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Comparison between single bolus dose administration and continuous infusion of remimazolam for general anesthesia induction in non-cardiac surgery: a single-center prospective randomized controlled trial

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Abstract

Background Remimazolam is a short-acting benzodiazepine anesthetic recommended for continuous infusion during anesthesia induction. However, the safety and efficacy of single bolus dose administration remain under investigation. This study compared continuous infusion with single bolus dose administration and assessed the safety of a single bolus dose administration.

Methods The participants were randomly assigned into three groups based on the method of remimazolam administration the day before surgery: (1) continuous infusion group (continuous infusion at 12 mg/kg/h), (2) single bolus dose administration of 0.1 group (single administration of 0.1 mg/kg), or (3) single bolus dose administration of 0.2 group (single administration of 0.2 mg/kg). The time between drug administration and loss of consciousness was determined, and hemodynamic monitoring was performed.

Results 67 patients (continuous infusion group ($n=22$), single bolus dose administration of 0.1 group ($n=22$), and single bolus dose administration of 0.2 group ($n=23$)) were included in the study. The different times to loss of consciousness were 88.2 ± 16.2 s, 59.5 ± 31.5 s, and 42.6 ± 11.4 s in the continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group, respectively. No significant differences were observed in the incidence of adverse events between the groups. The results are presented as mean ± standard deviation (SD).

Conclusions Single-dose remimazolam is a safe method for anesthesia induction, resulting in shorter time to loss of consciousness compared with continuous infusion, while maintaining a similar incidence of adverse events.

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Trial registration jRCTs061230049, registered on 17/08/2023.
Keywords Remimazolam, Intravenous anesthesia, Rapid induction, Rapid sequence induction

Introduction

Remimazolam, a short-acting benzodiazepine anesthetic, was approved as a general anesthetic in Japan in January 2020 [1]. It is rapidly converted to inactive metabolites by hepatic carboxylesterases [2], resulting in a short context-sensitive half-life (CSHT) [3], even after prolonged continuous administration [4]. This pharmacokinetic profile makes remimazolam suitable for continuous intravenous administration throughout the induction and maintenance phases of general anesthesia.

Although propofol plays a role similar to that of an intravenous anesthetic, notable differences exist between the two agents. Propofol induction is frequently associated with vascular pain during injection [5] and a higher incidence of hypotension [6, 7]. By contrast, clinical trials have shown that remimazolam does not cause vascular pain during injection [8, 9] and is associated with a lower frequency of blood pressure (BP) reduction compared with propofol [9–11]. Furthermore, it is unclear whether remimazolam induces involuntary movements such as motor agitation and choreiform movements. However, it is known that these rare side effects can occur following the administration of propofol, including significant motor agitation and choreiform movements [12–14].

Unlike propofol, which can be administered either as a continuous infusion or as a single bolus injection depending on the clinical setting, remimazolam is recommended solely for continuous infusion. The efficacy of single-dose remimazolam is currently being investigated, and available data regarding its effects are limited. Continuous infusion of 12 mg/kg/h remimazolam is typically used for general anesthesia induction. However, this method can lead to clinical challenges, such as a slow rise in blood levels, potentially requiring unnecessarily large doses unless the infusion rate is promptly adjusted after the patient loses consciousness.

Clinical trials have reported that a single bolus of remimazolam does not cause hypotension [8], suggesting milder circulatory depression. Lee et al. [15] compared continuous infusion (6 mg/kg/h) with single bolus doses (0.1 mg/kg and 0.2 mg/kg) of remimazolam for induction during cardiac surgery. They found that a single bolus (0.2 mg/kg) was the most favorable induction method. However, data on the use of single bolus administration in patients undergoing noncardiac surgery remain limited, and further research is needed to confirm its safety and utility for general anesthesia induction in these populations.

We hypothesized that a single bolus of remimazolam would be a safe and effective method for anesthesia induction, providing a faster time to loss of consciousness and a lower incidence of adverse events, such as hypotension, compared with continuous infusion. This single-center prospective randomized controlled trial was conducted to test this hypothesis.

Methods

This study was approved by the Ethics Committee of Hiroshima University Hospital (CRB-2023-0001) on July 31, 2023, as a specified clinical trial. It was conducted at Hiroshima University Hospital following registration in the Japan Registry of Clinical Trials (jRCTs061230049, registered on 17/08/2023, the study period is from February 7, 2024, when the first participant was recruited, to August 16, 2024, when the observation period for the last participant concluded). Written informed consent was obtained from the patient by the study physician at least 1 day prior to surgery. This study was conducted in accordance with the CONSORT guidelines for reporting randomized controlled trials.

Study participants and exclusion criteria

(1) Adults aged 18–80 years undergoing non-cardiac surgery under general anesthesia, (2) male or female patients, (3) patients with an American Society of Anesthesiologists physical status (ASA-PS) score of 1 or 2, (4) patients with body mass index (BMI) values of ≥ 18.5 kg/m^2 and < 30 kg/m^2, and (5) patients who voluntarily provided written informed consent after fully understanding the study protocol were included in the study.

By contrast, (1) patients consuming more than 60 g of pure alcohol per day, (2) those with current or past alcohol or drug dependence, (3) regular users of benzodiazepines, (4) patients with contraindications to remimazolam treatment (e.g., acute angle-closure glaucoma and myasthenia gravis), (5) those with severe psychiatric disorders, (6) patients with organic brain disorders, (7) pregnant or lactating individuals, (8) patients with direct ties to the research personnel, and (9) those deemed unsuitable for participation by the investigators were excluded.

Study protocols

Study participants were randomly assigned by computer to one of three groups based on the method of remimazolam administration the day before surgery: (1) continuous infusion group (continuous infusion at 12 mg/kg/h), (2) single bolus dose administration of 0.1 group (single administration of 0.1 mg/kg), or (3) single bolus

dose administration of 0.2 group (single administration of 0.2 mg/kg). The study protocol is shown in Fig. 1.

Monitors (electrocardiogram (ECG), sphygmomanometer, SpO_2, electroencephalogram monitor (Entropy, GE Healthcare Japan, Tokyo, Japan), and muscle relaxation monitor) were attached to the patients upon entering the operating room. Noninvasive BP measurements were taken every minute, and a peripheral venous route was established. After ensuring adequate oxygenation, a continuous infusion of remimazolam (12 mg/kg/h) was initiated in the continuous infusion group. Patient status was assessed every 10 s. After confirming loss of consciousness (not responding to a call with a light tap on the shoulder) (Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale score of < 2), the infusion rate was adjusted to 1 mg/kg/h of remimazolam. Concurrently, remifentanil 0.3 μg/kg/min was initiated. After the administration of rocuronium (0.6–0.9 mg/kg), tracheal intubation was performed when sufficient muscle relaxation was achieved, and remifentanil blood levels exceeded 4 ng/mL, according to the Minto model [16]. Following adequate oxygenation, remimazolam (single bolus dose administration of 0.1 group: 0.1 mg/kg; single bolus dose administration of 0.2 group: 0.2 mg/kg) was administered in the single bolus dose administration group. If the patient did not fall asleep after 2 min, an additional dose of 0.05 mg/kg of remimazolam was administered. If the patient failed to lose consciousness in the next minute, the study was discontinued, and an alternative sedative was administered. Thus, the patients were observed for 3 min. After confirming loss of consciousness (MOAA/S scale score of < 2), remimazolam was continuously administered at the infusion rate of 1 mg/kg/h. Remifentanil (0.3 μg/kg/min) was administered. After administering rocuronium (0.6–0.9 mg/kg), tracheal intubation was performed when sufficient muscle relaxation was achieved, and remifentanil blood levels exceeded 4 ng/mL according to the Minto model. Circulatory agonists were used if the systolic BP (SBP) level decreased below 70 mmHg on two consecutive NIBP measurements during the anesthesia induction period.

Outcomes

The primary outcomes were the time from the initiation of remimazolam treatment to loss of consciousness and the amount of remimazolam administered until loss of consciousness.

The secondary outcome was the ratio of changes in BP to heart rate before and after remimazolam administration. This ratio was calculated by dividing the BP or heart rate immediately before tracheal intubation by the BP or heart rate before the initiation of remimazolam treatment, which served as the baseline.

The incidence of adverse events, including hypoxia (SpO_2 < 90%), mask ventilation difficulty, bradycardia (heart rate < 50 bpm), hypotension (SBP < 80 mmHg),

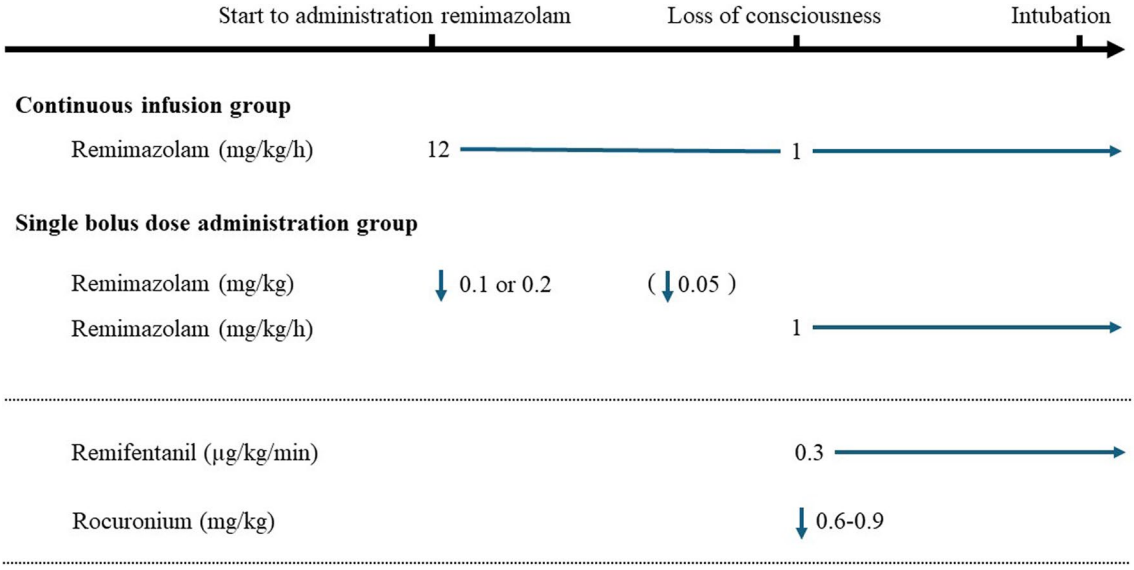

Fig. 1 Study protocols. Patients were attached to monitors (ECG, sphygmomanometer, SpO_2, EEG monitor, and muscle relaxation monitor) after entering the operating room. Noninvasive BP measurements were taken every minute. After adequate oxygenation, the continuous infusion group received a continuous infusion of remimazolam at 12 mg/kg/h. Patient status was assessed every 10 s. After confirming the loss of consciousness, the remimazolam infusion rate was reduced to 1 mg/kg/h. Simultaneously, remifentanil 0.3 μg/kg/min was initiated. After administering rocuronium at a dose of 0.6–0.9 mg/kg, tracheal intubation was performed. A single bolus dose administration of remimazolam (single bolus dose administration of 0.1 group: 0.1 mg/kg; single bolus dose administration of 0.2 group: 0.2 mg/kg) was administered in the single bolus dose administration group. If the patient failed to fall asleep after 2 min, an additional dose of 0.05 mg/kg of remimazolam was administered. If the patient failed to lose consciousness in the next minute, the study was discontinued, and another sedative was administered

ECG changes, oversedation (Entropy SE value < 20), and inadequate sedation (Entropy SE value > 80), was investigated to assess safety. Patients with a heart rate of < 50 bpm before anesthesia induction were excluded from the determination of bradycardia. Entropy values were assessed prior to tracheal intubation.

Furthermore, we examined whether the entropy (SE) at the time of loss of consciousness was ≤ 60, which is considered to indicate sufficient sedation.

Sample size calculation

The mean time from the start of administration to loss of consciousness following continuous infusion of remimazolam at 6 mg/kg/h or 12 mg/kg/h was previously reported as 100 ± 25 s and 90 ± 25 s, respectively [9]. The mean time from the start of administration to loss of consciousness after a single bolus dose administration of remimazolam at 0.2 mg/kg was reported to be 65 ± 5 s [17]. Assuming that the ratio of the time to loss of consciousness at 6 mg/kg/h and 12 mg/kg/h for the continuous infusion was similar to that at 0.1 mg/kg and 0.2 mg/kg for the single bolus dose administration, the average time from the start of infusion to loss of consciousness at a single bolus dose administration of 0.1 mg/kg was estimated to be 72 ± 5 s. Therefore, the estimated the mean times to loss of consciousness in the continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group were 90 ± 25 s, 72 ± 5 s, and 65 ± 5 s, respectively. The sample size calculation was performed using the SWOG statistical tools (https://stattools.crab.org/). When perform ing Welch's t-test with a two-sided significance level of 2.5% to adjust for multiplicity (Bonferroni method), the required sample size to achieve a statistical power of 80% or more for comparisons between the single bolus dose administration group 0.1 mg/kg and the continuous administration group and between single bolus dose administration group 0.2 mg/kg and the continuous administration group was calculated to be 23 patients per group, with a total of 69 patients for the three groups.

Statistical analysis

The full analysis set (FAS) was defined as the population of randomized study participants, excluding (1) patients who did not meet the eligibility criteria, (2) patients who did not receive any study treatment after randomization, and (3) patients with no available post-randomization data.

Primary outcomes: In the FAS population, the mean and standard deviation of the time from the start of remimazolam administration to loss of consciousness were calculated. The amount of remimazolam administered was also calculated and subsequently compared between the single bolus dose administration of 0.1 mg/kg group and the continuous infusion group, as well as between the single bolus dose administration of 0.2 mg/kg group and the continuous infusion group, using Welch's t-test. To adjust for multiplicity in two pairwise comparisons, a Bonferroni correction was applied, setting the two-sided significance level at 0.025 (0.05/2).

Secondary outcomes: In the FAS population, the mean and standard deviation of the percentage change in blood pressure and heart rate from baseline to post-induction of general anesthesia were calculated. These ratios were compared between the single bolus dose administration of 0.1 mg/kg group and the continuous infusion group, as well as between the single bolus dose administration of 0.2 mg/kg group and the continuous infusion group, using Welch's t-test. A Bonferroni correction was applied for multiple comparisons, setting the two-sided significance level at 0.025 (0.05/2).

Assessment for safety: With the FAS as the population for analysis, the incidence of adverse events during anesthesia induction was calculated and compared using Fisher's exact test between the single bolus dose administration of 0.1 mg/kg group and the continuous infusion group, as well as between the single bolus dose administration of 0.2 mg/kg group and the continuous infusion group. A Bonferroni correction was applied, setting the two-sided significance level at 0.025 (0.05/2).

Comparisons of the proportion of people with entropy (SE) of 60 or less were performed using chi-square test.

Results

Study patients

A total of 69 patients who consented to participate in the study between March and August 2024 were randomly assigned to three groups (continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group), with 23 patients in each group on the day before surgery. One patient from the continuous infusion group and one patient from the single bolus dose administration of 0.1 group were excluded from the study. Thus, 67 patients (continuous infusion group ($n = 22$), single bolus dose administration of 0.1 group ($n = 22$), and single bolus dose administration of 0.2 group ($n = 23$)) were included in the FAS (Fig. 2). The baseline characteristics of each group are presented in Table 1.

Primary outcomes

One patient in the single bolus dose administration of 0.1 group did not lose consciousness after the first single bolus dose administration, prompting the administration of an additional dose. However, the patient failed to lose consciousness 1 min after the additional dose, another intravenous anesthetic was administered according to the protocol. The patient was included in the analysis with a

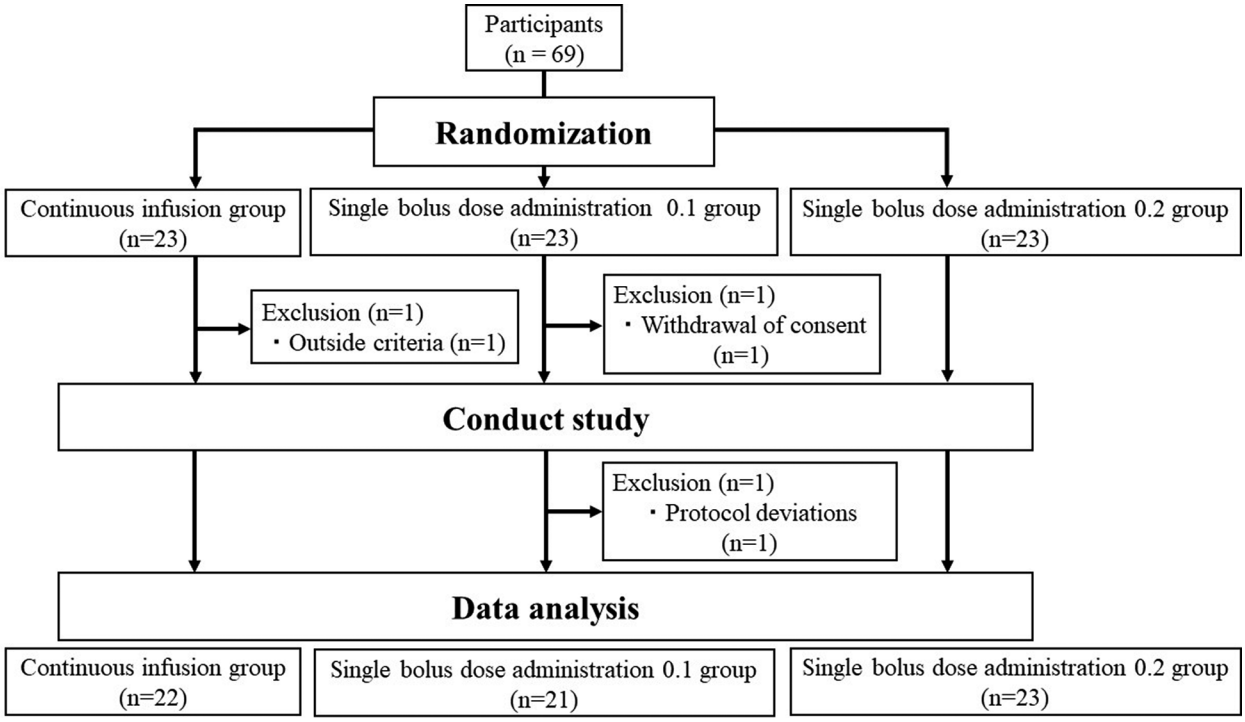

Fig. 2 Allocation of patients. All 69 patients who provided consent to participate in the study were randomly assigned into three groups (continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group), with each group comprising 23 patients, on the day before surgery. One patient in the continuous infusion group (who did not meet the selection criteria after randomization) and one patient in the single bolus dose administration of 0.1 group (who withdrew consent after randomization) were excluded from the study. Thus, only 67 patients (continuous infusion group ($n=22$), single bolus dose administration of 0.1 group ($n=22$), and single bolus dose administration of 0.2 group ($n=23$)) were included in the FAS

loss of consciousness time set to the maximum observation period of 180 s. The remaining patients in both the single bolus dose administration of 0.1 group and the single bolus dose administration of 0.2 group did not require an additional dose, as they achieved loss of consciousness after only the first single bolus dose administration. The times to loss of consciousness were 88.2 ± 16.2 s, 59.5 ± 31.5 s, and 42.6 ± 11.4 s in the continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group, respectively. Significant differences were observed between the continuous infusion group and the single bolus dose administration of 0.1 group, and between the continuous infusion group and the single bolus dose administration of 0.2 group (Fig. 3). The amounts of remimazolam used until loss of consciousness were 19.5 ± 4.8 mg, 6.1 ± 1.2 mg, and 12.2 ± 1.9 mg in the continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group, respectively. No significant differences were found between the continuous infusion group and the single bolus dose administration of 0.1 group, and between the continuous infusion group and the single bolus dose administration of 0.2 group (Fig. 4).

Secondary outcomes

One patient from the continuous infusion group and another from the single bolus dose administration of 0.1 group required a circulatory agonist. The other patients did not require a circulatory agonist. The ratios of change in BP before and after induction of anesthesia were 0.722 ± 0.129, 0.773 ± 0.134, and 0.767 ± 0.087 in the continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group, respectively. BP decreased in all three groups and did not differ between the groups. The ratios of change in heart rate before and after induction of anesthesia were 1.069 ± 0.141, 1.041 ± 0.157, and 1.087 ± 0.214 in the continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group, respectively. The heart rate increased in all three groups and did not differ between them (Table 2).

Assess for safety

No significant differences were found in the incidence of hypoxia, mask ventilation difficulty, bradycardia, hypotension, ECG changes, oversedation, or inadequate sedation between the continuous infusion group and the shot 0.1 group or between the continuous infusion group and the single bolus dose administration 0.2 group (Table 3).

Table 1 Patients' baseline characteristics

	Continuous infusion group (n = 22)	Single bolus dose administration 0.1 group (n = 22)	Single bolus dose administration 0.2 group (n = 23)	p value
Age (y)	58 ± 15	64 ± 11	56 ± 14	0.090
Sex (Male / Female)	12 / 10	12 / 10	11 / 12	0.872
Height (cm)	165 ± 9	161 ± 10	163 ± 8	0.420
Weight (kg)	66 ± 11	61 ± 12	61 ± 10	0.225
BMI (kg/m²)	24.2 ± 2.7	23.5 ± 3.0	23.0 ± 2.5	0.306
ASA-PS (1 / 2)	5 / 17	1 / 21	6 / 17	0.131
Heart rate (bpm)	77 ± 11	74 ± 17	77 ± 10	0.622
Systolic blood pressure (mmHg)	128 ± 14	123 ± 17	126 ± 15	0.534
SpO_2 (%)	98 ± 1	98 ± 1	98 ± 1	0.937
Type of surgery				
General Surgery	6	8	11	
Orthopedic surgery	4	5	2	
Gynecologic surgery	4	1	7	
Urological surgery	0	2	0	
Gastroenterological surgery	0	2	0	
Thoracic Surgery	2	1	1	
others	6	3	2	

The heart rate, systolic blood pressure, and SpO_2 were measured the day before surgery

BMI: Body mass index

ASA-PS: American Society of Anesthesiologists physical status

SpO_2: Saturation of percutaneous oxygen

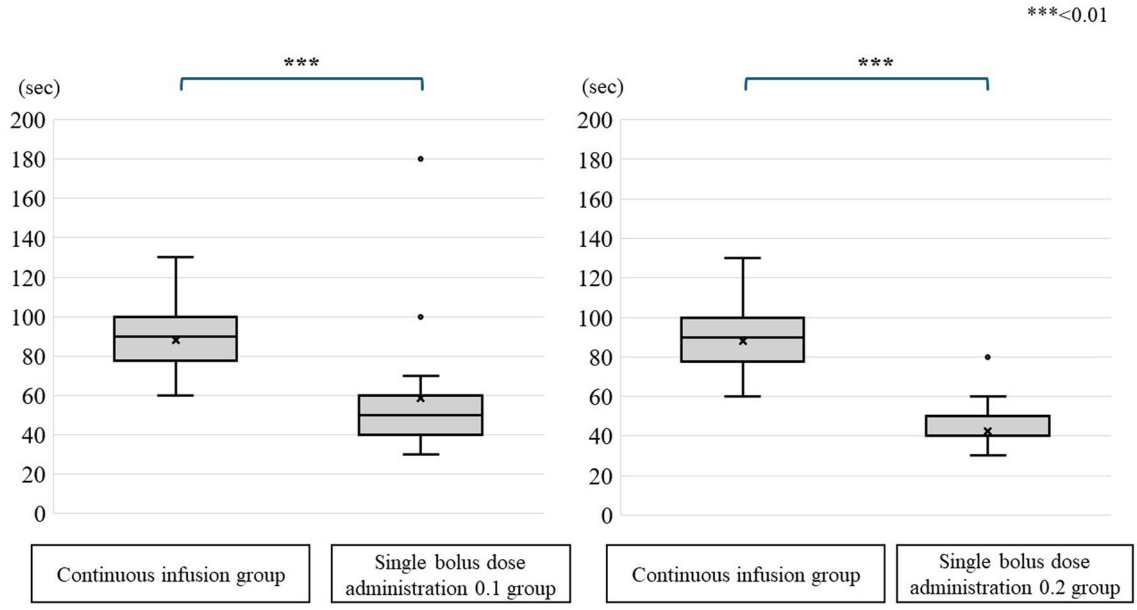

Fig. 3 Time to loss of consciousness. The box-and-whisker diagram illustrates the time from the start of remimazolam administration to loss of consciousness. The two ends of the whiskers indicate the maximum and minimum values, the boxes indicate the first to third quartiles, the lines in the boxes indicate the median values, and the crosses in the boxes indicate the mean values. Outliers exceeding 1.5 times the quartile range are marked as small black circles. Loss of consciousness was assessed every 10 s. Patients who did not fall asleep within the 180-second study observation period were considered to have fallen asleep at 180 s. The mean times to loss of consciousness were 88.2 ± 16.2 s, 59.5 ± 31.5 s, and 42.6 ± 11.4 s in the continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group, respectively. A significant difference was found between the single bolus dose administration of 0.1 group and continuous infusion group, and between the continuous infusion group and the single bolus dose administration of 0.2 group ($p < 0.01$)

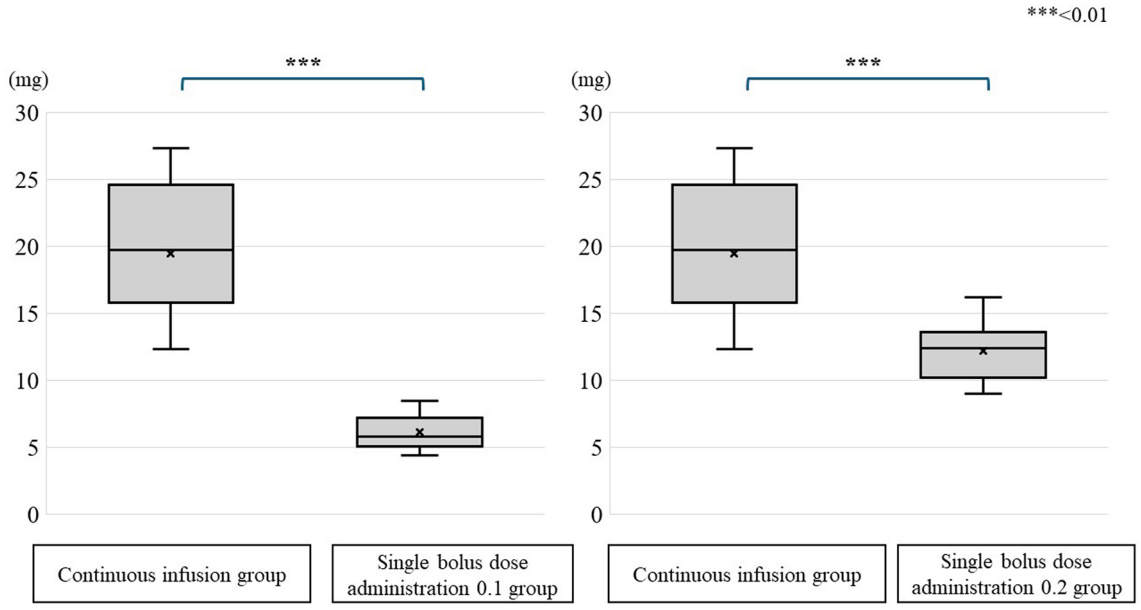

Fig. 4 Amount of remimazolam used until loss of consciousness. The amount of remimazolam used from the start of remimazolam administration to loss of consciousness is shown in the box-and-whisker diagram. The two ends of the whiskers indicate the maximum and minimum values, the boxes indicate the first to third quartiles, the line in the box indicates the median value, and the cross in the box indicate the mean value. The doses of remimazolam used were 19.5 ± 4.78 mg, 6.14 ± 1.20 mg, and 12.2 ± 1.20 mg in the continuous infusion group, single bolus dose administration of 0.1 group, and single bolus dose administration of 0.2 group, respectively. Significant differences were found between the continuous infusion group and the single bolus dose administration of 0.1 group, and between the continuous infusion group and the single bolus dose administration of 0.2 group. The difference between the continuous infusion and single bolus dose administration of 0.1 group was significant ($p < 0.01$)

Table 2 Ratio of changes in blood pressure and heart rate

The ratio of change in blood pressure				
			p value	
Continuous infusion group (n = 22)	Single bolus dose administration 0.1 group (n = 21)	Single bolus dose administration 0.2 group (n = 23)	C vs 0.1	C vs 0.2
0.723 ± 0.129	0.773 ± 0.138	0.767 ± 0.087	0.232	0.182
The ratio of change in heart rate				
			p value	
Continuous infusion group (n = 22)	Single bolus dose administration 0.1 group (n = 21)	Single bolus dose administration 0.2 group (n = 23)	C vs 0.1	C vs 0.2
1.069 ± 0.141	1.042 ± 0.161	1.087 ± 0.214	0.572	0.731

The ratio of change was determined before tracheal intubation to the initiation of remimazolam administration

Evaluation of sedation by entropy (SE)

The proportion of patients whose SE was ≤ 60 at the time of loss of consciousness was 12 out of 22 in the continuous infusion group, 13 out of 21 in the single bolus dose administration 0.1 group, and 7 out of 23 in the single bolus dose administration 0.2 group ($p = 0.09$). These results indicate that approximately half of the patients did not have an SE below 60 at the time of loss of consciousness.

Discussion

This study compared continuous infusion with single bolus dose administration remimazolam for general anesthesia induction in patients aged 18–69 years who underwent ASA-PS class 1 or 2 non-cardiac surgery. The results showed that a single bolus dose administration resulted in a faster time to loss of consciousness and required a lower amount of remimazolam compared with continuous infusion. Additionally, the single bolus dose administration was found to be a safer method for

Table 3 Incidence of adverse events

	Continuous infusion group (n = 22)	Single bolus dose administration 0.1 group (n = 21)	Single bolus dose administration 0.2 group (n = 23)	p value	
				C vs 0.1	C vs 0.2
Hypoxemia (SpO_2 < 90)	0	0	0	NA	NA
Mask ventilation difficulty	0	0	0	NA	NA
Bradycardia (< 50 bpm)	0	1	0	1	NA
Hypotension (sBP < 80 mmHg)	1	1	0	1	0.489
ECG change	0	0	0	NA	NA
Over sedation (SE < 20)	0	0	0	NA	NA
Inadequate sedation (SE > 80)	0	1	0	1	NA

SpO_2: Saturation of percutaneous oxygen

sBP: Systolic blood pressure

SE: State entropy

anesthesia induction, with no significant increase in the incidence of adverse events during anesthesia induction compared with continuous infusion.

Doi et al. [9] conducted a IIb/III clinical trial in Japan, comparing a continuous infusion of 6 or 12 mg/kg/h of remimazolam with a single bolus dose administration of propofol (2.0–2.5 mg/kg) for general anesthesia induction. In their study, the time to loss of consciousness was 88.7 ± 22.7 s for remimazolam at 12 mg/kg/h. Shi et al. [17] conducted a clinical trial in Japan, comparing a single dose of remimazolam (0.2 mg/kg) with a single dose of propofol (2 mg/kg) for general anesthesia induction in patients with cirrhosis undergoing endoscopic variceal ligation. The study reported a time to loss of consciousness of 65.9 ± 4.7 s for remimazolam at 0.2 mg/kg. Lee et al. [15] compared a continuous infusion of 6 mg/kg/h of remimazolam with a single bolus dose administration of 0.1 or 0.2 mg/kg of remimazolam for general anesthesia induction in patients undergoing elective cardiac surgery. In this study, the time to loss of consciousness was 137 ± 20 s for a continuous infusion of 6 mg/kg/h, 71 ± 35 s for a single bolus dose administration of 0.1 mg/kg, and 48 ± 9 s for a single bolus dose administration of 0.2 mg/kg. In our study, the times to loss of consciousness were 88.2 ± 16.2 s, 59.5 ± 31.5 s, and 42.6 ± 11.4 s in the continuous infusion group, single bolus of 0.1 mg/kg group, and single bolus of 0.2 mg/kg group, respectively. Overall, the time to loss of consciousness tended to be shorter compared to the results of Lee et al. This difference may be attributed to variations in the study populations, as the patients in Lee et al.'s study had cardiac disease, which could have led to a delayed drug onset due to impaired circulatory function and slower drug delivery to the effect site.

Ko et al. [18] conducted a meta-analysis of studies comparing remimazolam and propofol. This meta-analysis showed that remimazolam was associated with a significantly lower risk of hypotension during anesthesia induction compared with propofol. In many studies focusing on general anesthesia with remimazolam, propofol has been used as the comparison target. Therefore, reports comparing continuous infusion and bolus administration of remimazolam are limited. Lee et al. [15] compared a continuous infusion of 6 mg/kg/h of remimazolam with a single bolus dose administration of 0.1 or 0.2 mg/kg of remimazolam for general anesthesia induction in patients undergoing elective cardiac surgery. None of the study patients developed hypotension requiring treatment. In our study, BP decreased before and after remimazolam administration; however, the decrease was mild in both groups. Only one patient in the continuous infusion and another in the single bolus dose administration of 0.1 group required circulatory agonists. Upton et al. [19] showed that remimazolam can induce tachycardia in sheep, suggesting that it may be a compensatory response to a decrease in BP. However, in our study, no significant increase was observed in heart rate before and after remimazolam administration.

A single bolus dose administration of remimazolam was found to result in a shorter time to loss of consciousness and a lower risk of hypotension. Remimazolam, a benzodiazepine, is antagonized by flumazenil. Clinical studies have also shown that it does not cause vascular pain during injection [8, 9]. These characteristics make it particularly advantageous for patients undergoing rapid sequence induction. However, with a single bolus dose administration, accurately predicting the effect-site concentration at the time of loss of consciousness is challenging due to the rapid increase in the blood and effect-site concentrations. By contrast, continuous infusions have a slower increase in blood and effect-site concentrations, allowing for easier prediction of the effect-site concentration at the time of loss of consciousness. Knowing the effect-site concentration at the time of loss of consciousness is useful for determining the rate of administration for subsequent maintenance of anesthesia. EEG monitoring should be used to assess sedation during maintenance of anesthesia. However, caution is

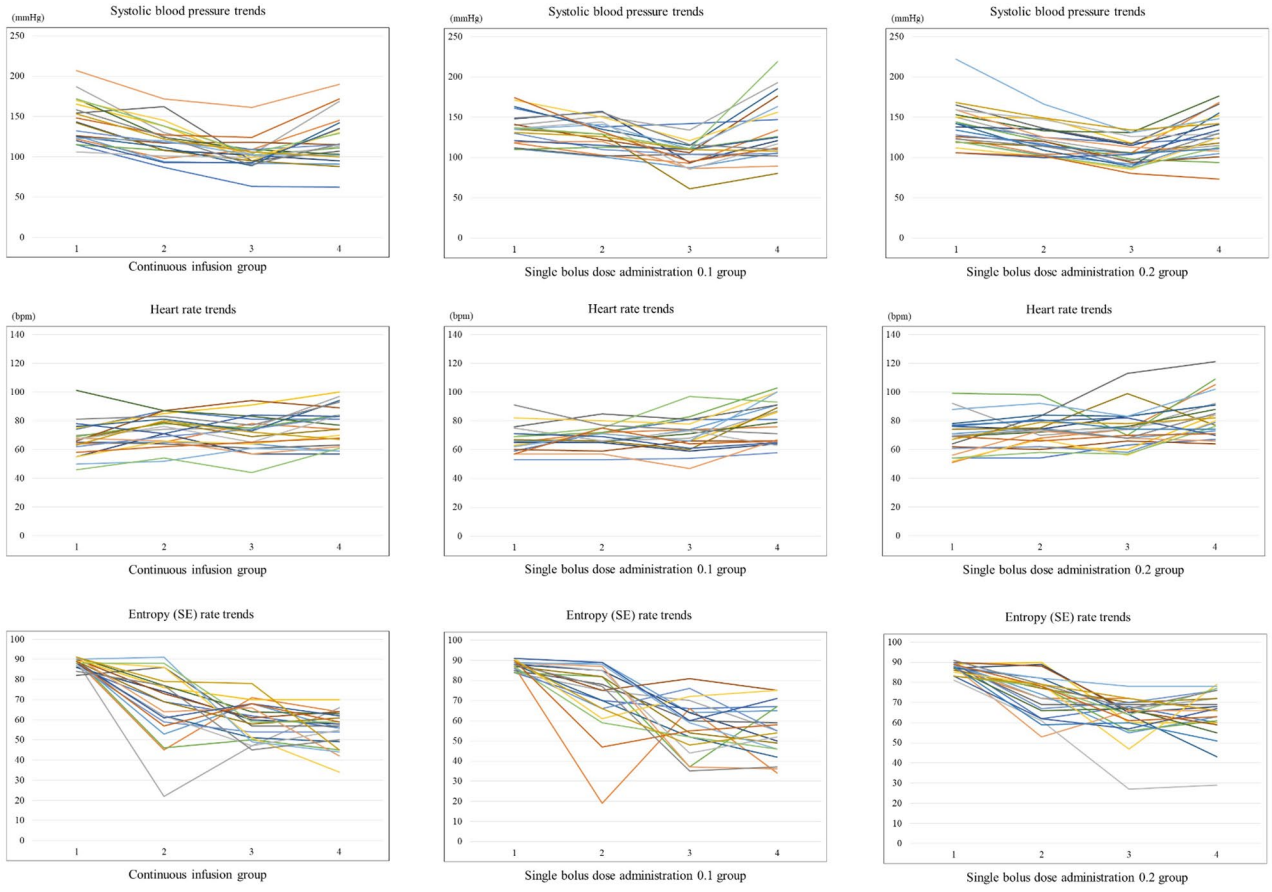

Fig. 5 Systolic blood pressure trends, heart rate trends, and entropy trends in each group. The horizontal axis corresponds to the following events: (1) start of remimazolam administration, (2) loss of consciousness, (3) before intubation, and (4) after intubation

required when interpreting EEG monitoring data when using drugs that are not included in the EEG monitoring database. As a sedation index, midazolam is less accurate for assessing the BIS compared with propofol [20]. The same may be true for remimazolam, a benzodiazepine similar to midazolam. In our study, some patients had high entropy values even after achieving loss of consciousness (See Results and Fig. 5). Approximately half of the patients did not have a state entropy (SE) value below 60 at the time of loss of consciousness. Furthermore, in the bolus administration group, a higher proportion of patients who received 0.2 mg/kg of remimazolam had SE values above 60, despite receiving a larger dose of the drug. This suggests that entropy may not be suitable for assessing sedation with remimazolam. Both single bolus dose administration and continuous infusions have their respective advantages and disadvantages. As the usefulness and safety of single bolus dose administrations are demonstrated, anesthesiologists should select the method of anesthesia induction for each patient based on an understanding of the advantages and disadvantages of both single bolus dose administrations and continuous infusions. We believe that this study provides valuable insights to guide such decisions.

This study has some limitations. First, it was not double-blinded. The study physicians who administered the anesthetic were aware of the group to which the patients were assigned. Owing to the difference between a single bolus dose administration method and a continuous infusion method, blinding was not feasible. We established a protocol for the timing of assessments after drug administration to minimize this bias. Second, the time to loss of consciousness was assessed every 10 s. This may have led to an overestimation of the time to loss of consciousness. For example, in this study, a patient who lost consciousness within 51 s would have been recorded as losing consciousness at 60 s. Third, the sample size for this study was calculated for comparing continuous infusion with a single bolus dose administration, limiting the ability to perform a meaningful comparison between single doses of 0.1 mg/kg and 0.2 mg/kg. Furthermore, we evaluated safety; however, some events have a low incidence rate and may not be adequately detected with the sample size of this study. To compare safety, including rare complications, a larger sample size is required for analysis. Fourth,

the study excluded patients aged ≥ 80 years or critically ill patients with an ASA-PS class of 3 or higher. Therefore, the results of this study may not be generalizable to all patients undergoing surgery under general anesthesia.

In conclusion, a single bolus dose administration of remimazolam is a safe method for anesthesia induction in patients aged 18–69 years undergoing ASA-PS class 1 or 2 non-cardiac surgery. It provides a faster time to loss of consciousness and a similar incidence of adverse events, such as hypotension.

Abbreviations

ASA-PS	American Society of Anesthesiologists Physical Status
BMI	Body mass index
BP	Blood pressure
CSHT	Context-sensitive half-time
ECG	Electrocardiogram
FAS	Full analysis set
jRCT	Japan Registry of Clinical Trials
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NIBP	Non-invasive blood pressure
SBP	Systolic blood pressure
SpO_2	Peripheral oxygen saturation

Supplementary Information

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Supplementary Material 1

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Author contributions

Material preparation, data collection and analysis were performed by TI, HM and RN. HM and TI contributed equally as co-first authors. The first draft of the manuscript was written by TI and HM. AS, KK, SO, TK, SN and YMT were collected the data. All authors contributed to the study conception and design. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hiroshima University Hospital (CRB-2023-0001) on July 31, 2023, as a specified clinical trial. It was conducted at Hiroshima University Hospital following registration in the Japan Registry of Clinical Trials (jRCTs061230049, the study period is from February 7, 2024, when the first participant was recruited, to August 16, 2024, when the observation period for the last participant concluded). Written informed consent was obtained from the patient by the study physician at least 1 day prior to surgery.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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