Original Article

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Effect of remimazolam and propofol anesthesia on autonomic nerve activities during Le Fort I osteotomy under general anesthesia: blinded randomized clinical trial

Yuto Tsuji, Kyotaro Koshika, Tatsuya Ichinohe

Department of Dental Anesthesiology, Tokyo Dental College, Tokyo, Japan

Background: This study evaluated the effect of remimazolam and propofol on changes in autonomic nerve activity caused by surgical stimulation during orthognathic surgery, using power spectrum analysis of blood pressure variability (BPV) and heart rate variability (HRV), and their respective associations with cardiovascular fluctuations.
Methods: A total of 34 patients undergoing Le Fort I osteotomy were randomized to the remimazolam (Group R, 17 cases) or propofol (Group P, 17 cases) groups. Observables included the low-frequency component of BPV (BPV LF; index of vasomotor sympathetic nerve activity), high-frequency component of HRV (HRV HF; index of parasympathetic nerve activity), balance index of the low- and high-frequency components of HRV (HRV LF/HF; index of sympathetic nerve activity), heart rate (HR), and systolic blood pressure (SBP). Four observations were made: (1) baseline, (2) immediately before down-fracture, (3) down-fracture, and (4) 5 min after down-fracture. Data from each observation period were compared using a two-way analysis of variance with a mixed model. A Bonferroni multiple comparison test was performed in the absence of any interaction. One-way analysis of variance followed by Tukey's multiple comparisons test was performed when a significant interaction was observed between time and group, with $P < 0.05$ indicating statistical significance.
Results: Evaluation of autonomic nerve activity in comparison with baseline during down-fracture showed a significant increase in BPV LF ($P < 0.001$), an increasing trend in HRV LF/HF in Group P, and an increasing trend in HRV HF in Group R. There were no significant differences in HR or SBP between the two groups.
Conclusion: During down-fracture of Le Fort I osteotomy, sympathetic nerve activity was predominant with propofol anesthesia, and parasympathetic nerve activity was predominant with remimazolam anesthesia.

Keywords: Autonomic Nervous System; Orthognathic Surgery; Propofol; Remimazolam.

INTRODUCTION

Painful stimulation of the body causes changes in the autonomic nervous system (sympathetic and parasympathetic nerve activity), as well as the immune and endocrine systems. In healthy individuals, these changes rarely cause problems, as they occur within the scope of an individual's functional reserve of vital organs. However, surgery under general anesthesia requires significant surgical stimulation, leading to a greater bodily response to painful stimuli [1,2], causing various systemic abnormalities beyond the functional reserve of vital organs. Therefore, measures are needed to suppress these excessive reactions. Pain induces an excitatory effect on the sympathetic nervous system, resulting in an increased blood pressure and heart

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Corresponding Author: Yuto Tsuji, Department of Dental Anesthesiology, Tokyo Dental College, 2-9-18 Kanda Misaki-cho, Chiyoda-ku, Tokyo 101-0061, Japan
Tel: +81-3-6380-9259 Fax: +81-3-5275-1851 E-mail: yuto_tsuj@yahoo.co.jp

rate [3]. Since the autonomic nervous system controls heart rate and blood pressure [4], the suppression of excessive autonomic nerve activity has gained significance.

Propofol, traditionally used as an intravenous anesthetic, has sympathoinhibitory activity [5,6]. However, sympathetic nerve activity increases during surgical stimulation via skin incision [7]. Remimazolam, a novel intravenous anesthetic, has been shown to reduce overall autonomic nerve activity without disturbing the balance between sympathetic and parasympathetic nerve activity during the induction of general anesthesia [8]; however, its impact on autonomic nerve activity associated with surgical stimulation remains unknown. Therefore, by determining the ability of remimazolam and propofol to suppress excessive autonomic nerve activity caused by surgical stimulation and clarifying the differences in cardiovascular fluctuations associated with their effects, it may be possible to select appropriate anesthetics for individual cases.

The Memcalc system is widely used for analyzing blood pressure variability (BPV) and heart rate variability (HRV) [9,10]. BPV is an indicator of autonomic function and can assess vasomotor sympathetic nerve activity by analyzing blood pressure variability. The low-frequency component (BPV LF; 0.04–0.15 Hz) indicates vasomotor sympathetic nerve activity [11,12]. HRV is used as an indicator of autonomic function and can assess cardiac sympathetic and parasympathetic nerve activity by analyzing the R-R interval variability of electrocardiographs (ECGs). The low-frequency component (HRV LF; 0.04–0.15 Hz) indicates sympathetic and parasympathetic nerve activities, while the high-frequency component (HRV HF; 0.15–0.4 Hz) indicates parasympathetic nerve activity. The HRV LF/HF ratio is used as an indicator of sympathetic nerve activity [9]. The HRV LF/HF increases if sympathetic nerve activity is dominant. Evaluating the relationship between HRV and BPV improves the reliability of autonomic activity assessments [12-14]. Therefore, in this study, we used BPV LF and HRV LF/HF as indices of sympathetic nerve activity, and HRV HF as an index of parasympathetic nerve activity.

In this study, patients were evaluated in two situations during oral surgery under general anesthesia: with and without surgical stimulation. The primary objective of this study was to evaluate the effects of remimazolam and propofol on changes in autonomic nerve activity caused by surgical stimulation during oral surgery and its association with cardiovascular disease. The secondary objective was to compare autonomic nerve activity and the associated heart rate and blood pressure immediately after the induction of general anesthesia using remimazolam and propofol.

METHODS

Participants

This randomized clinical trial was conducted after obtaining approval from the Tokyo Dental College Ethics Review Board (approval number: 1074) and registering in the University Hospital Medical Information Network Clinical Trials Registry (registration number: UMIN000045824). The study was conducted between October 2021 and March 2023. It adhered to the principles of the Declaration of Helsinki and was conducted in accordance with the CONSORT guidelines. The study included patients scheduled to undergo Le Fort I osteotomy under general anesthesia at the Tokyo Dental College Suidobashi Hospital. Patients aged between 18 and 45 years and classified as American Society of Anesthesiologists physical status (ASA-PS) I were included. Written informed consent was obtained from all the patients or their guardians. Patients aged < 20 years were allowed to participate in this study after obtaining written informed consent from their guardians. Patients who required emergency surgery, had contraindications for the medications used in this study, regularly took benzodiazepines or vasoactive drugs, or did not consent to participate in this study were excluded.

Anesthetic procedure

The patients were randomly assigned to either the propofol group (Group P) or remimazolam group (Group R) using a computer-generated random sequence list. One of the researchers performed the enrollment and randomization for assignment to the intervention group. Anesthesia was managed by an anesthesiologist who was not involved in the study. The surgeons, evaluators, and patients were not informed of their interventions. Separate investigators performed randomization and evaluation. None of the patients received premedication before surgery. After arriving in the operating room, the patients were placed in the supine position. Before the induction of general anesthesia, standard patient monitoring equipment was fitted, including a noninvasive automatic blood pressure monitor, pulse oximeter, ECG, capnography, and bispectral index (BIS) monitor. After starting the administration of remifentanil 0.5 μg/kg/min, propofol (target-controlled infusion, 4.0 μg/ml) or remimazolam (12 mg/kg/h) was administered. Following muscle relaxation with a 0.6 mg/kg bolus of rocuronium, the patients were intubated nasally. After intubation, an intraarterial catheter was inserted into the radial artery. Prior to the start of the surgery, 2% lidocaine with 1:80,000 epinephrine was administered around the maxillary bone via infiltration anesthesia. Anesthesia was maintained using air, oxygen, propofol, remimazolam, and remifentanil. The propofol dose rate was adjusted to maintain a BIS value between 40 and 60, whereas the remimazolam dose rate was adjusted to maintain a BIS value of approximately 60. Remifentanil was continuously administered at 0.2 μg/kg/min during surgery and increased or decreased in 0.05 μg/kg/min increments or reductions if the patient showed a 20% or higher increase or decrease in blood pressure compared with the measurements taken 5 min earlier. The patient's mechanical ventilation was set at a tidal volume of 6–10 ml/kg, a respiratory rate of 9–12 breaths/min, and a positive end-expiratory pressure of 5 cmH_2O, adjusted to maintain the end-tidal carbon dioxide pressure ($ETCO_2$) at 35 ± 5 mmHg.

Measurement of data

The ECG waveform and intra-arterial pressure waveform obtained during surgery were imported into an HRV/BPV real-time analysis program (MemCalc/Tonam2C®; GMS, Tokyo, Japan) and analyzed [10]. The following parameters were observed: vasomotor sympathetic nerve activity (BPV LF), parasympathetic nerve activity (HRV HF), sympathetic nerve activity (LF/HF), heart rate (HR), systolic blood pressure (SBP), BIS value, time from local anesthetic injection to down-fracture, local anesthetic volume, total epinephrine dose, and mean remifentanil dose rate. BPV LF, HRV HF, HRV LF/HF, HR, and SBP were measured four times at the following time points: (1) baseline (prior to administration of the local anesthetic), (2) immediately before down-fracture, (3) down-fracture, and (4) 5 min after down-fracture. Down-fracture was defined as the time point at which HR and SBP showed the highest readings. In (1)–(3), the mean measurements obtained over 60 s during the observation period were used, whereas in (4), the mean measurements obtained between 4 min 30 s and 5 min 30 s after the downward fracture were used. The rates of change in each observation item during each observation period relative to baseline measurements were compared between the P and R groups. The rate of change in each observation item during each observation period relative to baseline was calculated by dividing the measurement during each observation period by the measurement at baseline. The BIS value was defined as the mean value from the start of surgery to 5 min after the down-fracture.

Statistical analysis

The sample size was determined by post-hoc power analysis using G*Power (version 3.1.9.2, Heinrich Hein University, Duesseldorf, Germany), and data were collected until the power of the percentage change in BPV LF at down-fracture compared with baseline between the two groups was greater than 0.8.

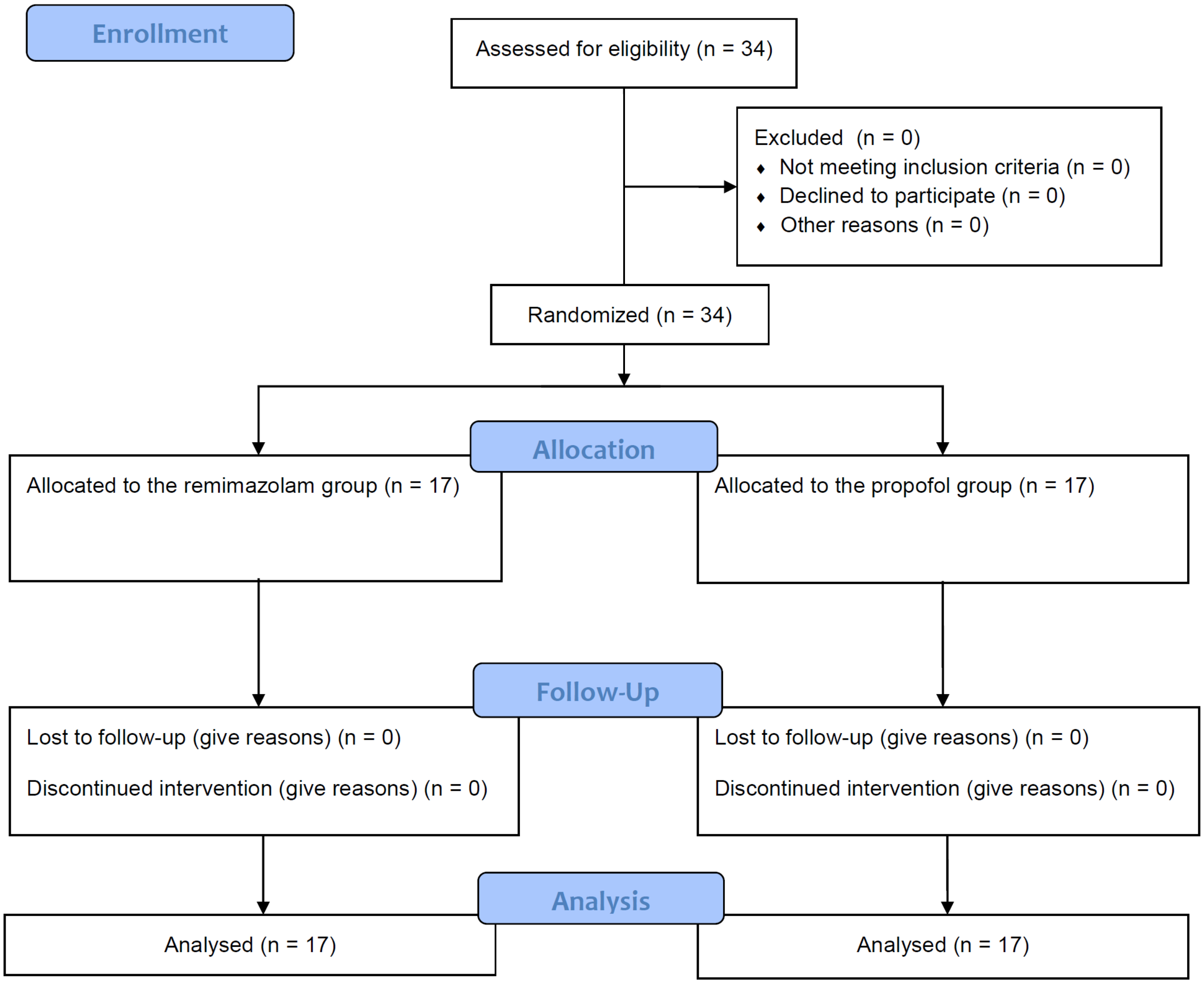

Fig. 1. Consolidated standards of reporting trials (CONSORT) flow diagram. N, number.

Patient demographics and anesthetic factors were compared using the t-test or chi-squared test. Data from each observation period were compared using a two-way analysis of variance with a mixed model. A Bonferroni multiple comparison test was performed in the absence of any interaction. In this study, interactions refer to the differences in autonomic nervous system activity between different anesthetics. One-way analysis of variance followed by Tukey's multiple comparisons test was performed when a significant interaction was observed between time and group with $P < 0.05$ indicating statistical significance. The confidence interval was set at 95%. Data were shown as mean ± standard deviation. SPSS software (version 28; IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

RESULTS

This study included 34 patients who were divided into two groups (Group R, 17 cases; Group P, 17 cases). No patients were excluded from the study (Fig. 1). The primary objective, the percent change in HRV and BPV at down-fracture compared to baseline between the two groups, exceeded power of 0.8 for BPV LF (BPV LF, 0.92; HRV HF, 0.13; HRV LF/HF, 0.44). The secondary

Table 1. Patient demographics and anesthetic factors

	Group R (n = 17)	Group P (n = 17)	P value
Sex (Male/Female)	6/11	9/8	0.477
Age (years)	28.2 ± 6.0	26.7 ± 7.1	0.515
Height (cm)	163.6 ± 7.0	164.7 ± 8.5	0.701
Body weight (kg)	57.6 ± 10.9	57.8 ± 9.7	0.944
BIS	56.8 ± 5.4	48.8 ± 5.0	< 0.001
Time from local anesthesia to down-fracture (min)	31.5 ± 10.0	32.5 ± 10.8	0.781
Local anesthetic volume (ml)	10.2 ± 1.9	9.8 ± 1.2	0.463
Epinephrine total dose (μg)	127.9 ± 23.3	122.8 ± 15.0	0.463
Remifentanil mean dose rate (μg/kg/min)	0.2 ± 0.0	0.2 ± 0.0	0.404

Data are expressed as the mean ± standard deviation or the number of patients.
BIS, bispectral index; Group P, propofol group; Group R, remimazolam group; n, number.

Table 2. Actual measurements of heart rate and blood pressure variability at baseline

	Group R	Group P	P value
BPV LF ($mmHg^2$)	4.6 ± 5.4	1.5 ± 0.9	0.032
HRV HF ($msec^2$)	20.6 ± 17.6	61.2 ± 49.9	0.006
HRV LF/HF ratio	10.1 ± 9.9	2.7 ± 2.0	0.008
Heart rate (bpm)	69.5 ± 9.8	61.3 ± 8.2	0.014
Systolic blood pressure (mmHg)	104.4 ± 11.6	98.7 ± 13.7	0.206

Data are expressed as the mean ± standard deviation.
BPV, blood pressure variability; Group P, propofol group; Group R, remimazolam group; HF, high frequency; HRV, heart rate variability; LF, low frequency; LF/HF, balance index of the low- and high-frequency components.

Table 3. The rates of change in each observation item during each observation period relative to the baseline measurement

	Group	Immediately before the down-fracture	Down-fracture	5 min after the down-fracture	P value		
					Main effect		Interaction
					Time	Group	(Time × Group)
BPV LF (%)	R	173.8 ± 254.0 (4.9 ± 4.9)	343.5 ± 301.1 (9.6 ± 8.2)*	65.0 ± 71.1 (1.7 ± 1.3)	< 0.001	0.004	0.002
	P	338.4 ± 523.6 (3.8 ± 5.8)	870.7 ± 546.4† (10.6 ± 8.2)*	252.1 ± 221.8 (2.9 ± 2.7)			
HRV HF (%)	R	234.9 ± 445.5 (22.6 ± 26.3)	1374.5 ± 2731.0 (110.1±199.9)*	931.1 ± 2290.9 (118.3 ± 352.6)	0.009	0.244	0.598
	P	148.3 ± 162.3 (71.7 ± 93.0)	752.5 ± 1163.2 (516.6 ± 979.0)*	276.1 ± 343.4 (129.8 ± 155.6)			
HRV LF/HF (%)	R	98.6 ± 113.1 (3.7 ± 2.2)	143.3 ± 222.6 (6.8 ± 8.7)*	43.9 ± 51.9 (1.9 ± 1.3)	0.029	0.054	0.052
	P	272.4 ± 435.6 (3.0 ± 3.0)	461.1 ± 668.0 (4.6 ± 4.0)*	379.1 ± 625.4 (3.4 ± 3.8)			
Heart rate variability (%)	R	108.2 ± 11.0 (74.7 ± 9.6)*	112.1 ± 14.1 (77.3 ± 10.5)*	110.0 ± 11.2 (75.7 ± 7.9)*	< 0.001	0.582	0.370
	P	108.2 ± 10.6 (66.1 ± 8.3)*	107.0 ± 11.8 (65.3 ± 9.1)*	108.6 ± 11.8 (66.2 ± 8.5)*			
Systolic blood pressure variability (%)	R	112.2 ± 16.9 (115.5 ± 13.6)*	128.5 ± 20.6 (132.3 ± 12.7)*	118.5 ± 22.2 (121.9 ± 14.6)*	< 0.001	0.623	0.832
	P	106.9 ± 25.2 (104.2 ± 23.1)*	126.8 ± 24.3 (123.5 ± 21.3)*	114.3 ± 21.2 (111.2 ± 18.1)*			

Values immediately before the down-fracture, down-fracture, and 5 min after the down-fracture are expressed as the percentage change ± standard deviation (actual measured value ± standard deviation) of each observed item during each observation period relative to the baseline measured value.
BPV, blood pressure variability; Group P, propofol group; Group R, remimazolam group; HF, high frequency; HRV, heart rate variability; LF, low frequency; LF/HF, balance index of the low- and high-frequency components.
*P < 0.05 versus baseline, †P < 0.05 versus Group R

objective, the power of HRV HF and HRV LF/HF at baseline compared between the two groups, also exceeded 0.8 (BPV LF, 0.65; HRV HF, 0.87; HRV LF/HF, 0.85).

Table 1 lists patient demographics. In our analysis of

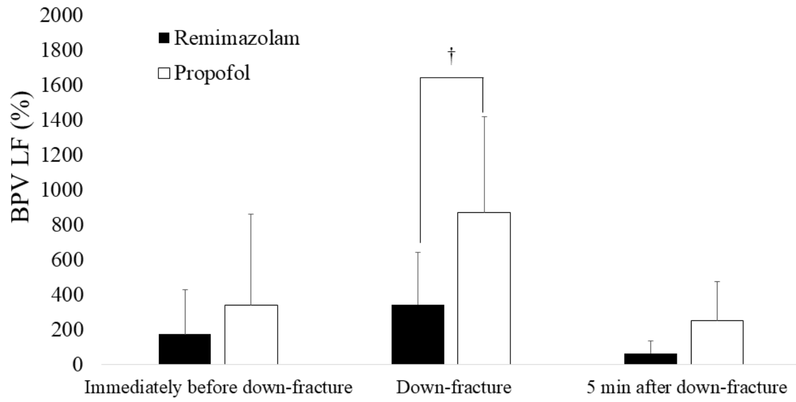

Fig. 2. Rate of change in the low frequency component in the blood pressure variability power spectrum analysis in comparison with baseline. The BPV LF during down-fracture is significantly larger in Group P. (mean ± standard deviation; n = 17 in both the remimazolam and propofol groups)
BPV, blood pressure variability; LF, low frequency.

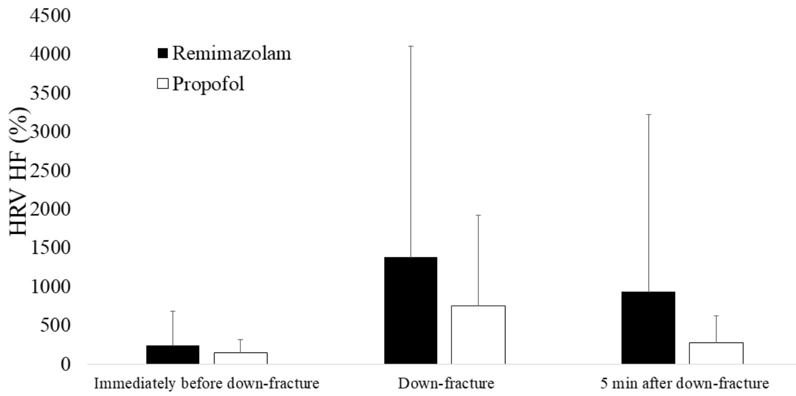

Fig. 3. Rate of change in the high frequency component in the heart rate variability power spectrum analysis in comparison with the baseline. Both groups show a maximal increase during down-fracture. In addition, this value tends to be larger in Group R. The values show no interaction. (mean ± standard deviation; n = 17 in both the remimazolam and propofol groups)
HF, high frequency; HRV, heart rate variability.

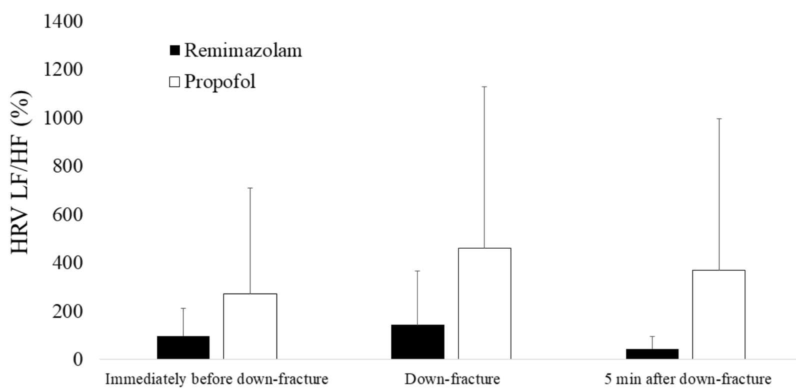

Fig. 4. Rate of change in the balance index of the low and high frequency components of the heart rate variability power spectrum in comparison with the baseline. Both groups show the maximal increase during down-fracture. In addition, this value tends to be larger in Group P. The values show no interaction. (mean ± standard deviation; n = 17 in both the remimazolam and propofol groups)
HRV, heart rate variability; LF/HF, balance index of low- and high-frequency components.

34 patients, no significant differences were observed between the two groups in terms of sex, age, height, body weight, time from local anesthetic injection to down-fracture, local anesthetic volume, epinephrine total

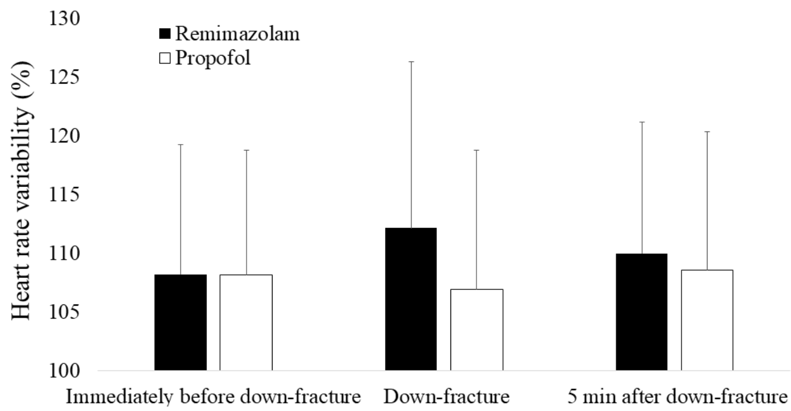

Fig. 5A. Rate of change in heart rate in comparison with the baseline. The two groups show no significant differences. (mean ± standard deviation; n = 17 in both the remimazolam and propofol groups)

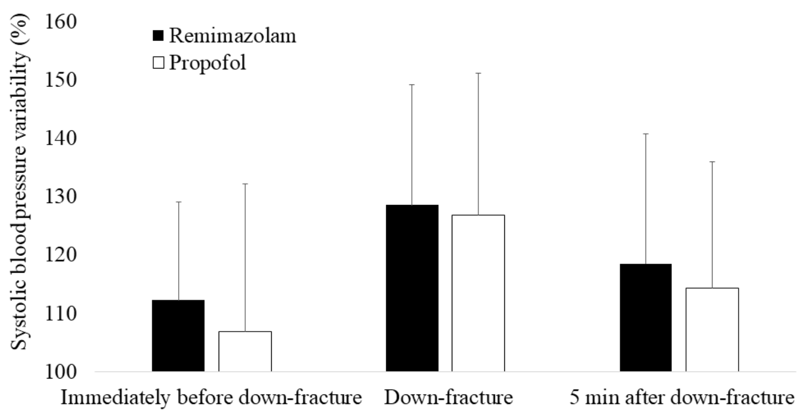

Fig. 5B. Rate of change in systolic blood pressure compared to baseline. The two groups showed no significant differences. (mean ± standard deviation; n = 17 in both the remimazolam and propofol groups).

dose, and remifentanil mean dose rate. BIS was significantly higher in Group R.

Table 2 lists baseline measurements. BPV LF and HRV LF/HF were significantly higher in Group R, while HRV HF was significantly higher in Group P. The HR was significantly higher in Group R. Although the two groups had no significant difference in SBP, the SBP tended to be higher in Group R (Group R: 104.4 ± 11.6 mmHg, Group P: 98.7 ± 13.7 mmHg; P = 0.206).

Table 3 lists the rates of change for each observation item during each observation period relative to the baseline measurements. The rate of change in vasomotor sympathetic nerve activity (BPV LF) was highest in both groups during down-fracture and tended to be higher in Group P. This showed an interaction and a significant difference during down-fracture (P = 0.002, Fig. 2). The rate of change in HRV HF (parasympathetic nerve activity) was highest in both groups during down-fracture and tended to be higher in Group R, while no interaction was observed (Fig. 3). The rate of change in HRV LF/HF (sympathetic nerve activity) was highest in both groups during down-fracture and tended to be higher in Group P, while no interaction was observed (Fig. 4). HR and SBP increased during each observation period, with no significant interaction observed (Fig. 5A, 5B).

DISCUSSION

We used BPV and HRV to evaluate the influence of remimazolam and propofol on autonomic nerve activity during surgical stimulation and to compare the link between these variables and cardiovascular fluctuations. Evaluation of autonomic nerve activity compared to baseline at down-fracture showed a significantly increased BPV LF (vasomotor sympathetic nerve activity) in Group P. Moreover, HRV HF (parasympathetic nerve activity) in Group R and HRV LF/HF (sympathetic nerve activity) in Group P tended to increase. However, the rates of change in HR and SBP showed no significant differences between the two groups, indicating almost no difference in the cardiovascular fluctuations of remimazolam and propofol due to surgical stimulation during oral surgery.

In Group P, sympathetic nerve activity tended to increase during down-fracture, whereas a significant difference in the BPV LF of Group R was observed, with no significant difference in HRV LF/HF between the two groups. Cardiac sympathetic nerve activity is caused by signals from vasomotor sympathetic nerve activity passing through the central nervous system to the heart [12,13]. Therefore, it is pssible that propofol directly inhibited the activation of cardiac autonomic nerve activity due to surgical stimulation or inhibited the transmission of signals from vasomotor sympathetic nerve activity to the heart, preventing a significant increase in the LF/HF ratio of HRV. Propofol may also have significantly increased BPV LF because it cannot inhibit vasomotor sympathetic nerve activity. Normally, HR and blood pressure increase when sympathetic nerves are excited. However, in this study, while vasomotor sympathetic nerve activity increased significantly in Group P, HR and SBP did not. This suggests that cardiac sympathetic nerve activity may be primarily responsible for the increases in HR and blood pressure. Thus, although propofol cannot suppress vasomotor sympathetic nerve activity caused by surgical stimulation during oral surgery, it may suppress excessive increases in HR and blood pressure by directly suppressing cardiac sympathetic nerve activity.

In Group R, parasympathetic nerve activity tended to increase during down-fracture. Midazolam, which belongs to the same benzodiazepine family as remimazolam, has been shown to effectively suppress sympathetic nerve activity during psychological stress [15]. In the autonomic nervous system, activation of either sympathetic or parasympathetic nerves inhibits the activity of the other [11,16]. Therefore, since remimazolam, similar to midazolam, inhibits sympathetic nerve activity during stress caused by stimuli, it is possible that parasympathetic nerve activity tends to become activated.

These results suggest that blood pressure and heart rate may not change during propofol anesthesia, despite sympathetic activation, when patients are subjected to stress, such as surgical stimulation. Conversely, when patients were subjected to invasive stimuli during remimazolam anesthesia, a trend toward parasympathetic activation was observed. Invasive stimuli can affect not only the circulatory system but also the metabolic, endocrine, and immune systems, leading to perioperative complications. Therefore, remimazolam may be safer than propofol during surgical stimulation.

In this study, the baseline measurements taken after general anesthesia induction showed that sympathetic nerve activity was significantly higher in Group R, while parasympathetic nerve activity was significantly higher in Group P. We believe this is the reason for the higher HR and tendency of SBP to remain higher in Group R than in Group P. Remimazolam has been reported to show lower incidence rates of hypotension during general anesthesia induction than propofol [17]. Thus, remimazolam may better maintain sympathetic nerve activity compared to propofol. Conversely, propofol allows parasympathetic nerve activity to be relatively dominant because it strongly suppresses sympathetic nerve activity [5]. In this study, propofol suppressed sympathetic nerve activity, which might have resulted in the lower HR and SBP in the Group P than in the Group R. Therefore, remimazolam is more suitable than propofol for suppressing the reduction in HR and blood pressure during the induction of general anesthesia.

HRV HF is derived from lung expansion and increased venous return to the heart with respiration and is affected by the respiratory rate and minute ventilation. However, because the ventilation settings were defined in this study, we believe that these settings caused no significant difference in the impact on HRV HF between the two groups.

Both remifentanil and 2% lidocaine with 1:80,000 epinephrine used in this study affected autonomic nerve activity. Lidocaine and remifentanil suppress sympathetic nerve activity, whereas epinephrine increases sympathetic nerve activity. However, as there was no significant difference in the doses of these drugs between the two groups in this study, we believe that there was no difference in the effects of these drugs on autonomic nerve activity.

The BIS value during general anesthesia was significantly higher in Group R (Group R: 56.8 ± 5.4, Group P: 48.8 ± 5.0; P < 0.001). The optimal BIS value during propofol anesthesia is considered to be 40–60. However, the optimal BIS value for remimazolam anesthesia was not known at the beginning of this study. In previous studies, the BIS value with remimazolam was higher than that with propofol, exceeding 60 [18,19]. Additionally, administration of remimazolam increases β waves, which may increase BIS value [20], potentially explaining why BIS value was significantly higher in Group R. However, in a study that simultaneously measured BIS value and Spectral Edge Frequency (SEF) of SedLine® during general anesthesia with remimazolam, some patients had mean BIS value > 60, while all patients, including those with BIS value > 60, were adequately sedated based on SEF [21]. In this previous study, the BIS values for remimazolam and propofol anesthesia ranged from 40.0 to 82.0 and 39.0 to 56.3, respectively, with similar anesthetic depths. The BIS values in the present study were similar to those in previous studies; therefore, the depth of anesthesia in both groups was considered adequate.

This study had several limitations. First, the study was terminated when the power of the percentage change in BPV LF at down-fracture compared with the baseline between the two groups exceeded 0.8. However, due to the small number of cases, some study items were underpowered. Therefore, further studies are required to examine these items. Second, the study participants were young healthy patients (ASA-PS 1). Therefore, it is unclear whether similar results can be obtained in patients with generalized health issues, older adults, or those taking benzodiazepines, among other conditions. Further research is required to investigate whether similar results can be obtained in patients from different backgrounds. In conclusion, during down-fracture of Le Fort I osteotomy, sympathetic nerve activity was predominant with propofol anesthesia, and parasympathetic nerve activity was predominant with remimazolam anesthesia. However, there was no difference in the percent change in heart rate and blood pressure compared to baseline. Therefore, differences in autonomic nerve activity during down-fracture with remimazolam and propofol anesthesia may be of little clinical significance.

AUTHOR ORCIDs

Yuto Tsuji: https://orcid.org/0009-0002-7362-030X
Kyotaro Koshika: https://orcid.org/0000-0002-2656-9698
Tatsuya Ichinohe: https://orcid.org/0000-0001-5793-3379

AUTHOR CONTRIBUTIONS

Yuto Tsuji: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft
Kyotaro Koshika: Data curation, Formal analysis, Methodology
Tatsuya Ichinohe: Supervision

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