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Comparison of hemodynamics during induction of general anesthesia with remimazolam and target-controlled propofol in middle-aged and elderly patients: a single-center, randomized, controlled trial

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Abstract

Background Remimazolam confers a lower risk of hypotension than propofol. However, no studies have compared the efficacy of remimazolam and propofol administered using target-controlled infusion (TCI). This study aimed to investigate hemodynamic effects of remimazolam and target-controlled propofol in middle-aged and elderly patients during the induction of anesthesia.

Methods Forty adults aged 45–80 years with the American Society of Anesthesiologists Physical Status 1–2 were randomly assigned to remimazolam or propofol group ($n=20$ each). Patients received either remimazolam (12 mg/kg/h) or propofol (3 μg/mL, TCI), along with remifentanil for inducing anesthesia. We recorded the blood pressure, heart rate (HR), and estimated continuous cardiac output (esCCO) using the pulse wave transit time. The primary outcome was the maximum change in mean arterial pressure (MAP) after induction. Secondary outcomes included changes in HR, cardiac output (CO), and stroke volume (SV).

Results MAP decreased after induction of anesthesia in both groups, without significant differences between the groups (−41.1 [16.4] mmHg and −42.8 [10.8] mmHg in remimazolam and propofol groups, respectively; mean difference: 1.7 [95% confidence interval: −8.2 to 4.9]; $p=0.613$). Furthermore, HR, CO, and SV decreased after induction in both groups, without significant differences between the groups. Remimazolam group had significantly shorter time until loss of consciousness than propofol group (1.7 [0.7] min and 3.5 [1.7] min, respectively; $p<0.001$). However, MAP, HR, CO, and SV were not significantly different between the groups despite adjusting time until loss of consciousness as a covariate. Seven (35%) and 11 (55%) patients in the remimazolam and propofol groups, respectively, experienced hypotension (MAP < 65 mmHg over 2.5 min), without significant differences between the groups ($p=0.341$).

Conclusions Hemodynamics were not significantly different between remimazolam and target-controlled propofol groups during induction of anesthesia. Thus, not only the choice but also the dose and usage of anesthetics are important for hemodynamic stability while inducing anesthesia. Clinicians should monitor hypotension while inducing anesthesia with remimazolam as well as propofol.

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Trial registration UMIN-CTR (UMIN000045612).

Keywords Hemodynamics, Hypotension, Remimazolam, Propofol, Target-controlled infusion

Background

Hypotension during general anesthesia is associated with adverse outcomes [1, 2]. Previous studies have suggested that intraoperative hypotension is associated with cardiovascular events and acute kidney injury in patients undergoing non-cardiac surgery [3–5]. Propofol contributes to hypotension during induction of anesthesia, and the risk increases with age [6–9]. Given the risk of perioperative complications in elderly patients [10–12], preventive measures are required against hypotension during general anesthesia.

Remimazolam, an ultra-short-acting benzodiazepine intravenous anesthetic, has an imidazobenzodiazepine skeleton with side chains containing ester bonds in the diazepine ring [13]. Remimazolam potentially has a favorable profile for circulation with a lower risk of hypotension during induction and maintenance of anesthesia than propofol [14–16]. However, previous studies reporting the superiority of remimazolam used bolus doses of 1.5–2.5 mg/kg propofol during induction [14–16], and no study has compared efficacy of remimazolam and propofol administered using target-controlled infusion (TCI). TCI requires a lower dose of propofol to achieve loss of consciousness during induction of anesthesia than manual infusion [17–19]. To verify the superiority of remimazolam over propofol, multiple methods used in clinical practice should be employed. Therefore, this study aimed to compare hemodynamics during induction of anesthesia using remimazolam and target-controlled propofol in middle-aged and elderly patients.

Methods

This study was reviewed and approved by the Ethics Committee of the Tokushima University Hospital (approval no. 4101). The protocol was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR, UMIN000045612). Prior written informed consents were obtained from all participants. The study complies with the CONSORT statement.

We included 40 patients aged 45–80 years with the American Society of Anesthesiologists Physical Status 1–2 and who underwent surgery under general anesthesia at the Tokushima University Hospital. We excluded patients with the following characteristics: emergency cases, cardiovascular disease, pregnant woman, severe liver dysfunction, dialysis, neurological disorder, intestinal obstruction, drug hypersensitivity, severe lipid metabolism disorder, body mass index ≥ 30 kg/m^2, or a predicted difficult airway. We also excluded patients who underwent surgeries in the lateral or prone position.

Patients were randomly assigned to the remimazolam or propofol group ($n=20$ each) by the sealed envelope system. Patients, but not anesthesiologists, were blinded to the group allocation. If the patient was taking antihypertensive drugs regularly, angiotensin receptor blockers (ARBs) were discontinued on the day of surgery, whereas Ca channel blockers were continued. Patients received Ringer solution acetate at 500 mL/h rate through a peripheral venous tract larger than 22G. Remimazolam 12 mg/kg/h or propofol 3 μg/mL (effect site concentration) using TCI system (TERFUSION Syringe Pump Type SS3 TCI, TERUMO Corporation, Tokyo, Japan) was administered along with remifentanil 0.3 μg/kg/min for induction of anesthesia. The TCI pump incorporated the Marsh model [20]. The loss of consciousness was confirmed when the patients failed to respond. Remimazolam was adjusted to 1–2 mg/kg/h and propofol to 2–5 μg/mL by adjusting the bispectral index (BIS) values between 40 and 60 after loss of consciousness. Rocuronium 0.6 mg/kg was administered after loss of consciousness, and endotracheal intubation was performed. After intubation, remifentanil was adjusted to 0.1–0.3 μg/kg/min, and mechanical ventilation was maintained by adjusting the end-tidal CO_2 between 35 and 45 mmHg. The noninvasive blood pressure was measured using an upper arm cuff every 2.5 min. Cardiac output (CO) and stroke volume (SV) were estimated using pulse wave transit time (estimated continuous cardiac output [esCCO], Nihon Koden, Tokyo, Japan). Hypotension (mean arterial pressure [MAP] < 65 mmHg over 2.5 min) was treated using 4–8 mg ephedrine.

The primary outcome measure was the maximum change in MAP after induction of anesthesia. Secondary outcome measures were the maximum change in heart rate (HR), CO, and SV. These hemodynamic changes were also examined after adjusting the time until loss of consciousness. Frequency of hypotension (MAP < 65 mmHg over 2.5 min) was also compared. The observation period was from induction of anesthesia to 10 min after endotracheal intubation. Figure 1 shows the research protocol.

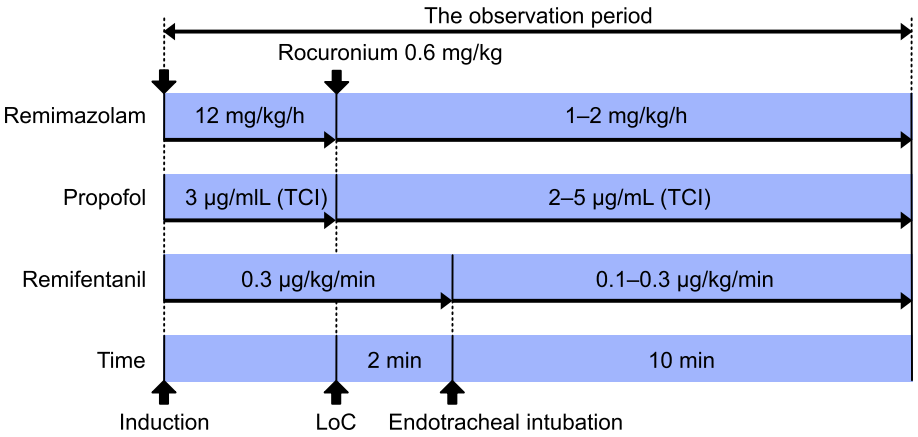

Fig. 1 The research protocol. TCI, target-controlled infusion; LoC, loss of consciousness

Statistical analysis

The study was designed as a superiority trial, and the sample size was determined as follows: The effect size was set to 1.0 with reference to previous studies that examined the difference in MAP reduction between remimazolam and propofol [15, 16]. After adjusting the α error to 0.05 and power to 0.8, the sample size was calculated to be 34. Therefore, considering a 10% loss of patients, we selected a sample size of 40 patients ($n=20$ per group).

Data are presented as mean (standard deviation or 95% confidence interval [CI]). Numerical variables between the groups were compared using the Welch's *t*-test. Analysis of covariance (ANCOVA) was performed to control the effects of covariates. Ratios were compared using the chi-square test or Fisher's exact test for ≤ 5 cells. All p values were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R version 4.0.1 (The R Foundation for Statistical Computing, Vienna, Austria), that provides statistical functions frequently used in biostatistics [21].

Results

This study was conducted at Tokushima University Hospital from November 2021 to February 2022. We initially included 69 patients, but 29 patients who met the exclusion criteria or declined to participate were excluded. Finally, 40 patients were enrolled to the study and randomly assigned to either the remimazolam or propofol group. All patients completed the protocol and were included in the primary endpoint analysis. Two patients in the propofol group were excluded from CO and SV analyses due to lack of esCCO data (Fig. 2).

The characteristics of patients in the groups are listed in Table 1. Eleven (55%) and 6 (30%) patients in the remimazolam and propofol groups, respectively, had antihypertensive drugs, without significant differences between the groups ($p=0.201$). All patients in the two groups achieved loss of consciousness with the dose of anesthetics specified in the protocol. The mean doses of remimazolam and propofol until loss of consciousness were 0.34 (0.14) mg/kg and 1.21 (0.29) mg/kg, respectively.

MAP decreased after induction in both groups, without significant differences between the groups (−41.1 [16.4] mmHg and −42.8 [10.8] mmHg in remimazolam and propofol group, respectively; mean difference: 1.7 mmHg [95% CI: −8.2 to 4.9]; $p=0.613$). Further, HR, CO, and SV decreased after induction of anesthesia in both groups, without significant differences between the groups (HR: -9.6 [6.6] bpm and −13.8 [9.9] bpm, $p=0.129$; CO: −18.4 [10.8]% and −24.6 [12.2]%, $p=0.101$; SV: −12.7 [8.4]% and −10.1 [5.7]%, $p=0.262$; in the remimazolam and propofol groups, respectively) (Table 2).

Theremimazolam group had a significantly shorter time until loss of consciousnessthan the propofol group (1.7 [0.7] min and 3.5 [1.7] min, respectively; meandifference: 1.8 min [95% CI: 0.8 to 2.6] $p < 0.001$). The time until loss ofconsciousness had no significant effect on MAP and SV decline (MAP: F[1, 37] =0.311, $p = 0.580$; SV: F[1, 36] = 2.49, $p = 0.123$), without significantdifferences between the groups despite adjusting the time until loss ofconsciousness (MAP: F[1, 37] = 0.535, p = 0.469; SV: F[1, 36] = 3.43, p =0.072). The time until loss of consciousness significantly affected HR and COdecline after induction of anesthesia (HR: F[1, 37] = 5.00, $p = 0.031$; CO: F[1,36] = 9.17, $p = 0.005$), and the degree of decline increased proportional totime until loss of consciousness. However, changes in HR and CO were notsignificantly different between the groups despite adjusting time until

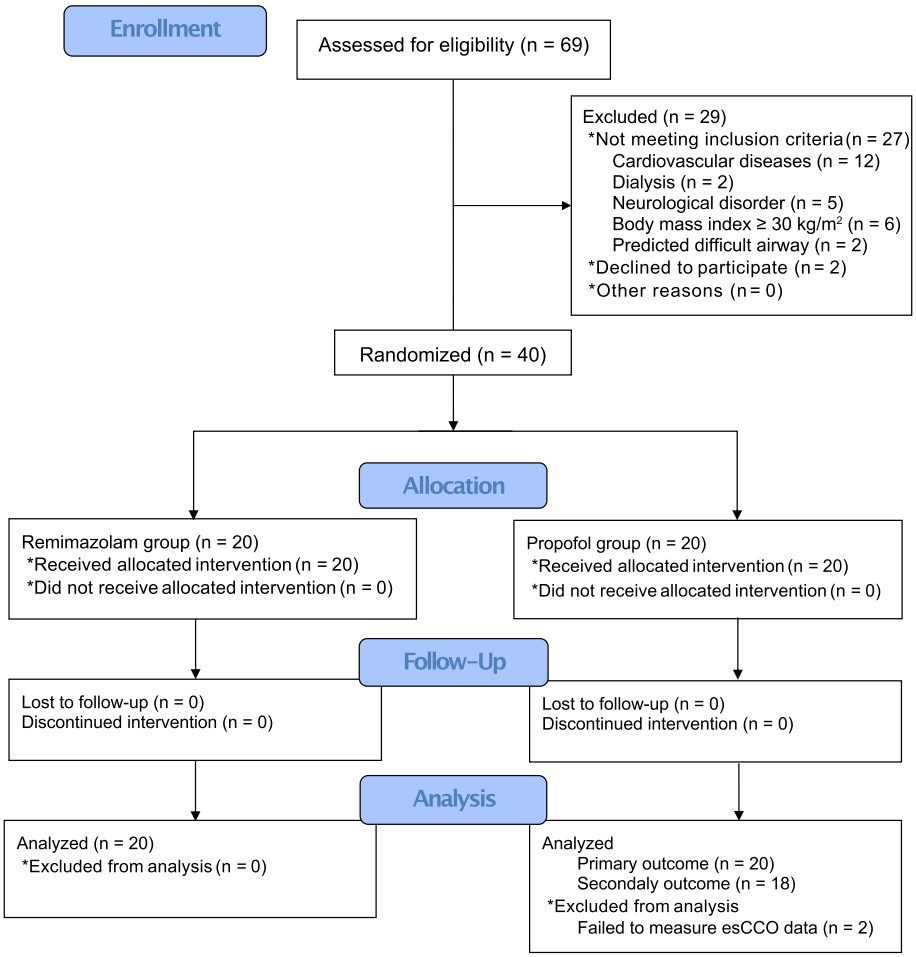

Fig. 2 Consort flow diagram. esCCO, estimated continuous cardiac output

Table 1 Demographic and clinical characteristics of patients

Characteristics	Remimazolam ($n=20$)	Propofol ($n=20$)
Age, years	67 (10)	62 (10)
Sex, male/female	6/14	4/16
ASA-PS, 1/2	5/15	4/16
Height, cm	157.8 (5.7)	157.5 (6.0)
Body weight, kg	59.2 (8.9)	57.1 (9.4)
BMI	23.7 (2.6)	23.1 (3.7)
Hypertension, +/−	11/9	7/13
Antihypertensive drug, +/−	11/9	6/14
ARBs with short to middle half-life	6	3
ARBs with long half-life	3	0
Ca channel blockers	4	5

Values are mean (standard deviation, SD) or the number of patients

Breakdown of antihypertensive drugs includes duplicates

n number, *ASA-PS* American society of anesthesiologists physical status, *BMI* Body mass index, *ARBs* Angiotensin receptor blockers

loss ofconsciousness (HR: F[1, 37] = 0.011, $p = 0.916$, CO: F[1, 36] = 0.05, $p = 0.824$). According to ANCOVA, the time until loss of consciousness andanesthesia group were not significantly associated for all variables (Table 3, Fig. 3).

Seven (35%) and 11 (55%) patients in the remimazolam and propofol groups, respectively, experienced hypotension (MAP < 65 mmHg over 2.5 min), without significant differences between the groups ($p = 0.341$). No postoperative complications related to hypotension, such as myocardial and kidney injuries, were observed in all patients.

Discussion

The reduction in MAP in the remimazolam and target-controlled propofol groups during induction of anesthesia in middle-aged and elderly patients was not significantly different between the groups, and the mean difference was very small. Moreover, the changes in HR, CO, and SV were not significantly different between the groups. The time until loss of consciousness was

Table 2 Hemodynamic changes after induction

Characteristics	Remimazolam ($n=20$)	Propofol ($n=20$)	Mean difference (95% CI)	*p* value
MAP changes, mmHg	−41.1 (9.6)	−42.8 (10.8)	−1.7 (−8.2 to 4.9)	0.613
HR changes, bpm	−9.6 (6.6)	−13.8 (9.9)	4.2 (−1.3 to 9.6)	0.129
CO changes, %	−18.4 (10.8)	−24.5 (12.2)	6.2 (−1.7 to 13.7)	0.101
SV changes, %	−12.7 (8.4)	−10.1 (5.7)	−2.6 (−7.2 to 2.0)	0.262

Values are the mean (standard deviation, SD)

n number, *CI* Confidence interval, *MAP* Mean arterial pressure, *HR* Heart rate, *bpm* Beats per minute, *CO* Cardiac output, *SV* Stroke volume

Table 3 Effects of anesthetic group allocation and time until loss of consciousness on hemodynamic changes after induction of anesthesia

Characteristics	Estimate	Std. error	95% CI	*p* value
MAP changes, mmHg				
Intercept	−42.3	3.1	−48.7 to −35.9	<0.001
Anesthetic group	−2.8	3.9	−10.9 to 5.1	0.469
Times until LoC	0.7	1.3	−1.8 to 3.3	0.580
HR changes, mmHg				
Intercept	−5.9	2.4	−10.8 to −0.9	0.021
Anesthetic group	−0.3	3.1	−6.5 to 5.9	0.916
Times until LoC	−2.1	1.0	−4.2 to 0.2	0.031
CO changes, %				
Intercept	−11.7	3.2	−18.2 to −5.3	<0.001
Anesthetic group	0.9	4.1	−7.4 to 9.2	0.82
Times until LoC	−3.9	1.3	−6.5 to −1.3	0.005
SV changes, %				
Intercept	−10.4	2.2	−14.8 to −6.0	<0.001
Anesthetic group	5.1	2.8	−0.5 to 10.7	0.072
Times until LoC	−1.4	0.9	−3.2 to 0.4	0.123

Std Standard, *CI* Confidence interval, *LoC* Loss of consciousness, *MAP* Mean arterial pressure, *HR* Heart rate, *CO* Cardiac output, *SV* Stroke volume

significantly shorter in the remimazolam group than in the propofol group. The time until loss of consciousness had no significant effect on the decrease in MAP and SV. A prolonged time until loss of consciousness correlated with greater degree of decline in HR and CO. Despite adjusting the time until loss of consciousness, MAP, HR, CO, and SV were not significantly different between the groups.

Previous studies showed that remimazolam administration for induction or maintenance of anesthesia led to a lesser reduction in blood pressure than propofol [14–16], as opposed to results of the present study. Differences in doses and mode of administration of remimazolam and propofol may influence the results. Doi et al. administered remimazolam (6 or 12 mg/kg/h) or propofol (2.0–2.5 mg/kg, bolus) along with remifentanil for inducing anesthesia [14]. Zhang J et al. administered remimazolam (0.2–0.4 mg/kg, bolus) or propofol (1.5–2.0 mg/kg, bolus), along with sufentanil for inducing anesthesia [15]. Zhang X et al. administered remimazolam (0.2 mg/kg, bolus) or propofol (1.5–2.0 mg/kg, bolus) for inducing anesthesia [16]. In the present study, we administered remimazolam (12 mg/kg/h) or target-controlled propofol (3.0 μg/mL) along with remifentanil for inducing anesthesia. Remimazolam 12 mg/kg/h is equivalent to 0.2 mg/kg/min. As patients required 1.7 (0.7) min to achieve loss of consciousness with remimazolam at 12 mg/kg/h, the dose of remimazolam necessary for loss of consciousness was 0.34 (0.14) mg/kg. Patients required 3.5 (1.7) min to achieve loss of consciousness with propofol at 3.0 μg/mL (TCI), and the dose of propofol until loss of consciousness was 1.21 (0.29) mg/kg; this dose is less than that of previous studies [14–16]. TCI requires a lower dose of propofol to achieve loss of consciousness than manual infusion [17–19]. Remimazolam and propofol decrease blood pressure in a dose-dependent manner [22–25]. The Food and Drug Administration recommends a 1.5 mg/kg maximum dose of propofol for inducing anesthesia in elderly patients [26]. The present study reaffirms that the factors affecting hemodynamics during anesthesia are the dose and usage, as well as the choice of drug.

In the present study, 35% and 55% of patients in the remimazolam and propofol groups, respectively, experienced hypotension (MAP < 65 mmHg over 2.5 min) during induction of anesthesia, although without significant differences between the groups. The number of cases ($n=40$) in the present study may be low to detect a significant difference in the secondary outcome—192 cases (96 per group) are required to compare the differences between 35 and 55% at α error of 0.05 and power of 0.8. However, even with 192 cases, a significant difference may not be achieved for the degree of MAP reduction (the primary outcome of this study) due to the extremely small mean difference. A previous study reported that MAP below an absolute threshold of 65 mmHg is related to both myocardial and kidney injuries [27]. Thus, hypotension should be closely monitored after induction of anesthesia with both remimazolam and propofol.

Eleven (55%) and 6 (30%) patients in the remimazolam and propofol groups, respectively, had medications for hypertension, without significant differences between

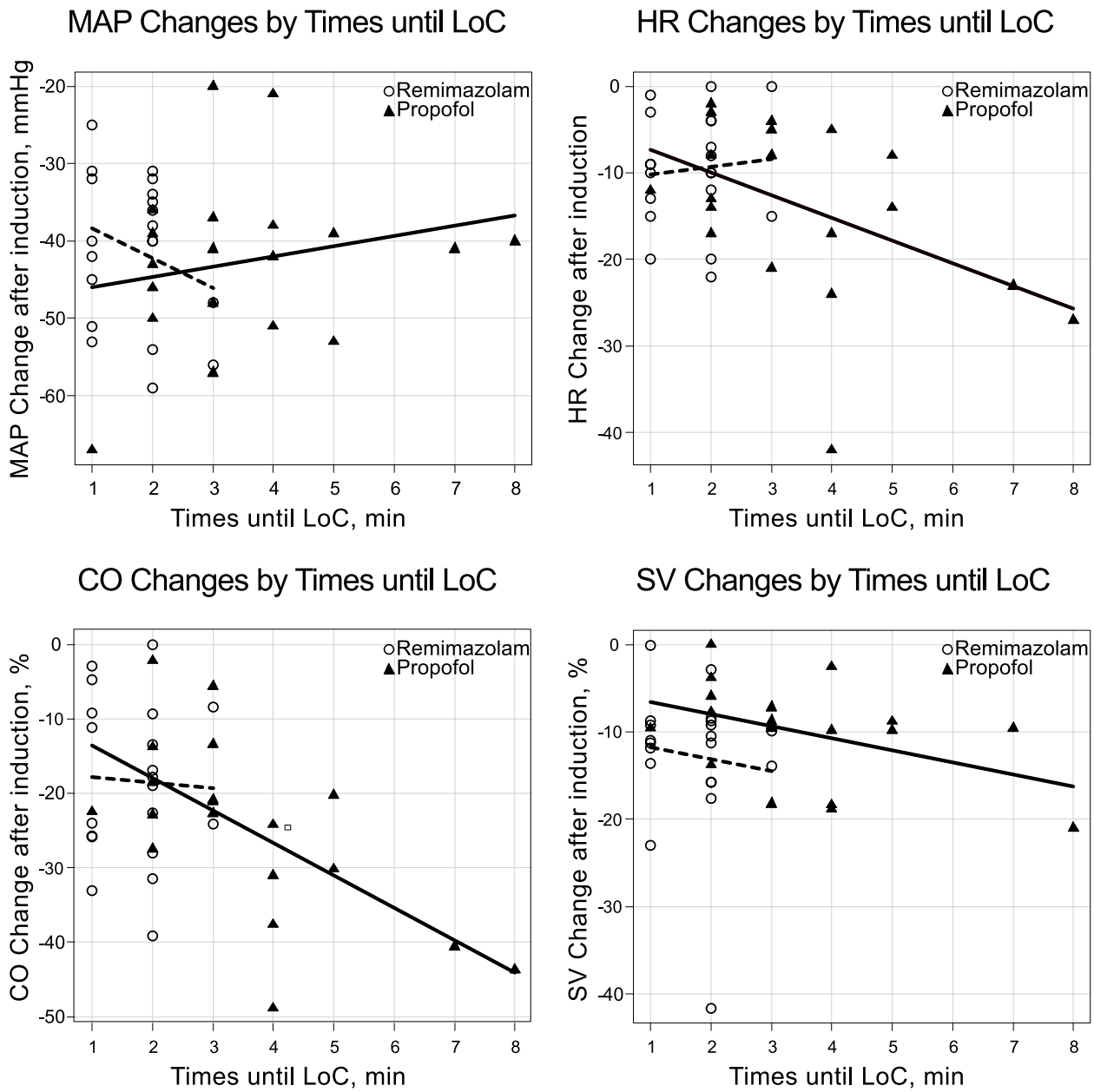

Fig. 3 Hemodynamic changes with time until loss of consciousness. LoC, loss of consciousness; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; SV, stroke volume

the groups. Some antihypertensive drugs are reported to contribute to hypotension during anesthesia [28]. Hojo et al. recently observed that ARBs/angiotensin-converting enzyme inhibitors (ACEIs) with a long half-life and β blockers, but not ARBs/ACEIs with a short–middle half-life and Ca channel blockers, increased the risk of hypotension during anesthesia [29]. Antihypertensive drugs, including ARBs with a long half-life, may have contributed to the hypotension in this study.

We used remimazolam or propofol in combination with remifentanil for induction of anesthesia. Remifentanil may have influenced the results of this study, given its cardiovascular depressant effects [30, 31]. The combination of propofol and remifentanil has been reported to contribute to hypotension during anesthesia [32–34], whereas the data about the interaction of remimazolam and remifentanil is currently lacking.

Future studies are needed to determine the cardiovascular effects of the combination of remimazolam and remifentanil.

This study has some limitations. First, we measured non-invasive blood pressure every 2.5 min. More detailed data may have been obtained if arterial blood pressure was continuously measured, such as by radial artery cannulation. However, invasive methods are deemed inappropriate based on patients' background. Second, for safety reasons, ephedrine was administered to treat persistent hypotension in the patients. The differences between the two groups can be more thoroughly examined if the blood pressure was monitored to its lowest level without treatment, although it is unethical. Third, we used the TCI system for administration of propofol, but not remimazolam. The comparison would have been more appropriate if the same administration method was used; however, administration of remimazolam by the TCI system is not established nor approved in Japan. Remimazolam was continuously administered at 12 mg/kg/h and propofol at 3 μg/mL using the TCI system in this study. Thus, the results may not apply for different doses and drugs. Fourth, the esCCO was used to estimate CO and SV that may differ from the actual values of CO and SV. However, the trending ability of esCCO is clinically acceptable and comparable with the currently available methods using arterial waveform analysis. As esCCO is better at evaluating relative than absolute values, we evaluated CO and SV based on percent changes [35, 36]. Fifth, we set the observation period from induction of anesthesia to 10 min after endotracheal intubation. Previous studies have observed that hypotension is prevalent at 0–10 min after induction of anesthesia or endotracheal intubation [9, 32, 37]. However, a longer observation period may show different results.

Conclusions

In conclusion, no significant differences in hemodynamics were observed after induction of anesthesia with remimazolam or target-controlled propofol. Thus, not only the choice of drug but also its dosage and usage are important for ensuring hemodynamic stability during induction of anesthesia. Clinicians should carefully monitor hypotension while inducing anesthesia with remimazolam or propofol.

Abbreviations

TCI	Target-controlled infusion
ARBs	Angiotensin receptor blockers
BIS	Bispectral index
CO	Cardiac output
SV	Stroke volume
esCCO	Estimated continuous cardiac output
MAP	Mean arterial pressure
HR	Heart rate
ANCOVA	Analysis of covariance
CI	Confidence interval
ACEIs	Angiotensin-converting enzyme inhibitors

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Authors' contributions

RS conceived and designed the study; collected, analyzed, and interpreted data; and prepared the manuscript draft. MK conceived and designed the study; collected, analyzed and interpreted data; and edited the manuscript. RK, NK, and YS collected, analyzed, and interpreted data; and edited the manuscript. KT conceived and designed the study; analyzed and interpreted data; and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the 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 the Tokushima University Hospital (approval no. 4101). Written informed consent was obtained from all participants or their parents/guardians. This study was registered at the UMIN-CTR (Number: UMIN000045612, Date of registration: 10/01/2021). All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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