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# The histamine $H_1$ receptor antagonist hydroxyzine enhances sevoflurane and propofol anesthesia: A quantitative EEG study

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HIGHLIGHTS

- Hydroxyzine, a histamine $H_1$ receptor antagonist, augmented α and δ bicoherence in both sevoflurane anesthesia and propofol anesthesia.
- Hydroxyzine augmented θ bicoherence in sevoflurane anesthesia but not in propofol anesthesia.
- Hydroxyzine enhances both sevoflurane anesthesia and propofol anesthesia at surgical anesthetic depth probably by facilitation of GABAergic neural circuit mechanisms.

ABSTRACT

*Objective:* The aim of this study was to determine the anesthesia-promoting effects of hydroxyzine on electroencephalograms during sevoflurane anesthesia and during propofol anesthesia.
*Methods:* We analyzed 40 patients scheduled for elective surgery under sevoflurane anesthesia (n = 20) or propofol anesthesia (n = 20). Anesthesia was adjusted at a bispectral index value of 50–60, and then 0.5 mg/kg of hydroxyzine was administered intravenously. We analyzed frontal electroencephalograms before and after hydroxyzine injection with power spectral and bicoherence analyses, which are suitable for assessing the anesthetic depth induced by γ-aminobutyric acid (GABA)ergic anesthetics.
*Results:* Hydroxyzine increased the α bicoherence peaks in both sevoflurane anesthesia (mean difference, 11.2%; 95% confidence interval (CI), 7.6 to 14.8; $P < 0.001$) and propofol anesthesia (mean difference, 5.6%; 95% CI, 1.7 to 9.4; $P = 0.008$). Hydroxyzine increased the averaged δ bicoherence values in both sevoflurane anesthesia (mean difference, 5.5%; 95% CI, 2.1 to 8.8; $P = 0.003$) and propofol anesthesia (mean difference, 3.9%; 95% CI, 1.0 to 6.8; $P = 0.011$).
*Conclusions:* Hydroxyzine enhances both sevoflurane anesthesia and propofol anesthesia probably by facilitation of GABAergic neural circuit mechanisms.
*Significance:* The findings provide a new insight into the role of histaminergic neurons during general anesthesia in humans.


## 1. Introduction

Hydroxyzine, a histamine $H_1$ receptor antagonist, has a mild hypnotic effect (Koner et al., 2011) and an antiemetic action (McKenzie et al., 1981). Hydroxyzine has been widely used during the perioperative period including preoperative administration for relieving anxiety (Koner et al., 2011) and intraoperative administration for prevention of postoperative nausea and vomiting (McKenzie et al., 1981). Although hydroxyzine is commonly given by anesthesiologists during the perioperative period, it has not

*Abbreviations:* BIS, bispectral index; CI, confidence interval; EEG, electroencephalogram; GABA, γ-aminobutyric acid; $GABA_A$, γ-aminobutyric acid type A; LORR, loss of righting reflex; PONV, postoperative nausea and vomiting; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus.

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been determined how hydroxyzine affects anesthetic depths during general anesthesia in a clinical setting.

The histaminergic neural system plays an important role in maintenance of arousal (Takahashi et al., 2006) and it originates in the tuberomammillary nucleus (TMN) of the posterior hypothalamus (Haas and Panula, 2003), which receives inhibitory γ-aminobutyric acid (GABA)ergic input from the ventrolateral preoptic nucleus (VLPO) (Szymusiak et al., 1998). Therefore, hydroxyzine is expected to facilitate the effects of anesthetics for general anesthesia such as propofol and volatile anesthetics, which act dominantly at GABA type A ($GABA_A$) receptors (Alkire et al., 2008; Akeju et al., 2014). However, Luo and Leung (2011) reported that the roles of histaminergic neurons for inducing hypnosis may differ in isoflurane anesthesia and propofol anesthesia in rats. Their roles have not been examined yet in humans. It is possible that they vary depending on species.

An unprocessed electroencephalogram (EEG) reflects the activity of the central nervous system, which is affected by anesthetic agents (Purdon et al., 2015). GABAergic anesthetics hyperpolarize the thalamic and cortical circuits and change the thalamus to the oscillatory mode (Franks, 2008). The robust connectivity between the cortex and thalamus leads to synchronous oscillations of cortical neurons (Franks, 2008). These oscillations are clearly visible by spectral analysis of an EEG, and the synchronous activities of the thalamus and cortex can be evaluated by applying bicoherence analysis, which shows the normalized degree of phase coupling (Hayashi et al., 2008; Araki et al., 2018). Thus, bicoherence analysis is suitable for assessing the anesthetic depth induced by GABAergic anesthetics.

In a clinical setting, propofol and sevoflurane, which is a widely used volatile anesthetic, have similar GABAergic neural circuit mechanisms for inducing unconsciousness (Akeju et al., 2014). Therefore, we hypothesized that hydroxyzine enhances both anesthesia induced by sevoflurane and that induced by propofol at a surgical anesthetic depth in humans. To test the hypothesis, we evaluated the effects of hydroxyzine on the anesthetic states induced by propofol and sevoflurane by using an EEG with spectral and bicoherence analyses.

## 2. Methods

### 2.1. Subjects

This prospective observational study was approved by our institutional ethical review board (No.4177) and was registered in a publicly accessible database (UMIN000035402). Written informed consent was obtained from each patient. We enrolled 43 patients (American Society of Anesthesiologists physical status I-II, 20–60 years of age) scheduled for elective surgery under general anesthesia in Shinshu University Hospital during the period from January 2019 to March 2020. Surgery types were orthopedic, gynecological, breast, urological and dental surgery. Patients were eligible for study when they had 2 or more risk factors of postoperative nausea and vomiting (PONV) including history of PONV, motion sickness, female gender, non-smoker and postoperative opioids or when attending anesthesiologists considered prophylactic use of antiemetics was needed. Patients with neurological or psychiatric disease were excluded from this study. Forty-three consecutive patients enrolled in this study were divided into 2 groups at the discretion of the attending anesthesiologist who did not know the purpose of this study.

### 2.2. Protocol

No premedication was given to patients before anesthesia. In all cases, monitoring included noninvasive arterial blood pressure, electrocardiogram, pulseoxymetry, end-tidal carbon dioxide, and bispectral index (BIS). All of the monitoring was started before induction of anesthesia. A BIS Quatro sensor was placed on the forehead. Anesthesia was induced with a bolus of propofol (1 mg/kg) combined with sevoflurane (end-tidal concentration, 2%) when sevoflurane was used as the sole agent for maintenance of general anesthesia (sevoflurane group). When propofol was used as the sole agent for maintenance of general anesthesia (propofol group), anesthesia was induced with propofol at 5 μg/ml of the effect-site concentration by using a target-controlled infusion device (Terufusion, TERMO, Tokyo Japan). At loss of verbal response, the effect-site concentration of propofol was decreased to 3 μg/ml. Rocuronium (0.6–1.0 mg/kg) was administered in order to facilitate tracheal intubation. Continuous infusion of remifentanil was started at an infusion rate of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 5 min before anesthesia induction for preventing a hemodynamic response to tracheal intubation. The patients were intubated and ventilated mechanically. After tracheal intubation, the end-tidal concentration of sevoflurane and the effect-site concentration of propofol were decreased to 1% and 2.5 μg/ml, respectively. The infusion rate of remifentanil was decreased to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after tracheal intubation and was maintained at that infusion rate throughout the study period. Anesthesia was adjusted at the discretion of the attending anesthesiologist in order to maintain BIS values between 50 and 60. Patients with a BIS value out of targeted range (50–60) were excluded from the study. After the end-tidal concentration of sevoflurane or the effect-site concentration of propofol had been kept constant for more than 10 min, we obtained EEG data for the subsequent 3 min as baseline data immediately before administration of hydroxyzine. Then a bolus of hydroxyzine (0.5 mg/kg), which is within the clinical dose range, was intravenously administered for prevention of postoperative nausea and vomiting. We obtained 3-min-long EEGs 10 min after the administration of hydroxyzine. Mean blood pressure was maintained at more than 60 mmHg by using phenylephrine. Ventilation was adjusted in order to maintain end-tidal carbon dioxide between 30 and 40 mmHg. All of the data for analysis were collected within 20–40 minutes after induction of anesthesia and the study was completed before surgery began.

### 2.3. Electroencephalographic recording and dataset

An EEG was recorded continuously using a BIS Quatro sensor placed on the forehead, which was connected to a BIS A-3000 monitor (BIS A3000; Medtronic, Mansfield, MA), and data were collected by a CAP system (Nihonkohden, Tokyo, Japan) at a sampling rate of 250 Hz. The bandpass filter was set at 0.25–45 Hz as default. The electrode impedance was maintained at 5 kΩ or lower throughout the study. BIS index data were collected every 60 sec automatically in anesthetic records. Baseline BIS index and BIS index after hydroxyzine injection were averaged values in the 3-min EEG recording periods at baseline and at 10 min after hydroxyzine injection, respectively. EEG analysis was carried out using collected EEG data after surgery had been completed. It was confirmed by an experienced investigator (S.T) that all datasets were free of noise and artifacts.

### 2.4. Spectral analysis

A power spectrum and spectrogram were calculated using the multitaper spectral analysis method implemented as the *pmtm* function in MATLAB R2018a (Mathworks, Natick, MA). The power spectrum was estimated using the following parameters: window length, 2 sec with no overlapping; time-bandwidth product, 3; number of tapers, 5. The spectrogram is a successive version of the power spectrum estimated using consecutive windows of

EEG. We computed the spectrogram using the following parameters: window length, 2 sec with 0.5 sec overlapping; time-bandwidth product, 3; number of tapers, 5. Power spectrum estimation was performed for each patient separately. Based on a previous study (Gaskell et al., 2017), the α and δ powers were defined as the peak powers in frequency bands of 8–17 Hz and 1.5–4 Hz, respectively. The averaged θ power was defined as the averaged power at frequencies of 4–8 Hz. The group level of the spectrum was calculated by averaging across all patients within each group. The power was represented as 10 times the log base 10 of squared amplitude.

### 2.5. Bicoherence analysis

Bicoherence values were calculated on the basis of a previously described method (Hagihira et al., 2001; Hayashi et al., 2008; Araki et al., 2018) using MATLAB R2018a. Bicoherence values were calculated in all pairs of frequencies between 1.5 and 20 Hz with 0.5-Hz intervals from the 3-min-long EEG segments just before and 10 min after hydroxyzine injection. The 3-min-long EEG segments were divided into a series of 2-sec epochs with 1.5-sec overlapping. After the Blackman window function had been applied to each epoch, *BIC (f1, f2)*, bicoherence values were calculated from the resulting 360 epochs using the following equations:

$$sTP(f_1,f_2) = \Sigma|X_j(f_1)X_j(f_2)X_j^*(f_1+f_2)|$$

$$B(f_1,f_2) = |\Sigma X_j(f_1)X_j(f_2)X_j^*(f_1+f_2)|$$

$$BIC(f_1,f_2) = 100 \times B(f_1,f_2)/sTP(f_1,f_2),$$

where *sTP ($f_1$, $f_2$)* is the sum of absolute triple products, and the subscript j refers to the epoch number. $X_j(f_1)$ is a complex value calculated by Fourier transformation of the *j*th epoch, and $X_j^*(f_1+f_2)$ represents the conjugate of $X_j(f_1+f_2)$. *B ($f_1$, $f_2$)* means a bispectrum. The diagonal bicoherence was defined as the bicoherence of the same pairs of the frequencies in a diagonal line. The α bicoherence peak was defined as the peak diagonal bicoherence at frequencies of 8–17 Hz. The averaged θ and averaged δ bicoherence were defined as averaged diagonal bicoherence at frequencies of 1.5–4 and 4–8 Hz, respectively. The group level of bicoherence was calculated by averaging diagonal bicoherence across all patients within each group.

### 2.6. Statistical analysis

The independent *t*-test and the chi-square test were used for comparing continuous data (age, height, body weight) and categorical data (sex, types of surgery), respectively, between the sevoflurane and propofol groups. We compared the calculated parameters derived from EEG signals obtained just before and 10 min after hydroxyzine injection using a paired *t*-test after confirming a normal distribution by using the Shapiro-Wilk normality test. Data that were not normally distributed were compared using Wilcoxon signed-rank analysis (frequency of α bicoherence peak). A two-sided $P < 0.05$ was considered statistically significant. Values are expressed as means (95% confidence interval; CI) when normally distributed and otherwise as medians [25th to 75th percentiles]. The difference in medians with the 95% CI was calculated by the Hodges Lehman method. The Shapiro-Wilk normality test and the Hodges Lehman method were performed using R: A language and environment for statistical computing (R Core Team (2019), R version 3.6.1, R Foundation for Statistical Computing, Austria, https://www.R-project.org/). Other statistical analyses were performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA).

Our primary outcome was changes in the α bicoherence peak after hydroxyzine injection. We obtained mean (10) and standard deviation (14) of α bicoherence changes after hydroxyzine injection from a pilot study (n = 4), and effect size (Cohen d) was calculated to be 0.71. Eighteen patients were required to provide 80% power with a type 1 error probability of 0.05 at least. In compensation for dropouts, we enrolled 20 patients in the sevoflurane group. In the propofol group, we enrolled 23 patients considering technical difficulty for adjusting the BIS value within 50 to 60 before hydroxyzine injection.

## 3. Results

We excluded 3 patients in the propofol group because the BIS value was out of the targeted range (50–60) before administration of hydroxyzine. Therefore, we analyzed 20 patients in each group. The characteristics of the patients did not statistically differ between the two groups (table 1). Mean blood pressure and end-tidal carbon dioxide were kept at approximately 70 mmHg and 35 mmHg, respectively, during the study period in both groups. After hydroxyzine injection, the BIS index significantly decreased from 57 (55 to 58) to 43 (42 to 45) in the sevoflurane group (mean difference, −13; 95% CI, −15 to −11; $P < 0.001$) and from 56 (54 to 57) to 40 (37 to 43) in the propofol group (mean difference, −16; 95% CI, −19 to −13; $P < 0.001$). The end-tidal concentration of sevoflurane during the study period was 1.0 (1.0 to 1.1)% in the sevoflurane group and the effect-site concentration of propofol was 2.5 (2.3 to 2.7) μg/ml in the propofol group. No patients experienced intraoperative awareness with explicit recall.

### 3.1. Changes in power spectral properties after hydroxyzine injection

Time courses of power spectrum changes after hydroxyzine injection are shown in Fig. 1 as spectrograms of two typical cases. Fig. 1**A** shows a spectrogram of a 38-year-old man in the sevoflurane group and Fig. 1**B** shows a spectrogram of a 46-year-old woman in the propofol group. In both cases, the α power peaks shifted to a lower frequency and δ power increased. As shown in Fig. 1, these effects of hydroxyzine on the power spectrum of EEG appeared about 2 minutes later and reached a maximum effect within 10 minutes after hydroxyzine injection. Fig. 2**A and B** show group levels of the power spectrum just before and 10 min after hydroxyzine injection in the sevoflurane and propofol groups, respectively. In the sevoflurane group, after hydroxyzine injection, the frequency of the α power peak decreased from 11.7 (11.3 to 12.2) to 10.4 (9.9 to 10.9) Hz (mean difference, −1.3 Hz; 95% CI, −1.7 to −0.9; $P < 0.001$) and the δ power increased from 8.7 (6.9 to 10.4) to 11.6 (10.2 to 13.0) dB (mean difference, 3.0 dB; 95% CI, 2.1 to 3.8; $P < 0.001$). The averaged θ power increased from

**Table 1**
Patient characteristics.

| | Sevoflurane (n = 20) | Propofol (n = 20) | *P* value |
|---|---|---|---|
| Female/Male | 15/5 | 17/3 | 0.43 |
| Age (yr) | 41 [20–58] | 44 [20–58] | 0.45 |
| Weight (kg) | 62 [40–93] | 59 [40–76] | 0.44 |
| Height (cm) | 162 [151–177] | 159 [136–170] | 0.31 |
| Types of surgery | | | 0.52 |
| Orthopedic | 10 (50) | 11 (55) | |
| Gynecologic | 3 (15) | 5 (25) | |
| Breast | 4 (20) | 2 (10) | |
| Urologic | 3 (15) | 1 (5) | |
| Dental | 0 | 1 (5) | |

Data are expressed as means [ranges] or numbers (%).

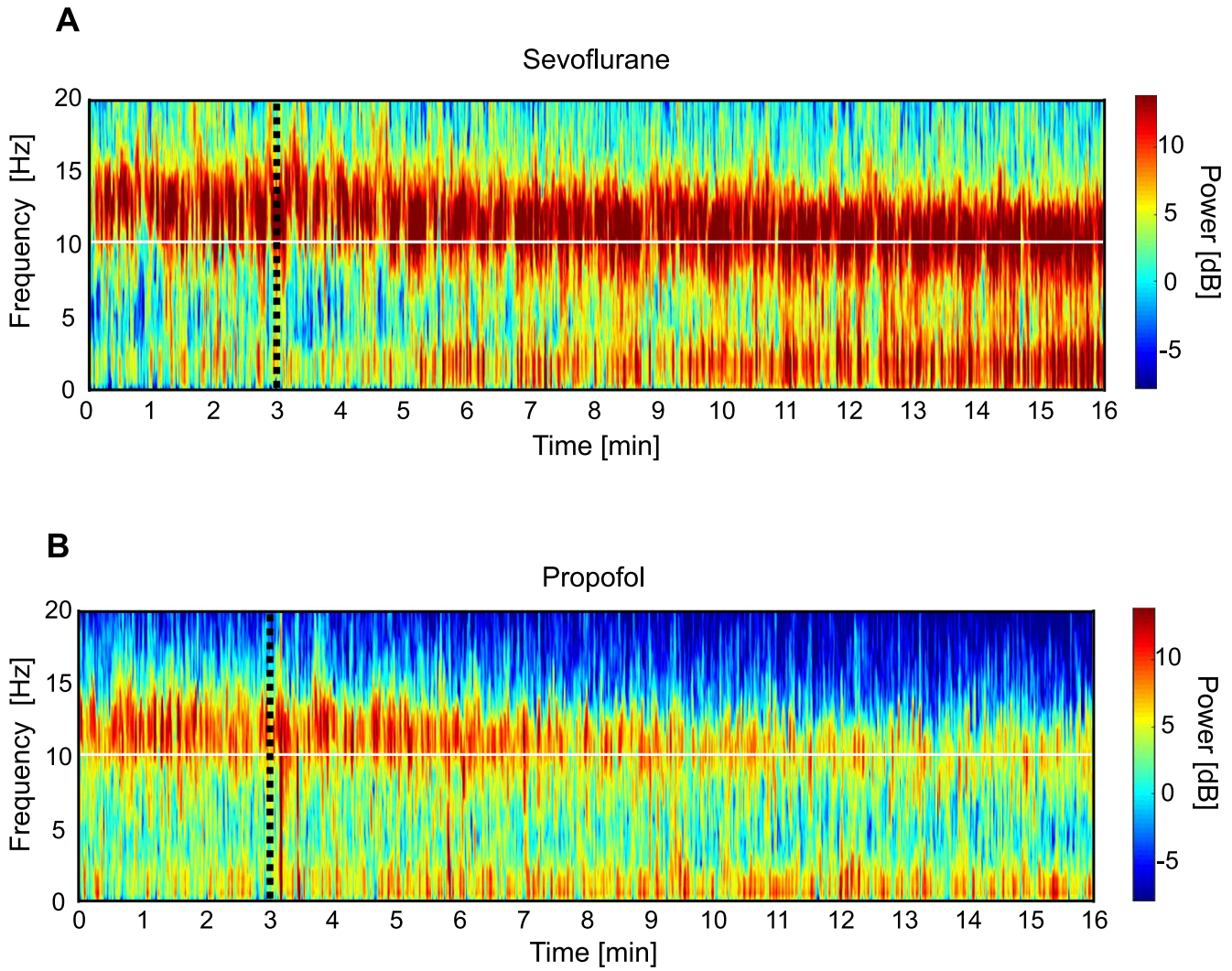


**Fig. 1.** Characteristic spectrograms of two patients before and after hydroxyzine injection. (A) Spectrogram of a 38-year-old man who received sevoflurane anesthesia and (B) spectrogram of a 46-year-old woman who received propofol anesthesia. Hydroxyzine was injected at the point of the dashed vertical line. Horizontal white lines represent frequency at 10 Hz. In both spectrograms, an increase of δ power and lower shift of α peak were observed.

5.6 (4.3 to 6.8) to 7.5 (6.0 to 8.9) dB (mean difference, 1.9 dB; 95% CI, 1.1 to 2.7; $P < 0.001$). In the propofol group, hydroxyzine also shifted the α power peak from 11.6 (11.2 to 11.9) to 10.8 (10.5 to 11.1) Hz (mean difference, −0.8 Hz; 95% CI, −1.0 to −0.5; $P < 0.001$) and increased the δ power from 8.8 (7.3 to 10.3) to 11.3 (9.6 to 13.0) dB (mean difference, 2.5 dB; 95% CI, 1.5 to 3.5; $P < 0.001$). The difference in the averaged θ power before and after hydroxyzine injection was not statistically significant (before: 4.9 (3.5 to 6.3) dB vs. after: 5.3 (3.9 to 6.7) dB; mean difference, 0.4 dB; 95% CI −0.1 to 1.0; $P = 0.107$).

### *3.2. Changes in bicoherence properties after hydroxyzine injection*

Fig. 3**A and B** show the averaged bicoherences just before and 10 min after hydroxyzine injection, respectively, in the sevoflurane group. Fig. 3**C** shows the averaged bicoherence at the diagonal line in the sevoflurane group. After hydroxyzine injection, the frequency of the α bicoherence peak shifted from 11.0 [10.5–12.0] to 10.0 [10.0–11.0] Hz (median difference, −0.9 Hz; 95% CI, −1.5 to −0.5; $P = 0.002$). The α bicoherence peak and the averaged δ bicoherence increased from 40.0 (34.8 to 45.2)% to 51.2(45.5 to 56.9)% (mean difference, 11.2%; 95% CI, 7.6 to 14.8; $P < 0.001$) and from 24.6 (20.1 to 29.1)% to 30.1(25.6 to 34.7)% (mean difference, 5.5%; 95% CI, 2.1 to 8.8; $P = 0.003$), respectively. The averaged θ bicoherence increased from 17.3 (15.4 to 19.2)% to 21.7 (19.4 to 24.0)% (mean difference, 4.4%; 95% CI, 3.0 to 5.8; $P < 0.001$). In the propofol group, the averaged bicoherences just before and 10 min after hydroxyzine injection are shown in Fig. 4**A and B**, respectively, and the averaged bicoherence at the diagonal line is shown in Fig. 4**C**. In the propofol group, hydroxyzine also shifted the frequency of the α bicoherence peak from 11.5 [10.9–12.1] to 10.8 [10.5–11.1] Hz (median difference, −0.6 Hz; 95% CI, −2.0 to 0; $P = 0.017$) and increased the α bicoherence peak from 35.6 (29.1 to 42.1)% to 41.2 (34.1 to 48.2)% (mean difference, 5.6%; 95% CI, 1.7 to 9.4; $P = 0.008$). The averaged δ bicoherence also increased from 16.7 (13.5 to 19.9)% to 20.6 (16.9 to 24.3)% (mean difference, 3.9%; 95% CI, 1.0 to 6.8; $P = 0.011$) after hydroxyzine injection. The differences in the averaged θ bicoherence before and after hydroxyzine injection was not statistically significant (before: 16.4 (14.1 to 18.6)% vs. after: 17.4(15.4 to 19.4)%; mean difference, 1.0%; 95% CI, −0.6 to 2.6; $P = 0.220$).

## 4. Discussion

The main findings of this study are as follows: (1) hydroxyzine at a clinically relevant dose shifted α power peaks to lower fre-

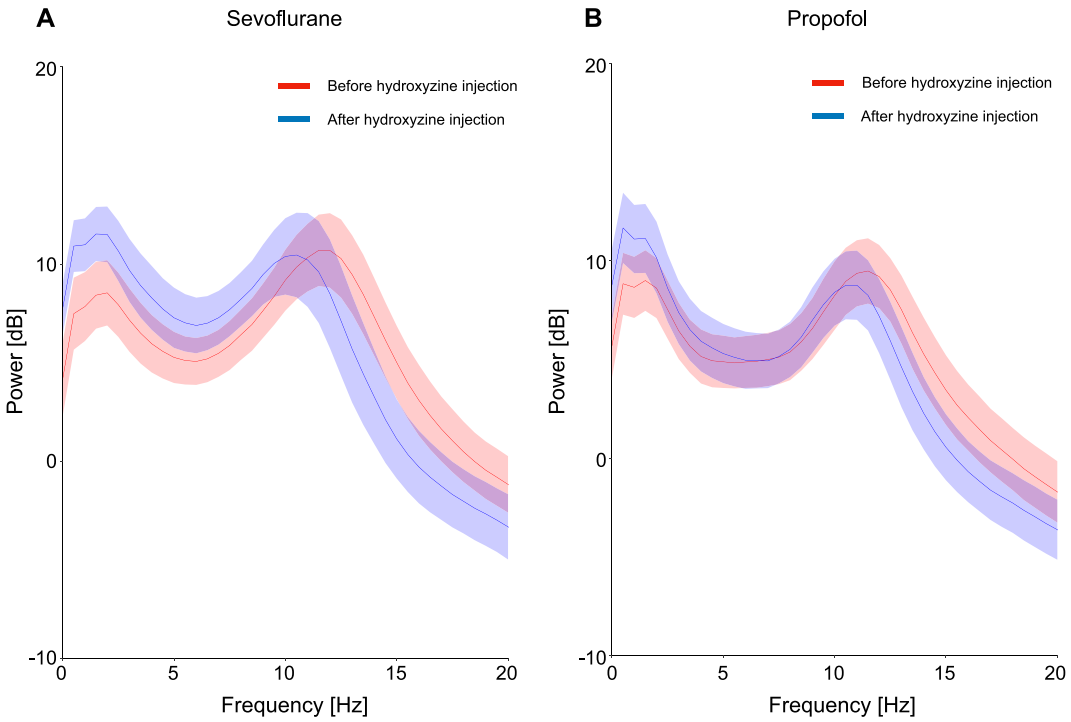


**Fig. 2.** Group levels of the power spectrum immediately before and 10 min after hydroxyzine injection in the sevoflurane group (A) and in the propofol group (B). Red and blue lines represent immediately before and 10 min after hydroxyzine injection, respectively. The shaded areas show the 95% confidence interval around each mean spectrum. n = 20 in each group. In both the sevoflurane and propofol groups, hydroxyzine significantly decreased the frequency of α peak ($P < 0.001$ and $P < 0.001$, respectively) accompanying an increase of δ power ($P < 0.001$ and $P < 0.001$, respectively).

quencies and increased δ power in both groups, (2) hydroxyzine also decreased the frequency of α bicoherence peaks and augmented α and δ bicoherence in both groups. This augmentation of oscillations in α and δ frequencies is a feature of an EEG induced by GABAergic anesthetics (Hayashi et al., 2008; Akeju et al., 2014; Akeju et al., 2016). Our results suggest that hydroxyzine enhances both sevoflurane anesthesia and propofol anesthesia via GABAergic neural circuits. Hydroxyzine deepens both sevoflurane anesthesia and propofol anesthesia from a light level (defined as a BIS value of about 60) to a deep level (defined as a BIS value of about 40). Although hydroxyzine is used for various purposes in the perioperative period, anesthetic management should be performed with due consideration of the profound effects of hydroxyzine on anesthetic depth.

The serum elimination half-time of hydroxyzine is relatively long (20–25 hours) after its administration (Simons et al., 1987), and a hypnotic effect of hydroxyzine administered intravenously emerges within 10 minutes and lasts for at least 30–60 min (Cornbleet. 1960). In addition, our study was initiated at least 10 min after keeping the concentrations of sevoflurane and propofol constant, which is sufficient time for achieving stabilization of the anesthetic effect-site concentration (Lerou and Booij, 2001, Marsh et al., 1991). These suggest that the effect of hydroxyzine on an EEG is expected to stably last for at least 30 min, and the data sampling in this study would be appropriate in order to evaluate the effect of antagonizing histaminergic neurons under general anesthesia on EEGs.

Luo and Leung (2011) found that the roles of histaminergic neurons for inducing hypnosis may differ in isoflurane anesthesia and propofol anesthesia by evaluating anesthetic sensitivity for achieving loss of righting reflex (LORR) in TMN-destroyed rats. In a rat study, LORR is usually used for confirming anesthetic efficacy (Franks, 2008). However, LORR does not necessarily correlate with loss of consciousness because it depends on skeletal muscle tone, which is regulated by the locus coelureus and spinal motor neurons (Mantz and Hemmings, 2011; Yu et al., 2018). On the other hand, we evaluated the effects of hydroxyzine on α and δ oscillations of an EEG, which are considered to be markers of loss of consciousness induced by GABAergic anesthetics in a clinical setting (Purdon et al., 2015). In our study, the effects of hydroxyzine on α and δ oscillations of an EEG were similar in sevoflurane anesthesia and propofol anesthesia. Therefore, based on our results, the relevance of histaminergic neurons to hypnosis induced by GABAergic anesthetics might not differ depending on the type of anesthetics in humans. Difference in the methods for evaluating anesthetic depth in addition to species difference may account for the difference between previous results and our findings.

Our results also provide a new insight into the role of histaminergic neurons during general anesthesia in humans. We showed that hydroxyzine facilitated both sevoflurane anesthesia and propofol anesthesia after loss of consciousness had been achieved. These results suggest that activities of histaminergic neurons in the TMN, which mostly cease during slow wave sleep (Franks and Zecharia, 2011; Leung et al., 2014), were not completely inhibited by general anesthetics at a surgical anesthetic depth. The firing rate of TMN neurons decreases prior to sleep onset and firing is ceased during slow wave sleep (Takahashi et al., 2006; Franks and Zecharia, 2011; Leung et al., 2014). During sleep, the cessation of the TMN and other arousal-promoting nuclei hyperpolarizes the thalamocortical circuits, resulting in sleep spindles and δ oscillations (Sleigh et al., 2011), which are to some extent similar to the EEG changes induced by GABAergic anesthetics. However, GABAergic anesthetics seem to generate α and δ oscillations via acting directly on the cortical and thalamic neurons (Ching et al., 2010), sparing the arousal-promoting nuclei in the brainstem

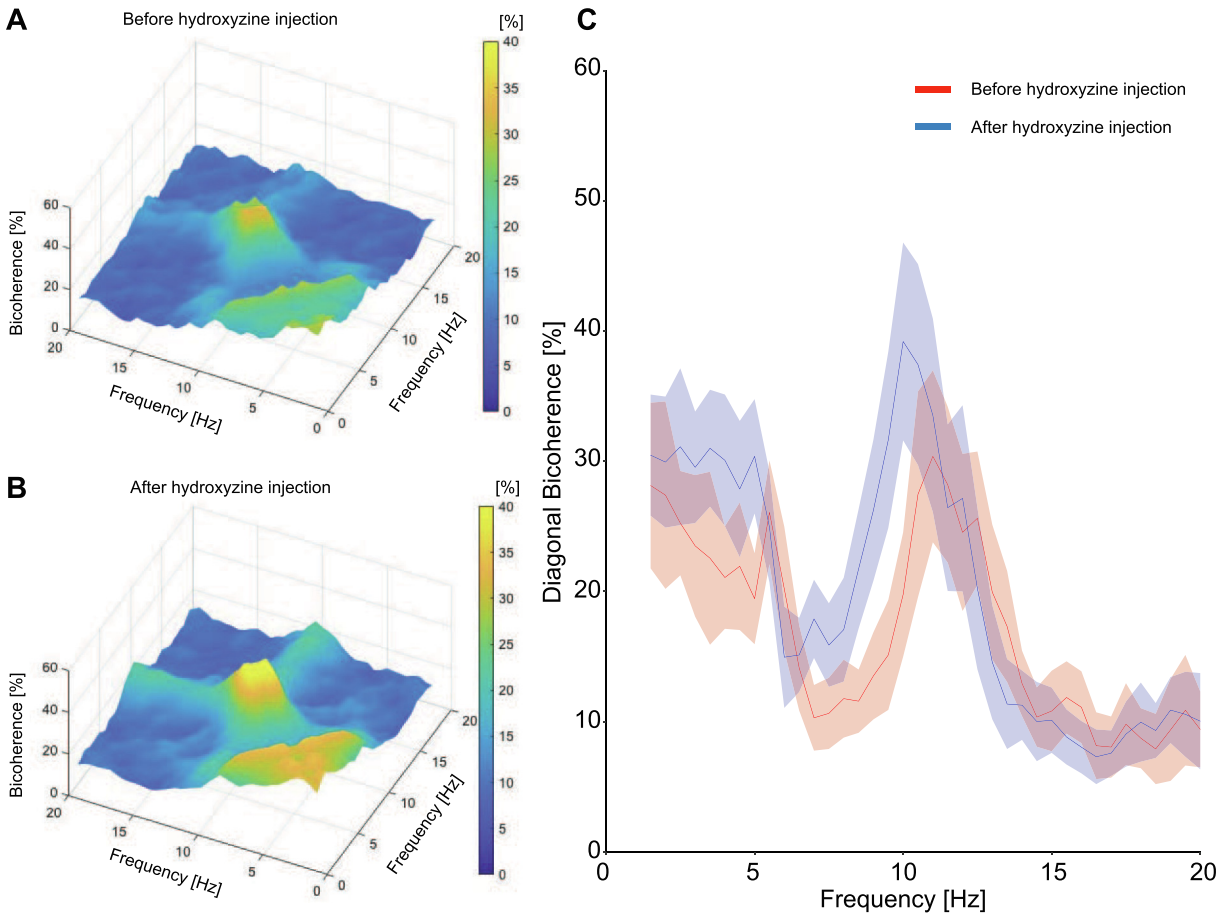


**Fig. 3.** Group levels of bicoherence in the sevoflurane group immediately before (A) and 10 min after (B) hydroxyzine injection. (C) Averaged bicoherence at the diagonal line (diagonal bicoherence) in the sevoflurane group. Red and blue lines represent immediately before and 10 min after hydroxyzine injection, respectively. The shaded areas show the 95% confidence interval around each mean bicoherence. n = 20.

(Sleigh et al., 2011). We speculate that both sevoflurane and propofol directly inhibited thalamocortical circuits in the presence of excitatory histaminergic input from the TMN, and thus hydroxyzine augmented the α and δ oscillations at a surgical anesthetic depth defined as a BIS value of 50–60.

Histamine receptors are 7-transmembrane G protein-coupled receptors and consist of 4 subtypes ($H_1$, $H_2$, $H_3$ and $H_4$ receptors) (Panula et al., 2015). The $H_1$ receptor is expressed at postsynaptic neurons and its agonism increases $Ca^{2+}$ influx, leading to membrane depolarization of postsynaptic neurons (Panula et al., 2015). The dominant action of hydroxyzine is antagonism of the $H_1$ receptor with a weak effect on antagonism of muscarinic and 5-$HT_2$ receptors (Snyder and Snowman, 1987; Koner et al., 2011). Our results suggest that antagonism of the $H_1$ receptor by hydroxyzine inhibits the depolarization of thalamocortical circuits, resulting in augmentation of α and δ oscillations. Muscarinic and 5-$HT_2$ receptors receive acetylcholine and serotonin from the basal forebrain and dorsal raphe nucleus, respectively, which are also known as arousal-promoting nuclei (Brown et al., 2010) and are not affected by histaminergic neurons (Gallopin et al., 2000). Thus, the effects of hydroxyzine on these receptors might have had some influence on the results.

In our study, hydroxyzine increased the θ power and bicoherence under sevoflurane anesthesia, while hydroxyzine did not affect those under propofol anesthesia. The neurophysiology of the θ oscillation is not fully understood. Therefore, it is not clear why hydroxyzine increased the θ power and bicoherence only in sevoflurane anesthesia. θ oscillation is observed in a pathologic state and is also known as thalamocortical dysrhythmia (Sarnthein et al., 2006). Thalamocortical dysrhythmia seems to be derived from dysfunction of the T-type calcium channel in the thalamus (Sarnthein et al., 2006), which is also modulated by volatile anesthetics (McDowell et al., 1999). As Akeju et al. (2014) discussed, the θ oscillation of sevoflurane anesthesia may indicate thalamic deafferentation from modulation of the T-type calcium channels in the thalamus by sevoflurane. We speculate that blockade of histaminergic receptors in the thalamus may facilitate thalamic deafferentation, which is a specific effect of sevoflurane on the thalamus.

This study has several potential limitations. First, we evaluated the effect of hydroxyzine on only surgical anesthetic depth defined as a BIS value of 50–60 in both sevoflurane anesthesia and propofol anesthesia. The primary target sites of anesthetics may differ depending on the anesthetic depth (Reshef et al., 2019). Elucidating the effects of hydroxyzine on various stages of anesthetic depth may become an issue in the future. Second, since this study was a prospective observational study, we did not randomize between the sevoflurane and propofol groups. However, as shown in table 1, there were no significant differences in patient characteristics between the two groups. Therefore, we presume that the background factors of the subjects had little impact on our results.

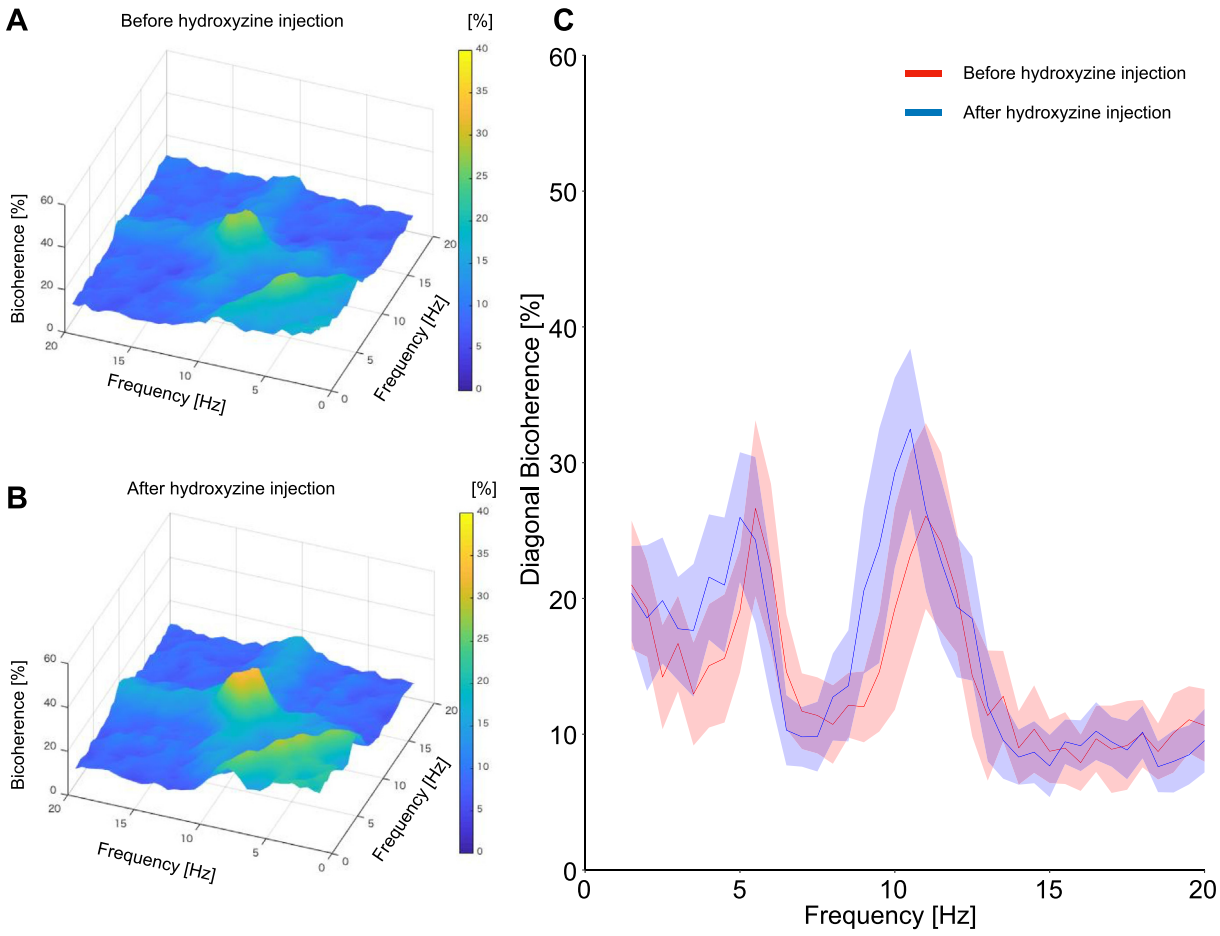


**Fig. 4.** Group levels of bicoherence in the propofol group immediately before (A) and 10 min after (B) hydroxyzine injection. (C) Averaged bicoherence at the diagonal line (diagonal bicoherence) in the propofol group. Red and blue lines represent immediately before and 10 min after hydroxyzine injection, respectively. The shaded areas show the 95% confidence interval around each mean bicoherence. n = 20.

## 5. Conclusions

Hydroxyzine enhances both sevoflurane anesthesia and propofol anesthesia at a surgical anesthetic depth in humans, probably via GABAergic neural circuit mechanisms.

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## Author contributions

R. Tanaka: This author designed the study, collected and analyzed the data, and prepared the manuscript.

S. Tanaka: This author designed the study, collected and analyzed the data, and prepared the manuscript.

K. Hayashi: This author gave advice for data analysis and revised the manuscript.

K. Iida: This author collected data and prepared the manuscript.

T. Sawa: This author gave advice for data analysis and revised the manuscript.

M. Kawamata: This author conducted the study and revised the manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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