2$ receptors in memory and learning [13]. Based on these receptor mechanisms, it is suspected that flumazenil antagonized the sedative effects of $\alpha 1\beta 2\gamma 2$ receptors, while it did not antagonize the muscle relaxant and motor coordination effects of $\alpha 2,3\beta\gamma 2$ receptors. Both the flumazenil and non-flumazenil groups exhibited similar recovery patterns for psychomotor and equilibrium functions. The order of psychomotor function recovery was NDM, DSST, and MDDM, while the order of equilibrium function recovery was TUG, gravimetric speed, and gravimetric area. Therefore, functional recovery from general anesthesia with remimazolam occurs in the order of (1) sedation level, (2) psychomotor function, and (3) equilibrium function, regardless of flumazenil administration. This is consistent with previous studies investigating recovery after midazolam administration [14-15].

The strength of this study is that recovery of multiple functions was observed simultaneously, whereas many studies have focused only on psychomotor or equilibrium

functions. We believe that using the same anesthesia conditions likely led to more accurate results. However, the weaknesses of this study were that the subjects whose MOAA/S scores were measured were different from those assessed for psychomotor and equilibrium functions and that the statistical power for psychomotor and equilibrium function was small.

This study had some limitations. First, individuals who participated in psychomotor and equilibrium function measurements differed from those who participated in sedation score measurements. This design was chosen because some patients required more than 30 minutes of awake time during the preliminary study. We planned not to study the same subjects due to concerns about measurement difficulties. Although the same method of general anesthesia was used for both measurements, we could not rule out the possibility of some errors due to the inclusion of different study groups. Second, the sample size was small. Initially, the gravimetric test was set as the primary outcome in the post-hoc analysis. However, due to the large sample size required to achieve a power of 0.8, data for psychomotor and equilibrium function measurements were collected to match the sample size that achieved a power of 0.8 for the MOAA/S score. It is possible that the results could have differed with a larger sample size.

The third limitation relates to the dosages of remimazolam and flumazenil. We adjusted the dosage of remimazolam based on the BIS value. However, since general anesthesia with remimazolam has been reported to result in higher BIS values [5], an overdose of remimazolam may have been administered when attempting to lower the BIS value. Anil et al. [7] suggested that an increased dosage of midazolam may lead to insufficient antagonistic action of flumazenil. Additionally, Maeda et al. [2] reported that an increased dosage of flumazenil may result in faster recovery of function. Therefore, if an overdose of remimazolam was administered in the present study, we cannot rule out the possibility that an increased dosage of flumazenil resulted in faster recovery of psychomotor and equilibrium functions. However, Masui et al. reported that administering 0.2 mg or more of flumazenil increased the risk of re-sedation [16], highlighting the need for caution when using flumazenil.

In conclusion, the administration of flumazenil under remimazolam anesthesia resulted in faster recovery of consciousness. However, it did not affect the recovery of psychomotor and equilibrium functions, and a decline in function was observed up to 90 minutes after extubation. Recovery times for psychomotor and equilibrium functions were comparable with and without flumazenil. Patient observation for 120 minutes after extubation is recommended in ambulatory settings when general anesthesia is performed using remimazolam, regardless of flumazenil administration. In the future, we aim to improve our research by collecting more data on psychomotor and equilibrium functions.

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REFERENCES

1. Friedlander DF, Krimphove MJ, Cole AP, Marchese M, Lipsitz SR, Weissman JS, et al. Where is the value in ambulatory versus inpatient surgery? Ann Surg 2021; 273: 909-16.
2. Cukierman DS, Cata JP, Gan TJ. Enhanced recovery protocols for ambulatory surgery. Best Pract Res Clin Anaesthesiol 2023; 37: 285-303.
3. Mitchell M. Home recovery following day surgery: a patient perspective. J Clin Nurs 2015; 24: 415-27.
4. Bailey CR, Ahuja M, Bartholomew K, Bew S, Forbes L, Lipp A, et al. Guidelines for day-case surgery 2019: guidelines from the association of anaesthetists and the british association of day surgery. Anaesthesia 2019; 74: 778-92.
5. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. 2020; 34: 543-53.
6. Maeda S, Miyawaki T, Higuchi H, Shimada M. Effect of flumazenil on disturbance of equilibrium function induced by midazolam. Anesth Prog 2008; 55: 73-7.
7. Gupta A, Lind S, Eklund A, Lennmarken C. The effects of midazolam and flumazenil on psychomotor function. J Clin Anesth 1997; 9: 21-5.
8. Jaeger J. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. J Clin Psychopharmacol 2018; 38: 513-9.
9. Yoshida A, Kurata S, Kida K, Tsubokawa T. Anesthetic management for the sleep-awake-sleep technique of awake craniotomy using a novel benzodiazepine remimazolam and its antagonist flumazenil. JA Clin Rep 202; 7: 14.
10. Shimizu T, Takasusuki T, Yamaguchi S. Remimazolam compared to propofol for total intravenous anesthesia with remifentanil on the recovery of psychomotor function: a randomized controlled trial. Adv Ther 2023; 40: 4395-404.
11. Maeda S, Miyawaki T, Shimada M. The effects of flumazenil on sedation, and disturbance of equilibrium function by midazolam. J Jpn Dent Soc Anesthesiol 1994; 22: 455-65.
12. Maeda S, Miyawaki T, Shimada M. The effects of flumazenil on sedation and disturbance of equilibrium function by midazolam: part 2. J Jpn Dent Soc Anesthesiol 1995; 23: 111-7.
13. Blednov YA, Benavidez JM, Black M, Chandra D, Homanics GE, Rudolph U, et al. Linking GABA(A) receptor subunits to alcohol-induced conditioned taste aversion and recovery from acute alcohol intoxication. Neuropharmacology 2013; 67: 46-56.
14. Ibrahim AE, Ghoneim MM, Kharasch ED, Epstein RH, Groudine SB, Ebert TJ, et al. Sevofluranesedation study group. speed of recovery and side-effect profile of sevoflurane sedation compared with midazolam. Anesthesiology 2001; 94: 87-94.
15. Fujisawa T, Takuma S, Koseki H, Kimura K, Fukushima K. Study on the usefulness of precise and simple dynamic balance tests for the evaluation of recovery from intravenous sedation with midazolam and propofol. Eur J Anaesthesiol 2007; 24: 425-30.
16. Masui K. Remimazolam besilate, a benzodiazepine, has been approved for general anesthesia!! J Anesth 2020; 34: 479-82.