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Abstract

Purpose: Elderly patients with proximal femoral fractures are known to be a high-risk group for postoperative delirium (POD). The aim of this study was to determine the association of the benzodiazepine drug remimazolam with POD in elderly patients with proximal femoral fractures.

Methods: In this single-center retrospective observational study, we included patients aged 65 years or older who underwent general anesthesia for proximal femoral fractures. We collected data for the incidence of POD within three days after surgery. We also obtained data for complications, preoperative blood examinations, maintenance anesthetic and intraoperative vital data. The occurrence of POD in patients who received remimazolam for general anesthesia (remimazolam group) was compared to that in patients who received general anesthesia with other anesthetic agents (other group). We finally conducted multivariate analysis to assess the independent association of remimazolam with the risk of POD.

Results: A total of 230 patients, including 54 patients who received remimazolam for maintenance anesthesia, were included in this study. Incidence of POD in the patients was 26.1%. The incidence of delirium within three days after surgery was significantly lower in the remimazolam group than in the other group (14.8% vs. 29.5%, p=0.03). The multivariate analysis showed that the use of remimazolam independently reduced the occurrence of POD (adjusted odds ratio=0.42, p=0.04).

Conclusion: This retrospective observational study showed that the use of remimazolam is independently associated with a reduced incidence of POD. Remimazolam may be considered as an option to reduce POD in elderly patients with proximal femoral fractures.

(249words)

Introduction

Remimazolam, a sedative drug that can be used for induction and maintenance of general anesthesia, was approved for clinical use in Japan in 2020 [1]. Remimazolam is structurally similar to midazolam and exerts its sedative effects rapidly by acting on benzodiazepine receptors and indirectly enhancing the action of gamma-aminobutyric acid (GABA). Remimazolam is metabolized by tissue esterases in plasma, and its hypnotic effect quickly disappears even after prolonged administration. Furthermore, remimazolam's antagonist, flumazenil, can rapidly reverse its effects. These characteristics make remimazolam useful as a sedative, and its efficacy and safety have been proven in adults [2].

In the field of intensive care, observational studies, mainly with midazolam, have shown that "benzodiazepines are a risk factor for the development of delirium", as stated in the guidelines [3]. Compared to midazolam, remimazolam is short-acting and its effects disappear quickly after discontinuation of administration. Therefore, remimazolam may potentially reduce the incidence of postoperative delirium (POD).

With the aging of populations, the number of patients with proximal femoral fractures is increasing worldwide. These fractures are primarily the result of falls and occur in individuals with an average age of 80 years, with over 75% of the fractures occurring in individual aged 75 years or older [4]. In patients with proximal femoral fractures, being 75 years or older is considered to be an independent risk factor for POD [5]. POD itself is associated with impaired cognitive function, worsened activities of daily life (ADL), and worsened long-term prognosis after discharge from hospital [6]. Additionally, the presence of POD may impede early postoperative rehabilitation. The occurrence of POD should be prevented, but sufficient prevention has not been achieved.

Remimazolam's pharmacological properties suggest that it may prevent delirium, but there has been no study on its usefulness in elderly patients with proximal femoral fractures. In the present study, we investigated the effect of intraoperative use of remimazolam on the occurrence of POD in these patients.

Methods

Study design and participants

This single-center retrospective observational study was approved by the Ethics Committee of the Hyogo Prefectural Tamba Medical Center (Approved on 28th /July/2023 No. 1128, Chairman: S. Kawasaki). The requirement for informed consent was waived due to the retrospective design of the study. We screened patients aged 65 years or older with proximal femur fractures who underwent general anesthesia at Tamba Medical Center during the period from July 2019 to June 2023. Patients with missing preoperative information, such as information on smoking and drinking habits and body weight and patients with incomplete information on preoperative blood examinations were excluded.

Data collection

We reviewed anesthetic records and electronic medical records to obtain information on patients' characteristics including sex, age, body weight, smoking and drinking habits, American Society of Anesthesiologists physical status (ASA-PS), preoperative blood examinations (albumin, hemoglobin, estimated glomerular filtration rate (eGFR)), presence of comorbid illness (diabetes,

hypertension, ischemic heart disease, valvular disease, cerebrovascular diseases, cognitive impairment (including dementia and cognitive dysfunction), depression, Parkinson's disease), preoperative use of benzodiazepines, fracture site, duration from admission to surgery, anesthetic time, operation time, maintenance anesthetic (remimazolam, propofol, desflurane, and sevoflurane), amounts of vasopressors (etilefrine, phenylephrine, noradrenaline), intraoperative blood pressure, intraoperative heart rate, dosages of fentanyl and remifentanil, amount of intraoperative fluid transfusion, amount of intraoperative bleeding, intraoperative urine output, intraoperative use of midazolam and dexmedetomidine, intraoperative use of non-narcotic analgesic drugs (acetaminophen, flurbiprofen), intraoperative use of flumazenil, use of nerve blocks in the lower extremities, postoperative use of fentanyl, stay in the high care unit (HCU), and length of stay in the HCU.

Standard anesthesia

No premedication was given to patients before surgery. In patients for whom the remimazolam was used, anesthesia was induced with remimazolam at 12 mg/kg/h,

remifentanil at 0.1-0.2 μg/kg/min, and fentanyl at 1-2 μg/kg with or without rocuronium to facilitate the insertion of a supraglottic airway (SGA). Anesthesia was maintained with remimazolam at 0.5-1.0 mg/kg/h with fentanyl and remifentanil. We defined this group as the remimazolam group.

In patients for whom anesthetics other than remimazolam were used, anesthesia was induced with propofol at 1-2 mg/kg, remifentanil at 0.1-0.2 μg/kg/min, and fentanyl at 1-2 μg/kg with or without rocuronium to facilitate the insertion of an SGA. Anesthesia was maintained with propofol at 3-5 mg/kg/h or 3-5 vol % desflurane or 0.8-1.5 vol % sevoflurane with fentanyl and remifentanil. We defined this group as the other group.

In patients in both groups, a peripheral nerve block was performed at the discretion of the attending anesthesiologists after induction of anesthesia. Vasopressors (etilefrine, phenylephrine, noradrenaline) were also used at the discretion of the attending anesthesiologists. Non-narcotic analgesic drugs (acetaminophen, flurbiprofen) were used for postoperative analgesia.

Outcome

The primary outcome of this study was the occurrence of POD within 3 days after surgery. Information on POD was obtained from the descriptions of delirium provided by orthopedists or nurses in electronic medical records (chart-based method) and diagnosis of delirium using an interview by the Confusion Assessment Method (CAM) [7] conducted by attending anesthesiologists. The chart-based delirium detection method generally has better power than that of the interview by CAM [8].The secondary outcomes of this study were the daily occurrence of POD over a period of 3 days.

Statistical analysis

Categorical data were reported as numbers with percentages (%). Continuous data were reported as medians with interquartile ranges (IQRs). Patients were categorized into the remimazolam group and the other group (propofol, desflurane, and sevoflurane). Statistical differences between the two groups were compared using Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data.

Since a reliable multivariate model requires 5 to 9 events per predictor variable

[9], we estimated that in our dataset we could perform a multivariate logistic regression analysis using 6 to 10 variables. Multivariate logistic regression analysis was used to adjust for known predictors of the incidence of POD including, advanced age, pre-existing cognitive impairment, cerebrovascular disease, use of benzodiazepines, and low albumin levels [10,11]. We checked for multicollinearity in the multivariate analysis using the variance inflation factor. To investigate the association between the use of flumazenil and the incidence of POD in the remimazolam group, we compared its usage in patients with POD to that in patients without POD. Data were reported on the basis of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12]. Statistical analyses were performed using the statistical program EZR [13]. A p value of < 0.05 was considered to indicate a statistically significant difference.

Results

Study flow (Figure 1)

A total of 294 patients aged 65 years or older underwent surgery for proximal femur fracture during the observation period. Sixty-four patients were excluded due to incomplete preoperative data. A total of 230 patients were included in this study. Among them, 54 patients were administered remimazolam for maintenance of anesthesia (remimazolam group) and the remaining 176 patients received other anesthetics including propofol (N=13), desflurane (N=65), and sevoflurane (N=98) (other group).

Comparison of the characteristics of patients in the remimazolam group and the other group

Table 1 shows the preoperative characteristics of the patients. There were no significant differences between the two groups in baseline characteristics, preoperative blood examinations, presence of comorbid illness, preoperative use of benzodiazepines and fracture site. However, patients in the remimazolam group had a significantly lower rate of hypertension (p=0.02).

Table 2 shows the intraoperative and postoperative characteristics of the patients. There were no significant differences between the two groups in anesthetic time,

operation time, amount of norepinephrine, intraoperative blood pressure, dosage of fentanyl, amount of intraoperative intravenous fluid, amount of intraoperative bleeding, intraoperative urine output, intraoperative use of midazolam, postoperative use of fentanyl, stay in the HCU, and length of stay in the HCU. Additionally, intraoperative dexmedetomidine was not used.

Patients in the remimazolam group received less vasopressors (including etilefrine and phenylephrine) than those for patients in the other group ($p<0.001$ and $p=0.04$, respectively).

In the remimazolam group, the intraoperative heart rate and dosage of remifentanil were significantly higher than those in the other group ($p=0.022$ and $p<0.001$, respectively). The frequency of use of peripheral nerve blocks in the remimazolam group was significantly lower than in the other group ($p=0.002$), while the frequency of use of acetaminophen was significantly higher than in the other group ($p<0.001$).

Primary and Secondary Outcomes

Table 3 shows the outcomes of this study. The incidence of POD in all patients

was 26.1% (60/230). In the remimazolam group, the overall incidence of POD was 14.8% (8/54) within 3 days after surgery, and the incidence was significantly lower than the incidence of 29.5% (52/176) in the other group (p=0.03). On postoperative day 0, the incidence of POD in the remimazolam group was 1.9% (1/54), which was significantly lower than the 15.3% (27/176) in the other group (p=0.007). However, there were no significant differences between the two groups in the incidences of POD on postoperative days 1, 2, and 3.

Multivariate analysis

Table 4 shows the results of multiple logistic regression analysis. We found that the use of remimazolam is independently associated with a reduced incidence of POD even after adjusting for age, preoperative benzodiazepine usage, cognitive impairment, cerebrovascular disease and albumin levels (p=0.04).

Discussion

Summary of the results

Our study revealed that the use of remimazolam is associated with a decrease in the occurrence of POD in patients aged 65 years or older with proximal femoral fractures. Even after adjusting for age, preoperative benzodiazepine use, cognitive impairment, cerebrovascular disease and nutritional status, the use of remimazolam was still independently associated with a reduction in the occurrence of POD. This study is the first manuscript to demonstrate the effectiveness of remimazolam in preventing POD in elderly patients with proximal femoral fractures.

Comparison with previous studies

The relationship between the use of remimazolam and POD was examined in three previous studies.

In a retrospective exploratory study, Kaneko et al. examined the incidence of POD within three days after transcatheter aortic valve implantation in 98 patients who underwent general anesthesia [14]. In that study, a group in which remimazolam was used was compared with a group in which propofol was used. The results showed that the remimazolam group had a significantly lower

incidence of POD than that in the propofol group (8% in the remimazolam group vs. 26% in the propofol group, p=0.032). The median age of patients in both groups in that study was 84 years, which is similar to the age range in our study. Therefore, the results of our study are in line with the results of that study.

In a prospective cohort study, Aoki et al. investigated the incidence of POD over a period of five days in a group of 200 patients who underwent elective cardiovascular surgery [15]. In that study, a group that received remimazolam was compared with a group that received other anesthetic drugs (desflurane, sevoflurane and propofol). The results showed no significant difference in the incidence of POD between the remimazolam group and the group receiving other anesthetic drugs (30.3% in the remimazolam group vs. 26.6% in the other group, p=0.63). It is important to note that the patients in that study were approximately ten years younger than the patients in our study and underwent more invasive surgical procedures, which may explain the difference in results.

In a prospective randomized controlled trial (RCT), Yang et al. investigated the incidence of POD within three days after orthopedic surgery in a cohort of 320 patients [16]. In that study, a group that received remimazolam was compared

with a group that received propofol. The results showed no significant difference in the incidence of POD between the remimazolam group and the propofol group (15.6% vs. 12.4%, p=0.42). Additionally, most patients in that RCT underwent spinal surgery, and patients who underwent hip-joint surgery accounted for only 9.5% of the patients in the remimazolam group and only 7.2% of the patients in the propofol group. Furthermore, the patients in that study were, on average, approximately 20 years younger than the patients in our study (with both groups in that study having an average age of 68 years). There are two potential reasons for the contrasting results of our study and the study by Yang et al. One is the considerably younger age of patients in Yang's cohort. The other is the notably low representation of patients with proximal femoral fractures in Yang's cohort, a condition that often occurs in frail elderly individuals who are at a high risk of delirium.

It is important that the patient cohorts in both Aoki's study and Yang's study were, on average, about 10-20 years younger than the patients in both Kaneko's study and our study. As previously stated, advanced age has been recognized as a potential factor contributing to POD.

Interpretation of the results

In our study, although there was no significant difference in intraoperative blood pressure, the frequency of use of ephedrine and phenylephrine was significantly lower in the remimazolam group. Furthermore, heart rate during surgery was significantly higher in the remimazolam group. This suggests that remimazolam causes less circulatory depression than that caused propofol, sevoflurane, and desflurane, being consistent with previous reports [17–19]. Intraoperative hypotension is known to be a factor contributing to the development of POD [20]. The impact of intraoperative hypotension in patients with hypertension may be greater and more likely to contribute to POD compared to patients without hypertension. In this study, although there was no significant difference in intraoperative blood pressure, the significantly larger number of patients with hypertension in the other group may be related to the higher incidence of POD in that group.

In this study, the incidence of POD on postoperative day 0 was significantly lower in the remimazolam group. However, there was no significant difference

between the two groups in the incidence of POD after postoperative day 0. This might be due to the pharmacological properties of remimazolam, which is ultra-short-acting with very rapid metabolism and minimal accumulation [1].

Furthermore, due to differences in drug clearance from the central nervous system, inhalation anesthetics are known to result in increased emergence agitation [21]. The residual presence of inhalation anesthetics may be involved not only in emergence agitation but also in "delirium-like mental changes" after awakening. In this study, inhalation anesthetics were used for 93% of the patients in the other group. This could potentially impact the results on postoperative day 0.

In this study, we examined the incidences of POD in the remimazolam group with and without reversal by flumazenil, but we did not find a significant difference between the two groups (supplemental file 1). Patients who received flumazenil may have had delayed emergence due to the accumulation of remimazolam, possibly caused by overdosing. On the other hand, patients who did not receive flumazenil were likely to awaken quickly. In the flumazenil group,

it is likely that the use of flumazenil antagonized the effects of remimazolam and improved cognitive function, and in the flumazenil non-user group, it is likely that the rapid off-set of remimazolam contributed to the swift improvement in cognitive function. These are probably the reason for no significant difference being found in the incidence POD between the two groups.

Limitations

This study has several limitations. First, this study was a retrospective study conducted at a single facility, and the number of patients in the study was relatively small. Consequently, we investigated the effect of propofol, sevoflurane, and desflurane as a single group, and direct comparisons between each anesthetic and remimazolam were therefore not possible. Second, due to the retrospective nature of this study, evaluation of the quality of emergence from anesthesia was not possible. It is difficult to distinguish between "delirium-like mental changes" caused by residual anesthetic agents after awakening and POD on postoperative day 0. As a result, it is a possible that the assessment of postoperative delirium was inaccurate. Third, the CAM was used for assessment

of POD in this study, but it was only applied to some patients. For the remaining patients, POD assessments were based on information in electronic health records. As a result, there is a possibility that the assessment of POD was inadequate. Due to the variable nature of delirium, chart-based methods are superior for detecting delirium. On the other hand, interviews using the CAM are superior for diagnosing delirium. A combination of both methods has been reported to be the most effective method for diagnosing delirium [8]. Chart-based methods were mainly used for the diagnosis of delirium in this study. Therefore, false positives might have been included. Additionally, we did not assess the specific types of delirium.

Postoperative pain is also known to be associated with POD [11]. Based on the outcomes of this study, POD on postoperative day 0 might have been related to postoperative pain. In this study, administration of non-narcotic analgesics, administration of opioids, and nerve blocks were used as methods for postoperative pain control. However, we did not routinely evaluate NRS scores or VAS scores postoperatively. Therefore, we were unable to make a precise assessment of the relationship between postoperative pain and the occurrence of

delirium on postoperative day 0. It remains unclear how these differences in pain management may have influenced pain outcomes.

Conclusion

In this study, the use of remimazolam was independently associated with a reduction in the incidence of POD in patients aged 65 years or older who had proximal femoral fractures. As this result may be skewed by lack of information such as quality of emergence from anesthesia, assessment of postoperative pain or other bias, further study is needed to refute or confirm our findings.

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Author contributions

DF designed the study, collected data, and analyzed the data. DF, NO and SM wrote the manuscript.

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Table 1. Preoperative characteristics of patients

		Remimazolam group (n=54)	Other group (n=176)	*p* value
Female gender (%)		38 (70.4)	141 (80.1)	0.14
Age (years)		85.0 [81.0, 89.0]	87.0 [81.0, 91.3]	0.20
Body weight (kg)		45.3 [40.4, 54.9]	46.0 [38.7, 53.0]	0.54
Smoking habit (%)		14 (25.9)	33 (18.8)	0.25
Drinking habit (%)		5 (9.3)	11 (6.2)	0.54
ASA-PS (%)	1	1 (1.9)	1 (0.6)	0.097
	2	45 (83.3)	127 (72.2)	
	3	8 (14.8)	48 (27.3)	
Albumin (g/dL)		3.7 [3.0, 4.0]	3.6 [3.1, 3.9]	0.88
Hemoglobin (g/dL)		11.5 [10.2, 13.1]	11.1 [9.7, 12.5]	0.1
eGFR (ml/min/1.73m^2)		56.8 [42.1, 66.7]	50.0 [35.8, 65.0]	0.14
Diabetes (%)		10 (18.5)	38 (21.6)	0.71
Hypertension (%)		28 (51.9)	122 (69.3)	0.022
Ischemic heart disease (%)		5 (9.3)	24 (13.6)	0.49
Valvular disease (%)		6 (11.1)	20 (11.4)	1
Cerebrovascular disease (%)		7 (13.0)	39 (22.2)	0.17
Cognitive impairment (%)		19 (35.2)	45 (25.6)	0.17
Depression (%)		0 (0.0)	5 (2.8)	0.59
Parkinson's disease (%)		2 (3.7)	5 (2.8)	0.67
Preoperative use of benzodiazepine (%)		5 (9.3)	23 (13.1)	0.64
Fracture site (%)	neck	31 (57.4)	81 (46.0)	0.36
	trochanteric	23 (42.6)	94 (53.4)	
	sub-trochanteric	0 (0.0)	1 (0.6)	
Duration from admission to surgery (day)		1[1,2]	2[1,3]	0.064

Data are presented as medians [25%,75% interquartile ranges] or numbers (percentages).

ASA-PS: American Society of Anesthesiologists physical status

eGFR: estimated glomerular filtration rate

Table 2. Intraoperative and postoperative characteristics of patients

	Remimazolam group (n=54)	Other group (n=176)	*p* value
Anesthetic time (min)	111 [91, 123]	108 [91, 124]	0.96
Operation time (min)	50 [39, 61]	53 [37, 67]	0.5
Etilefrine (mg)	0.0 [0.00, 3.8]	2.0 [0.50, 4.0]	<0.001
Phenylephrine (mg)	0.0 [0.0, 0.7]	0.3 [0.04, 0.70]	0.04
Noradrenaline (mg)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.21
Blood pressure (mmHg)			
Diastolic	57 [50, 69]	60 [52, 68]	0.39
Mean	67 [62, 77]	72 [64, 82]	0.064
Systolic	96 [87, 120]	103 [92, 116]	0.23
Heart rate (bpm)	78 [70, 85]	72 [65, 81]	0.022
Dosage of fentanyl (μ g/kg)	3.01 [2.19, 4.42]	3.08 [2.22, 4.13]	0.67
Dosage of remifentanil (μ g/kg/min)	0.16 [0.12, 0.18]	0.06 [0.03, 0.08]	<0.001
Amount of fluid transfusion (ml)	675 [500, 888]	600 [500, 850]	0.41
Amount of bleeding (ml)	50 [31, 98]	60 [25, 120]	0.88
Urine output (ml)	60 [40, 85]	50 [25, 81]	0.17
Use of midazolam (%)	0 (0)	1 (0.6)	1
Use of dexmedetomidine (%)	0 (0)	0 (0)	1
Use of non-narcotic analgesic drugs	53 (98.2)	104 (59.1)	<0.001
Acetaminophen (%)	32 (59.3)	43 (24.4)	<0.001
flurbiprofen (%)	21 (38.9)	61 (34.7)	0.63
Use of flumazenil (%)	30 (55)	0 (0)	<0.001
Use of nerve block (%)	24 (44.4)	121 (68.8)	0.002
Postoperative use of fentanyl (%)	1 (1.9)	0 (0)	0.235
Stay in HCU (%)	5 (9.3)	12 (6.8)	0.56
Length of HCU stay (days)	0 [0, 0]	0 [0, 0]	0.55

Data are presented as medians [25%,75% interquartile ranges] or numbers (percentages).

HCU: high care unit

Table 3. Outcomes of this study

	Remimazolam group (n=54)	Other group (n=176)	*p* value
Total incidence of POD (%)	8 (14.8)	52 (29.5)	0.034
Daily incidence of POD (%)			
postoperative day 0	1 (1.9)	27 (15.3)	0.007
postoperative day 1	3 (5.6)	28 (15.9)	0.067
postoperative day 2	3 (5.6)	18 (10.2)	0.42
postoperative day 3	4 (7.4)	12 (6.8)	1

Data are presented as numbers (percentages).

POD: postoperative delirium

Table 4. Multiple logistic regression analysis

	Adjusted odds ratio	95% CI	*p* value
Age	1.04	(0.99, 1.08)	0.097
Preoperative use of benzodiazepine	1.78	(0.75, 4.20)	0.19
Cognitive impairment	1.39	(0.71, 2.71)	0.34
Cerebrovascular disease	1.02	(0.49, 2.14)	0.96
Albumin	1.50	(0.85, 2.63)	0.16
Use of remimazolam	0.42	(0.18-0.97)	0.041

Risk factors for delirium after adjusting for confounders of delirium

Figure legends

Figure 1. Study flow

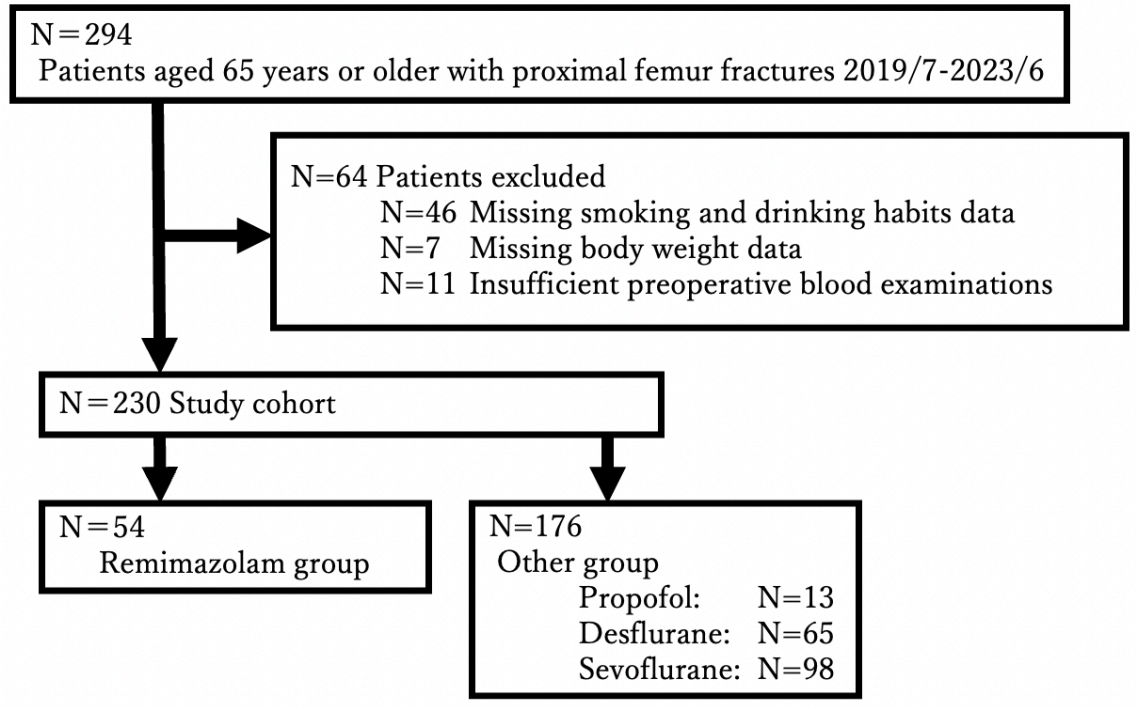

Figure 1. Study flow

Supplemental file 1. Use of flumazenil in the remimazolam group

	No use of flumazenil (n=24)	Use of flumazenil (n=30)	*p* value
Incidence of POD (%)	12.5 (3)	16.7 (5)	0.72

POD: postoperative delirium