ANESTHESIOLOGY

Electroencephalographic Features of Elderly Patients during Anesthesia Induction with Remimazolam: A Substudy of a Randomized Controlled Trial

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ANESTHESIOLOGY 2024; 141:681–92

ABSTRACT

Background: Although remimazolam is used as a general anesthetic in elderly patients due to its hemodynamic stability, the electroencephalogram characteristics of remimazolam are not well known. The purpose of this study was to identify the electroencephalographic features of remimazolam-induced unconsciousness in elderly patients and compare them with propofol.

Methods: Remimazolam (n = 26) or propofol (n = 26) were randomly administered for anesthesia induction in surgical patients. The hypnotic agent was blinded only to the patients. During the induction of anesthesia, remimazolam was administered at a rate of 6 mg · kg^{-1} · h^{-1}, and propofol was administered at a target effect-site concentration of 3.5 μg/ml. The electroencephalogram signals from eight channels (Fp1, Fp2, Fz, F3, F4, Pz, P3, and P4, referenced to A2, using the 10 to 20 system) were acquired during the induction of anesthesia and in the postoperative care unit. Power spectrum analysis was performed, and directed functional connectivity between frontal and parietal regions was evaluated using normalized symbolic transfer entropy. Functional connectivity in unconscious processes induced by remimazolam or propofol was compared with baseline. To compare each power of frequency over time of the two hypnotic agents, a permutation test with *t* statistic was conducted.

Results: Compared to the baseline in the alpha band, the feedback connectivity decreased by averages of 46% and 43%, respectively, after the loss of consciousness induced by remimazolam and propofol (95% CI for the mean difference: –0.073 to –0.044 for remimazolam [$P < 0.001$] and –0.068 to –0.042 for propofol [$P < 0.001$]). Asymmetry in the feedback and feedforward connectivity in the alpha band was suppressed after the loss of consciousness induced by remimazolam and propofol. There were no significant differences in the power of each frequency over time between the two hypnotic agents (minimum q value = 0.4235).

Conclusions: Both regimens showed a greater decrease in feedback connectivity compared to a decrease in feedforward connectivity after loss of consciousness, leading to a disruption of asymmetry between the frontoparietal connectivity.

(ANESTHESIOLOGY 2024; 141:681–92)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Because of its superior cardiovascular stability, remimazolam may have advantages over propofol as an induction agent in elderly patients
- The electroencephalographic features of remimazolam in elderly patients have not been well characterized

What This Article Tells Us That Is New

- During induction of anesthesia, remimazolam caused patterns in electroencephalographic spectral power similar to those seen with propofol
- Remimazolam nearly halved the directed electroencephalogram alpha-band connectivity from the frontal to the parietal lobes of the brain—again almost identical to the propofol effects on functional connectivity

Remimazolam is an ultra-short-acting hypnotic agent that combines the pharmacologic properties of midazolam with the metabolic properties of remifentanil.[1] In

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). H.K. and B.-K.M. contributed equally to this work.

Submitted for publication August 16, 2023. Accepted for publication January 4, 2024. Published online first on January 9, 2024.

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 ANESTHESIOLOGY 2024; 141:681–92. DOI: 10.1097/ALN.0000000000004904

<zdoi;10.1097/ALN.0000000000004904>

2021, remimazolam was approved by the Korean Ministry of Food and Drug Safety for use in the induction and maintenance of anesthesia. For the induction of anesthesia, remimazolam was approved for continuous intravenous administration (6 or 12 mg · kg^{-1} · h^{-1}), which was determined based on the results of a phase 3 trial conducted in Japan.[2] As remimazolam shows superior hemodynamic stability during anesthesia induction compared to propofol,[3,4] its usage is gradually increasing among elderly patients undergoing general anesthesia.

Several studies have reported that general anesthesia affects functional connectivity in the brain.[5–8] It has been observed that the frontal-to-parietal feedback connectivity is significantly reduced when γ-aminobutyric acid (GABA)–mediated hypnotics are administered.[6,7] As remimazolam is a benzodiazepine, it affects GABA and consequently alters the level of consciousness. However, few studies have been conducted to explore the electroencephalogram (EEG) features of remimazolam-induced loss of consciousness. A better understanding of the EEG characteristics of remimazolam could help the effective management of elderly patients undergoing general anesthesia with this drug. In particular, the EEG features of remimazolam can be better understood by making a comparison with the EEG characteristics of elderly patients anesthetized with propofol.

Many data-driven and theory-driven EEG indices have been developed to quantitatively evaluate the effects of anesthetics on the level of consciousness. The EEG indices were defined based on various properties of EEG signals, including spectral properties, complexity, and network properties.[9,10] While these indices have been effective in distinguishing between conscious and unconscious states, the reliability of each index has only been tested using a limited data set. In this study, we investigated the impact of two hypnotic agents (remimazolam and propofol) on the level of consciousness by utilizing feedback/feedforward connectivity in EEG signals between the frontal and parietal regions. In several previous studies, selective disruption of feedback connectivity was observed with various anesthetics.[5–7] Additionally, the reliability of feedback/feedforward connectivity has been evaluated in several other studies.[8,11–13] In a recent study that assessed several EEG measures, it was reported that the loss of normalized symbolic transfer entropy, which quantifies feedback connectivity, was closely associated with connectedness (an individual's sensory awareness of the world around them) among the tested indices.[14] In this study, we aimed to characterize the EEG features of remimazolam-induced unconsciousness in elderly patients under general anesthesia.

Materials and Methods

Patient Population

This study was conducted as a substudy of the parent study to examine the difference in postoperative delirium incidence in elderly patients undergoing elective gastric surgery when anesthetized with remimazolam or propofol. This substudy was conducted with patients who agreed to EEG measurement. The parent study was approved by the Institutional Review Board of Asan Medical Center (Seoul, Korea, approval No. 2021-1668, approval date: November 25, 2021) and registered on an international clinical trials registry platform (https://cris.nih.go.kr, KCT0006877, principal investigator: Byung-Moon Choi, date of registration: December 27, 2021) before the enrollment of the first subject. Written informed consent was obtained from all participating patients. The patients were enrolled in this substudy between September 2022 and January 2023. The hypnotic agent was blinded only to the patients. We included patients who were aged 65 yr or older; had an American Society of Anesthesiologists Physical Status classification of I, II, or III; and were scheduled for gastric surgery. The exclusion criteria were as follows: history of an allergic response to remimazolam or propofol, history of neurologic or psychologic disease, or a history of chronic pain.

Study Procedure

All patients fasted for 6 to 8 h before surgery without receiving any premedication. In the operating room, all patients were monitored with electrocardiogram, pulse oximetry, noninvasive blood pressure, train-of-four, end-tidal carbon dioxide partial pressure (Carescape B850; GE Healthcare, USA), and the Bispectral Index (Medtronic, Ireland). Throughout surgery, all data were continuously downloaded to personal computers. The Bispectral Index values were recorded every 5 s. Patients were randomly assigned to either the remimazolam or propofol group at a 1:1 ratio. A computer-generated random allocation sequence was performed using simple randomization. Patient randomization was conducted by a coordinator who was not involved in the study. For patients assigned to the remimazolam group, remimazolam was continuously administered intravenously at a rate of 6 mg · kg^{-1} · h^{-1} for anesthesia induction. In the case of the propofol group, anesthesia was induced using a target effect-site concentration-controlled infusion of propofol at a target concentration of 3.5 μg/ml (Perfusor Space; B. Braun Melsungen AG, Germany) using the Schnider model.[15,16] The time to loss of consciousness was determined by the absence of response to a verbal command ("open your eyes") every 30 s after the infusion of remimazolam or propofol was initiated. After confirming the loss of consciousness, rocuronium (0.6 mg/kg) was administered, followed by the administration of remifentanil using target effect-site concentration-controlled infusion.[17] The target concentration of remifentanil was set at 2 ng/ml, and when the systolic blood pressure remained above 90 mmHg, it was increased to 3 ng/ml, and tracheal intubation was performed. After tracheal intubation, the infusion rate of remimazolam and the target concentration of propofol were not changed until the EEG measurement was completed. Maintenance of and emergence from anesthesia were performed in accordance with the standard operating procedure of Asan Medical Center.[18] In the case of the remimazolam group, 0.2 mg of flumazenil was administered to all patients after the operation was completed. Oxycodone (2 to 4 mg) was administered to patients with a numerical rating scale score of 4 or higher in the postanesthesia care unit (PACU).

EEG Measurement

The EEG signals from eight channels (Fp1, Fp2, Fz, F3, F4, Pz, P3, and P4, referenced to A2, using the 10 to 20 system) were recorded while the subject's eyes were closed using the QEEG-8 system (Laxtha Inc., Korea). The sampling rate was 256 Hz. Baseline EEG was recorded for 5 min before the administration of remimazolam or propofol.

EEG was recorded continuously during the induction of anesthesia. The induction period was divided into two sections. The first section (induction 1) refers to the period from the start of propofol or remimazolam administration until the time of loss of consciousness. To effectively compare the EEG characteristics during the induction of anesthesia using two different hypnotic agents, the time spans of the induction 1 section were rescaled to the average time of loss of consciousness caused by propofol, which resulted in the timelines of induction 1 section of both hypnotic agents becoming the same. This technique is used to compare the EEG characteristics of different drugs.[7] To statistically distinguish when changes in EEG features occur, the induction 1 section was divided into four equal segments, labeled A1, A2, A3, and A4. The second section (induction 2) refers to the 5min period after the loss of consciousness. EEG was measured for 5 min using the same method in the PACU at least 30 min after transfer from the operating room. In the PACU, Bispectral Index was manually recorded every minute.

EEG Analysis

The data were examined for artifacts using the EEGLAB open-source toolbox for MATLAB,[19] followed by bandpass filtering within the range of 0.1 to 40 Hz. A 10-s window with 8 s of overlap between two consecutive windows was subsequently used for the analysis. The analyses then focused on the power spectrum and normalized symbolic transfer entropy in the various frequency bands (delta, 0.1 to 4 Hz; theta, 4 to 7 Hz; alpha, 7 to 12 Hz; beta, 12 to 20 Hz; and gamma, 20 to 40 Hz). Because elderly patients were analyzed, the frequency range of the alpha band was determined to be lower than the typical alpha band due to the lower alpha peak in the resting state of the elderly.[20,21] Subjects with line noise exceeding 300 μV were excluded from the analysis.

Power Spectrum and Topographic Analysis

The "spectrogram.m" function in the MATLAB Signal Processing Toolbox, which utilizes the short-time Fourier transform, was used to calculate spectral power. To compare the power spectrum of the two hypnotic agents at a frequency over time, 294 frequency bins were obtained in the frequency domain by dividing the range of 0.1 to 40 Hz into intervals of 0.1357 Hz (nonequispaced fast Fourier transform = 1,850). The time window was set to 3 s using a Hamming window with an 81.6% overlap, resulting in a bin size of 2,066. By considering both time and frequency, a total of 607,404 (294 × 2,066) group comparisons are possible. The topographic maps of spectral power were generated using extrapolation and smoothing techniques and were aligned with the axial coordinates of the brain.

Analysis of Functional Connectivity

Symbolic transfer entropy (STE) and transfer entropy (TE) are methods used to detect information exchange between two signal sources, such as different areas of the brain.[22] These surrogate measures have already been used in several studies as reliable indices for quantifying directed functional connectivity.[6,23,24] Transfer entropy measures the mutual information between the past of signal X (X^P) and the future of signal Y (Y^F) when the past of Y (Y^P) is known according to the following formula:

$$\mathrm{TE}_{X\to Y} = \mathrm{I}\left(Y^F;X^P/Y^P\right) = \mathrm{H}\left(Y^F/Y^P\right) - \mathrm{H}\left(Y^F/X^P,Y^P\right) \quad (1)$$

where $\mathrm{H}\left(Y^F/Y^P\right)$ is the entropy of the process Y^F conditional on its past.

The symbolic transfer entropy method uses symbolized vector points instead of embedded vector points to avoid subjective decisions regarding bin size in probability calculation. It has greater robustness and computational efficiency compared to transfer entropy.[25,26] Normalized symbolic transfer entropy is a dimensionless measure that eliminates the bias of symbolic transfer entropy by subtracting the shuffled symbolic transfer entropy from the original symbolic transfer entropy and then dividing the subtracted result by the entropy within the target signal as follows:

$$\mathrm{NSTE}_{X\to Y} = \frac{\mathrm{STE}_{X\to Y} - \mathrm{STE}^{\mathrm{Shuffled}}_{X\to Y}}{H(Y^F|Y^P)} \in [0,1] \quad (2)$$

where $\mathrm{STE}^{\mathrm{Shuffled}}_{X\to Y} = H(Y^F|Y^P) - H(Y^F|X^P_{\mathrm{Shuffled}}, Y^P)$

Normalized symbolic transfer entropy (NSTE) represents the proportion of information in the target signal Y that is not accounted for by its own past but rather by the past of the source signal X. To reduce the bias of symbolic transfer entropy for a given EEG data set, the shuffled data method was applied. This method retains the same signal characteristics as the original signal but eliminates causal relationships. Only the source signal X was shuffled, while the target signal Y remained unchanged.

The asymmetry between $NSTE_{X\to Y}$ and $NSTE_{Y\to X}$ was defined by equation 3.

$$DF_{X\to Y} = \frac{NSTE_{X\to Y} - NSTE_{Y\to X}}{NSTE_{X\to Y} + NSTE_{Y\to X}} \in [-1, 1] \quad (3)$$

If $DF_{X\to Y}$ has a positive value, the connectivity from X to Y is dominant, and *vice versa* for a negative value. The frontal-to-parietal (feedback) and parietal-to-frontal (feedforward) functional connections in the frontoparietal network were evaluated using $NSTE_{f\to p}$ and $NSTE_{p\to f}$ in 52 patients (26 propofol, 26 remimazolam). The average $\overline{NSTE}_{f\to p}$ and $\overline{NSTE}_{p\to f}$ were calculated for each patient over the nine pairs of EEG channels between the frontal (Fz, F3, and F4) and parietal (Pz, P3, and P4) regions using the following equation:

$$\overline{NSTE}_{f\to p} = \frac{1}{n_f \times n_p} \sum_{(i,j)=1}^{n_f, n_p} NSTE_{i\to j} \quad (4)$$

where $n_f = 3$ and $n_p = 3$. The asymmetry of information flow between the two brain regions was defined as $\overline{DF}_{f\to p}$ (eq. 3) for each patient.

The embedding dimension was set to 3 because it produced normalized symbolic transfer entropy patterns that were similar to those with the smallest dimension. The time delay (τ) was calculated in the range of 1 to 30 (corresponding to a range between 11.7 and 351 ms) to maximize the normalized symbolic transfer entropy. The prediction time (δ) was chosen based on the time lag that resulted in the maximum cross-correlation, assuming that the time lag represents the interaction delay between the source and target signals. The range of time lags considered was from 1 to 100 (corresponding to a range of 3.9 to 390 ms).

The feedback or feedforward connectivity of each section was defined as the average connectivity value calculated over 10 small windows. For each small window, the average NSTE, $\overline{NSTE}_{f\to p}$, and $\overline{NSTE}_{p\to f}$ between three frontal and three parietal EEG channels were calculated. The small window size of 10 s may satisfy pseudostationary conditions for NSTE calculation, and the mean value over 10 small windows may reflect the connectivity of a section.

Statistical Analysis

The primary objective of this study is to assess whether there is a reduction in feedback connectivity and maintenance of feedforward connectivity after the induction of loss of consciousness by remimazolam. Because remimazolam acts on the $GABA_A$ receptor like propofol, it was assumed that it would reduce feedback connectivity and maintain feedforward connectivity similarly to propofol. In our previous study, the mean ± SD of normalized symbolic transfer entropy before propofol administration was 4.5 ± 0.8, and a decrease of more than 10% was observed after loss of consciousness.[7] In addition, the mean ± SD normalized symbolic transfer entropy value of feedforward connectivity before propofol administration was 3.1 ± 0.9, and it remained within 10% even after loss of consciousness.[7] To detect a decrease of more than 10% in feedback connectivity, 9 patients were included in the calculation using a one-sample test with 90% power at an alpha level of 0.05. Assuming that the feedforward connectivity would remain within 10% after the administration of remimazolam compared to before, the sample size for the equivalence test was calculated with 90% power at an alpha level of 0.05. In this case, 24 patients receiving remimazolam were included. To compare the connectivity of feedforward and feedback in the four segments of the induction 1 section and the induction 2 section with the baseline period within each hypnotic agent, we conducted a one-way repeated ANOVA followed by a *post hoc* Holm–Sidak test or Friedman repeated ANOVA by rank followed by a *post hoc* Tukey's test. The secondary endpoints included differences in the power spectrum, time to loss of consciousness, and Bispectral Index values during the anesthesia induction process between the two groups. To compare the temporal power of frequency between the two hypnotic agents, a permutation test with *t* statistic was conducted. To compare the power of frequency over time of the two hypnotic agents, a permutation test with *t* statistic was conducted.[7] For multiple hypothesis testing considering all powers of frequency, the q values were calculated to control the positive false discovery rate.[27] A q value (discovery rate–adjusted *P* value) of less than 0.05 was considered to indicate a statistically significant difference. Variability in topographic plots was quantified by the coefficient of variation, which was calculated as follows.

$$\text{Coefficient of variation } (\%) = \text{SD}/\text{mean} \times 100 \quad (5)$$

The time to loss of consciousness between the two hypnotics was compared using the Mann–Whitney rank-sum test. In the case of Bispectral Index, it was determined that there was no difference if it was within 6, which is 10% of 60, the reference point during general anesthesia. Before commencing the parent study, a pilot study was conducted on eight patients. According to the study on Bispectral Index smoothing time,[28] the mean ± SD Bispectral Index at approximately 12 s after loss of consciousness was 78.0 ± 9.1 in the propofol group and 79.7 ± 9.4 in the remimazolam group. Based on these parameters, a sample size of 26 patients in each group was calculated for the equivalence test. The power was set at 80% with an alpha level of 0.05. To compare the Bispectral Index value over time of the two hypnotic agents, we applied the same statistical methods used to evaluate feedforward/feedback connectivity.

To determine the effect size for the mean difference, Cohen's *d* was calculated using the formula below.[29]

$$\text{Cohens } d = \frac{\bar{X}_R - \bar{X}_P}{SD_{\text{pooled}}} \quad (6)$$

where $\bar{X}_R$ and $\bar{X}_P$ refer to the mean of remimazolam and propofol at each secondary endpoint, and SD_{pooled} refers to the pooled SD.

Statistical analysis was conducted using SigmaStat software version 3.5 for Windows (Systat Software, Inc., USA) or R (version 4.3.0, R Foundation for Statistical Computing, Austria). The data are expressed as mean ± SD for normally distributed continuous variables, median (25 to 75%) for non-normally distributed continuous variables, and n (%) for categorical variables. Patient characteristics between two groups were compared using the two-sample *t* test, Mann–Whitney rank-sum test, or chi-square test as appropriate. A *P* value less than 0.05 was considered to indicate a statistically significant difference.

Results

First, the EEG data of 70 patients (35 patients in each group) were screened. Of these, data points from 18 patients (9 patients in each group) were excluded from the analysis due to excessive noise, and data from a total of 52 patients (n = 26 for remimazolam and n = 26 for propofol) were included in the analysis. Power spectrograms of 18 patients who were excluded from the analysis are shown in Supplemental Digital Content S1 (https://links.lww.com/ALN/D442). The physical characteristics of the patients included in the analysis are presented in table 1. The time required to reach loss of consciousness after the administration of propofol or remimazolam was significantly longer in the propofol group (95% CI for the difference between the two groups: 0.233 to 2.617 min, *P* = 0.013, Cohen's *d* = 1.05), which can be interpreted as a result of differences in the method of drug administration. The dynamics of the EEG spectrogram during the study period are shown in figure 1. In the remimazolam group, alpha and delta oscillations were observed during the induction of anesthesia. There were no significant differences in the power of each frequency over time between the two hypnotic agents (minimum q value = 0.4235) including the baseline period. Zero was included in all 95% CI (607,404) of differences in the power of each frequency over time using the Bonferroni correction. Among the total of 607,404, there were 8,228 (1.35%) with an effect size greater than 0.8. Topographic electroencephalographic maps displaying the spectral power of each frequency band are presented in figure 2. The topographic map shows an anteriorization of the alpha band after the loss of consciousness in both hypnotic agents. The mean powers and coefficients of variation of the alpha band, as depicted in the topographic plots, are presented in the Supplemental Digital Content S2 (https://links.lww.com/ALN/D443). Changes in normalized symbolic transfer entropy in feedback/feedforward connectivity, according to each frequency band, during anesthesia induction after the administration of remimazolam or propofol, are shown in figure 3. In all frequency ranges except the gamma band, the decrease in feedback connectivity was greater than the decrease in feedforward connectivity after the loss of consciousness compared to the baseline (Supplemental Digital Content S3, https://links.lww.com/ALN/D444). For feedback connectivity in the alpha band, remimazolam showed a decrease of approximately 16% in the induction 1 section compared to baseline (95% CI for the difference between A3 and baseline: −0.036 to −0.011; *P* < 0.001, 95% CI for the difference between A4 and baseline: −0.063 to −0.035; *P* < 0.001). Propofol also showed a decrease of approximately 28% (95% CI for the difference between A2 and baseline, −0.051 to −0.022 [*P* < 0.001]; 95% CI for the difference between A3 and baseline, −0.056 to −0.032 [*P* < 0.001]; and 95% CI for the difference between A4 and baseline, −0.068 to −0.042 [*P* < 0.001]). Significant differences were observed in the induction 2 section for each drug. In the feedforward connectivity of the alpha band, remimazolam and propofol exhibited a decrease of 12% and 20%, respectively, in the induction 1 section compared to the baseline. The asymmetries between the feedback and feedforward connectivity in each frequency band are depicted in figure 4. After the loss of consciousness, a disruption of asymmetry was observed with both hypnotic agents. However, in the gamma band, no disruption of asymmetry

Table 1. Patient Characteristics and Variables Related to EEG Measurement

Characteristic	Remimazolam (n = 26)	Propofol (n = 26)	*P* Value
Male/female	15/11	20/6	0.237
Age, yr	72.5 (69–76)	70 (66–72)	0.060
Height, cm	159.0 ± 9.5	162.3 ± 9.1	0.190
Weight, kg	60.5 ± 9.4	65.2 ± 10.5	0.095
ASA Physical Status, I/II/III	0/24/2	1/23/2	0.600
Time to loss of consciousness,* min	2.3 (2.0–2.5)	4.2 (2.0–5.2)	0.013
Time to EEG measurement at the PACU,† min	42.0 (39.5–44.5)	43.3 (38.5–49.3)	0.694

The data are expressed as mean ± SD, median (25 to 75%), or count. Patient characteristics were compared using the two-sample *t* test, Mann–Whitney rank sum test, or chi-squared test, as appropriate.

*The time to loss of consciousness was determined by the absence of response to verbal command ("open your eyes") after initiating remimazolam or propofol infusion. †The time to EEG measurement at the PACU is the interval from the time the patient arrived at the recovery room to the start of EEG measurement.

ASA, American Society of Anesthesiologists; EEG, electroencephalogram; PACU, postanesthesia care unit.

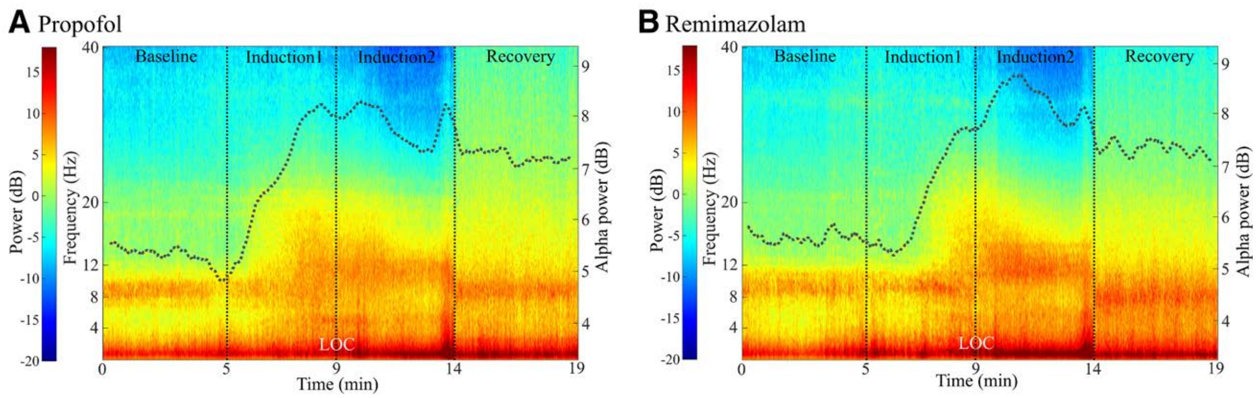

Fig. 1. Dynamics of the mean electroencephalographic spectrogram during the induction period and recovery period in elderly patients receiving propofol (*A*) or remimazolam (*B*). A group-level absolute power spectrogram was presented using a 0.1- to 40-Hz bandpass filter. The mean power of the alpha band (7 to 12 Hz) is represented by the *black dotted line*. The baseline shows the level before the administration of remimazolam or propofol, induction 1 shows the level until the loss of consciousness after administration of propofol or remimazolam, induction 2 shows the level until 5 min after loss of consciousness, and recovery shows the level until at least 30 min after the end of surgery. To effectively compare the electroencephalogram (EEG) characteristics during the anesthesia induction by the two hypnotic agents, the time spans of the induction 1 section were rescaled to the average time of loss of consciousness of propofol, which resulted in the timelines of the induction 1 section for both hypnotic agents becoming the same.

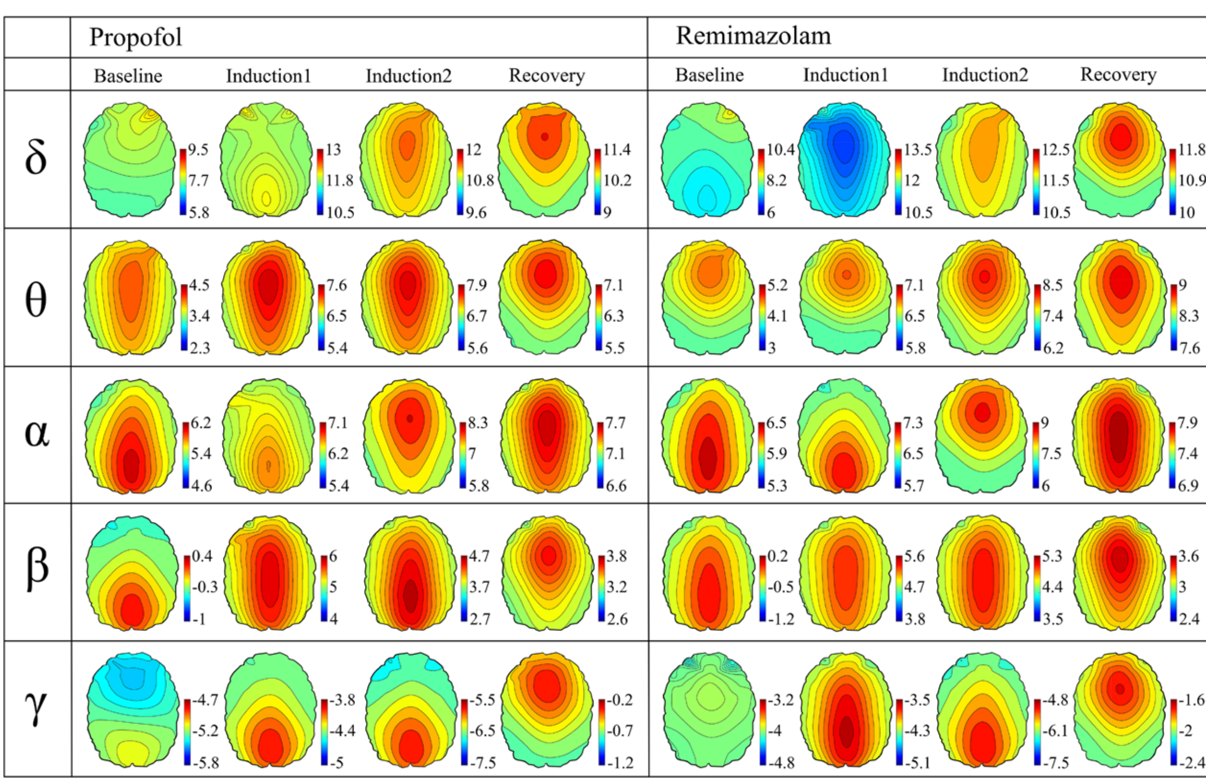

Fig. 2. Topographic electroencephalographic maps of the spectral power of each frequency band for propofol and remimazolam. Delta (δ) was 0.1 to 4 Hz, theta (θ) was 4 to 7 Hz, alpha (α) was 7 to 12 Hz, beta (β) was 12 to 20 Hz, and gamma (γ) was 20 to 40 Hz. Group-level spatial distributions are shown as topographic maps. The unit of power is dB. The baseline shows the level before the administration of remimazolam or propofol, induction 1 shows the level until the loss of consciousness after administration of propofol or remimazolam, induction 2 shows the level 5 min after loss of consciousness, and recovery shows the level until at least 30 min after the end of surgery.

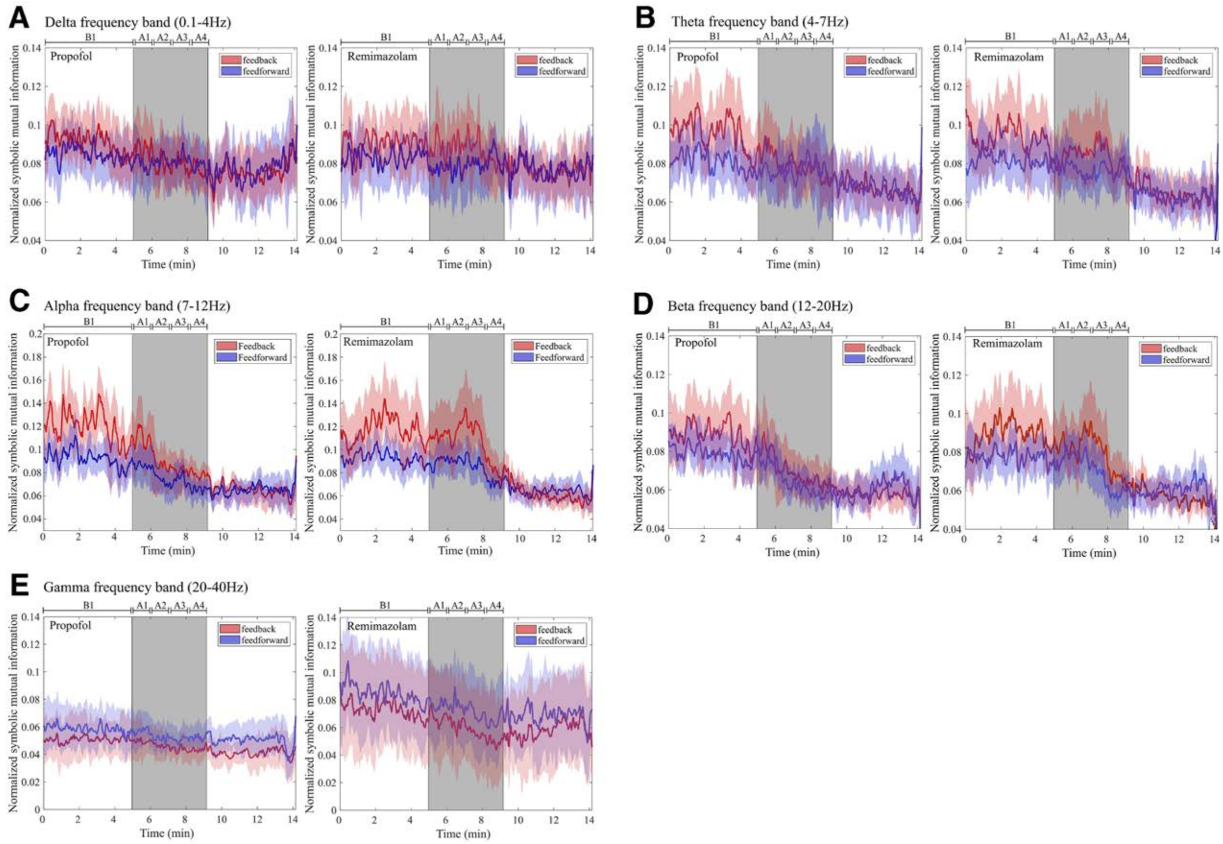

Fig. 3. Feedback and feedforward connectivity between the frontal and parietal regions in each frequency band. The *red* and *blue solid lines* represent the means of feedback connectivity and feedforward connectivity, respectively. The areas shaded with *red* and *blue* represent the standard deviations of the normalized symbolic transfer entropy values of the feedback and feedforward connectivity, respectively. (*A*) Delta. (*B*) Theta. (*C*) Alpha. (*D*) Beta. (*E*) Gamma. The *B1 sections* show the baseline levels (before the administration of remimazolam or propofol). The gray area indicates the induction 1 section (until the loss of consciousness after the administration of propofol or remimazolam). To effectively compare the electroencephalographic characteristics during the anesthesia induction by the two hypnotic agents, the time spans of the induction 1 section were rescaled to the average time of loss of consciousness of propofol, which resulted in the timelines of induction 1 section for both hypnotic agents becoming the same. To statistically distinguish when the change in values of normalized symbolic transfer entropy, the induction 1 section was divided into four equal segments, labeled *A1*, *A2*, *A3*, and *A4*.

was observed, and feedforward connectivity was always dominant, so the value of normalized symbolic transfer entropy was always negative. In the induction 1 section, the asymmetry of remimazolam temporarily increased, but the difference was not statistically significant in the alpha band (A1 *vs.* A2: $P = 0.226$, A1 *vs.* A3: $P = 0.991$). It is observed that both drugs have values close to 0 at the time of loss of consciousness and remain less than 0 after loss of consciousness. The changes in Bispectral Index values observed during the EEG measurement process are presented in figure 5. The two groups were compared at a total of 190 time points during the period of EEG measurement, including the baseline. The mean ± SD of the absolute difference in Bispectral Index values at each time point between the two groups was 3.5 ± 2.2. No statistically significant differences were observed between the two groups at any time point. Among the total of 190 time points, there were 3 (1.58%) that had an effect size greater than 0.8.

Discussion

In this study, we found that the EEG features observed during the induction of anesthesia with remimazolam were generally similar to those of propofol. Before remimazolam or propofol were administered, the feedback connectivity in the alpha band was superior to the feedforward connectivity, indicating an asymmetry between the two types of connectivity. After inducing loss of consciousness through the administration of these hypnotic agents, there was a greater decrease in feedback connectivity compared to feedforward connectivity, which led to the disruption of asymmetry.

In the propofol group, the time required to reach loss of consciousness was significantly longer because

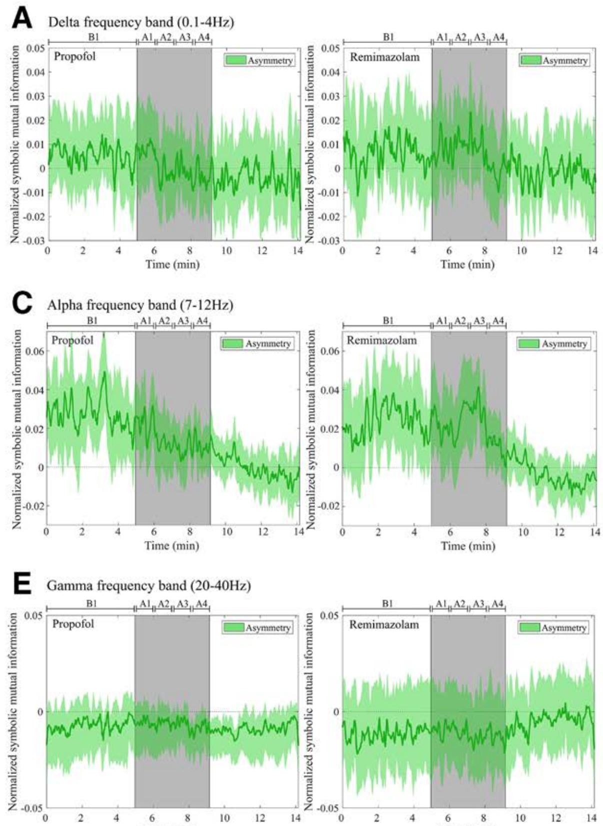

Fig. 4. Asymmetry between the feedback and feedforward connectivity in elderly patients receiving propofol or remimazolam. The *green solid line* in each figure represents the mean. The *green-shaded areas* represent the standard deviations of the normalized symbolic transfer entropy values, which indicate the asymmetry between the feedback and feedforward connections. (*A*) Delta. (*B*) Theta. (*C*) Alpha. (*D*) Beta. (*E*) Gamma. The *B1 sections* show the baseline levels (before the administration of remimazolam or propofol). The *gray areas* indicate the induction 1 section (until the loss of consciousness after the administration of propofol or remimazolam). To effectively compare the electroencephalographic characteristics during the anesthesia induction by the two hypnotic agents, the time spans of the induction 1 section were rescaled to the average time of loss of consciousness of propofol, which resulted in the timelines of the induction 1 section for both hypnotic agents becoming the same. To statistically distinguish when the change in values of normalized symbolic transfer entropy, the induction 1 section was divided into four equal segments, labeled *A1*, *A2*, *A3*, and *A4*.

propofol was administered using the target effect-site concentration-controlled infusion method. If administered as a bolus injection, such as 2 mg/kg, the time to loss of consciousness would be faster than that of the remimazolam group. Since this study was conducted as a substudy of the main study to evaluate the quality of the recovery process including the incidence of postoperative delirium of propofol and remimazolam, the two hypnotic agents were administered separately according to the method used in the clinical field. In Korea, it is common to administer propofol using the target effect-site concentration-controlled infusion method instead of zero-order infusion. A pharmacokinetic model for target-controlled infusion of remimazolam has been developed,[30] but it has not yet been integrated into a commercially available target-controlled infusion pump. Therefore, the administration of remimazolam in this study was according to the regimen approved by the Korean Ministry of Food and Drug Safety.

In the case of remimazolam, alpha oscillation became remarkable after the loss of consciousness, whereas in the case of propofol, it was observed before the loss of consciousness. This is most likely because the time to loss of consciousness could not be accurately measured due to the large variation in the time to reach loss of consciousness after propofol administration. Time to loss of consciousness could have been assessed more accurately if the time interval were shorter than 30 s. Anteriorization is a characteristic of EEG that can be observed after propofol administration, which refers to a spatial shift in power from posterior regions to frontal regions.[31] Anteriorization can be understood as a result of the differential effect of hypnotic agents on thalamic nuclei with different spatial projections.[32] Increased GABAergic inhibition in thalamocortical networks may result in persistent and

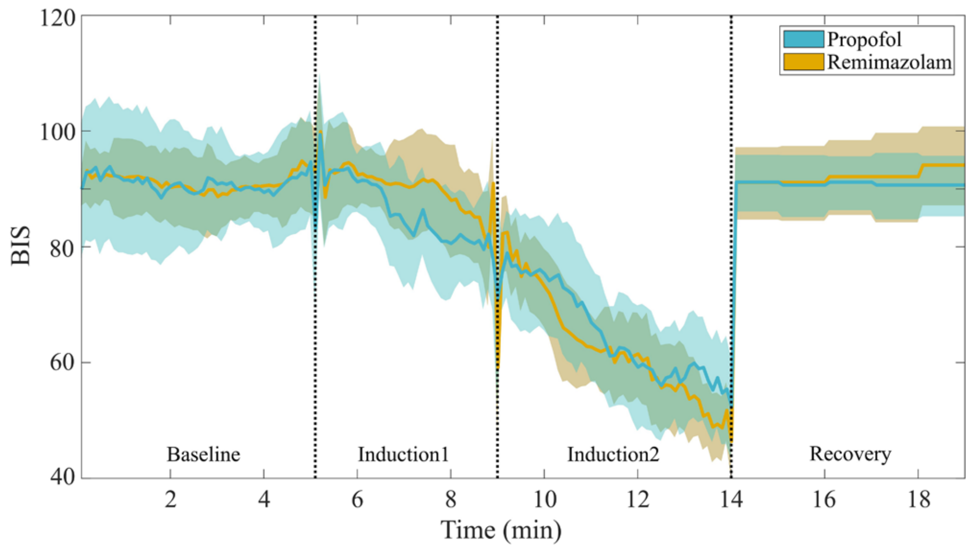

Fig. 5. Changes in Bispectral Index (BIS) during anesthesia induction and recovery in elderly patients anesthetized with propofol or remimazolam. The *solid blue* and *orange lines* represent the mean Bispectral Index values of propofol and remimazolam. The *shaded areas* represent the SD of the Bispectral Index of patients assigned to each group. The baseline shows the level before the administration of remimazolam or propofol, induction 1 shows the level until the loss of consciousness after administration of propofol or remimazolam, induction 2 shows the level 5 min after loss of consciousness, and recovery shows the level at least 30 min after the end of surgery. To effectively compare the electroencephalographic characteristics during the anesthesia induction by the two hypnotic agents, the time spans of induction 1 section were rescaled to the average time of loss of consciousness of propofol, which resulted in the timelines of the induction 1 section for both hypnotic agents becoming the same.

synchronized alpha activities in the frontal cortex, which can impair the ability to respond to external stimuli, ultimately leading to a loss of consciousness.[33] Because remimazolam also acts on $GABA_A$ receptors, anteriorization may be also observed in the topographic maps in figure 2. Topographic maps in each frequency domain with the same power scale are also presented in Supplemental Digital Content S4 (https://links.lww.com/ALN/D445).

The alpha band has distinct characteristics compared to other frequency bands. The alpha rhythms are believed to filter out irrelevant sensory inputs, enhance attentional focus, and facilitate efficient top-down control and the transmission of pertinent information.[34,35] They may also contribute to the coordination and synchronization of neural activities across different brain regions, facilitating effective information transfer and cognitive processing.[36] In fact, in a previous study, the degree of change in the level of consciousness after the administration of propofol or dexmedetomidine was evaluated by examining the alteration in alpha band frontal connectivity.[37] In addition to this study, many other studies obtained significant results by analyzing the alpha frequency band.[38,39]

In this study, the inhibition of feedback connectivity was more pronounced than feedforward in remimazolam as well. Compared to a previous study,[7] feedforward connectivity decreased slightly from baseline, and values of normalized symbolic transfer entropy quantifying asymmetry decreased overall. The reason for these phenomena is likely the difference in age. In the previous study, the average age of the propofol group was 50 yr, and younger patients than in this study were included in the analysis. As age increases, there are several changes observed in the alpha band power and variability—the alpha peak shifts to a lower frequency, and the Lempel–Ziv complexity of the alpha wave decreases.[20,40,41] These changes with increasing age lead to a decrease in the absolute amount of information contained in the EEG signal, and as a result, the amount of information transmitted to feedback/feedforward connectivity inevitably decreases. For this reason, as the feedback/feedforward values decrease together, the asymmetry value, which is the relative difference divided by the sum of feedback/feedforward connectivity, also appears to decrease. Despite thoroughly reviewing the existing literature, we were unable to provide a clear explanation for the reversal of feedback/feedforward connectivity specifically in the gamma band. In the topographic map of the gamma band, the persistence of high posterior power even after loss of consciousness may provide a clue. However, in our study the same phenomenon was observed in the gamma band for both hypnotic agents; this finding suggests that the electroencephalographic features of the two drugs are similar.

If burst suppression occurs, the analysis of feedback/feedforward connectivity may be affected. Burst suppression is defined as an EEG finding consisting of a continuous alternation between high-voltage slow waves (bursts) and periods of depressed electrical activity.[42] Fortunately, burst suppression was not observed in the EEG data of the patients included in the analysis. It may be assumed that the neuronal activity in the brain was not significantly suppressed because remimazolam or propofol was administered using a zero-order infusion or target-controlled infusion method rather than a bolus method. Although the Bispectral Index is widely used in clinical practice as a surrogate measure for the central nervous system effects of various hypnotic agents, there is a lack of research on whether it accurately represents the effect of remimazolam.[43] The development of the Bispectral Index algorithm did not include remimazolam EEG data,[44] and a previous study found that the Bispectral Index was not a reliable predictor for patients sedated with midazolam.[45] However, in this study, when remimazolam was administered for anesthesia induction, the changes in Bispectral Index values before and after the loss of consciousness were similar to those observed with propofol, suggesting that the Bispectral Index can be used to titrate remimazolam during general anesthesia. However, if remimazolam is used for sedation, further research is needed to investigate the correlation between remimazolam concentration and Bispectral Index value.

There are limitations in this study that need to be considered. First, it is difficult to rule out the possibility that remifentanil administered after hypnotic-induced loss of consciousness affected the EEG. However, the dose of remifentanil in our study was much lower than the doses known to have a direct effect on the EEG.[46] Second, because EEG was not measured during the emergence period, it was not confirmed whether the reduced feedback connectivity had returned to baseline. When patients wake up from anesthesia, they often make many unintentional movements, making it difficult to obtain a clean EEG signal without noise. Because the parent study of this substudy was not designed to measure EEG, EEG during the emergence period was not measured. Third, due to limitations in our ability to control the EEG quality in this study, we utilized three EEG indices that are appropriate for the current EEG data: power spectrum and its topography (conventional), feedback/feedforward connectivity (most thoroughly tested), and Bispectral Index (commercialized). We assumed that these limited but commonly used EEG indices would be sufficient to capture the similarity in the effects of the two hypnotic anesthetics on EEG at different levels of consciousness.

In conclusion, the EEG features observed during anesthesia induction induced by remimazolam were similar to those of propofol. Disruption of frontal–parietal connectivity in the alpha band, a common metric for general anesthesia, was also observed with remimazolam and propofol.

Acknowledgments

The authors thank Joon Seo Lim, Ph.D., from the Scientific Publications Team at Asan Medical Center (Seoul, Republic of Korea) for editorial assistance in preparing this article.

Research Support

Supported by Hana Pharmaceutical, Co., Ltd., Seoul, Korea, which had no role in the study design, data analysis, data interpretation, or writing of the article. This work was also supported by the Convergent Technology R&D Program for Human Augmentation through grant No. 2020M3C1B8081319 (to Dr. Min), which is funded by the Korean government through the National Research Foundation (Seoul, Korea). This work was also supported by Institute for Basic Science (Seoul, Korea) grant No. IBS-R015-Y3.

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: byungmoonchoi7@gmail.com. Raw data available at: byungmoonchoi7@gmail.com.

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Supplemental Digital Content

Supplemental Digital Content S1. Spectrograms of patients excluded from analysis, https://links.lww.com/ALN/D442

Supplemental Digital Content S2. Powers and coefficients of variation in topograms, https://links.lww.com/ALN/D443

Supplemental Digital Content S3. Values of normalized symbolic transfer entropy, https://links.lww.com/ALN/D444

Supplemental Digital Content S4. Topographic maps with same power scale, https://links.lww.com/ALN/D445

References

1. Kim KM: Remimazolam: Pharmacological characteristics and clinical applications in anesthesiology. Anesth Pain Med (Seoul) 2022; 17:1–11
2. Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H, Sakamoto A: Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA class III): Results of a multicenter, randomized, double-blind, parallel-group comparative trial. J Anesth 2020; 34:491–501
3. Liu T, Lai T, Chen J, et al.: Effect of remimazolam induction on hemodynamics in patients undergoing valve replacement surgery: A randomized, double-blind, controlled trial. Pharmacol Res Perspect 2021; 9:e00851

4. Wu X, Wang C, Gao H, et al.: Comparison of remimazolam and propofol about safety outcome indicators during general anesthesia in surgical patients: A systematic review and meta-analysis. Minerva Anestesiol 2023; 89:553–64
5. Imas OA, Ropella KM, Ward BD, Wood JD, Hudetz AG: Volatile anesthetics disrupt frontal–posterior recurrent information transfer at gamma frequencies in rat. Neurosci Lett 2005; 387:145–50
6. Lee U, Kim S, Noh GJ, Choi BM, Hwang E, Mashour GA: The directionality and functional organization of frontoparietal connectivity during consciousness and anesthesia in humans. Conscious Cogn 2009; 18:1069–78
7. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA: Disruption of frontal–parietal communication by ketamine, propofol, and sevoflurane. Anesthesiology 2013; 118:1264–75
8. Jordan D, Ilg R, Riedl V, et al.: Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. Anesthesiology 2013; 119:1031–42
9. Sarasso S, Casali AG, Casarotto S, Rosanova M, Sinigaglia C, Massimini M: Consciousness and complexity: A consilience of evidence. Neurosci Consciousness 2021; niab023
10. Seth AK, Dienes Z, Cleeremans A, Overgaard M, Pessoa L: Measuring consciousness: Relating behavioural and neurophysiological approaches. Trends Cogn Sci 2008; 12:314–21
11. Pal D, Silverstein BH, Lee H, Mashour GA: Neural correlates of wakefulness, sleep, and general anesthesia: An experimental study in rat. Anesthesiology 2016; 125:929–42
12. Liu X, Lauer KK, Ward BD, Rao SM, Li SJ, Hudetz AG: Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory. Hum Brain Mapp 2012; 33:2487–98
13. Ferrarelli F, Massimini M, Sarasso S, et al.: Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. Proc Natl Acad Sci U S A 2010; 107:2681–6
14. Casey CP, Tanabe S, Farahbakhsh ZZ, et al.: Evaluation of putative signatures of consciousness using specific definitions of responsiveness, connectedness, and consciousness. Br J Anaesth 2023; 132:300–11
15. Schnider TW, Minto CF, Gambus PL, et al.: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998; 88:1170–82
16. Schnider TW, Minto CF, Shafer SL, et al.: The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90:1502–16
17. Minto CF, Schnider TW, Egan TD, et al.: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997; 86:10–23
18. Park JH, Choi SM, Park JH, et al.: Population pharmacokinetic analysis of propofol in underweight patients under general anaesthesia. Br J Anaesth 2018; 121:559–66
19. Delorme A, Makeig S: EEGLAB: Una caja de herramientas de código abierto para el análisis de la dinámica de EEG de un solo ensayo, incluido el análisis de componentes independientes. J Neurosci Methods 2004; 134:9–21
20. Purdon PL, Pavone KJ, Akeju O, et al.: The ageing brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br J Anaesth 2015; 115(Suppl 1):i46–57
21. Li D, Puglia MP, Lapointe AP, et al.: Age-related changes in cortical connectivity during surgical anesthesia. Front Aging Neurosci 2019; 11:371
22. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA: Disruption of frontal–parietal communication by ketamine, propofol, and sevoflurane. Anesthesiology 2013; 118:1264–75
23. Ku SW, Lee U, Noh GJ, Jun IG, Mashour GA: Preferential inhibition of frontal-to-parietal feedback connectivity is a neurophysiologic correlate of general anesthesia in surgical patients. PLoS One 2011; 6:e25155
24. Blain-Moraes S, Mashour GA, Lee H, Huggins JE, Lee U: Altered cortical communication in amyotrophic lateral sclerosis. Neurosci Lett 2013; 543:172–6
25. Schreiber T: Measuring information transfer. Phys Rev Lett 2000; 85:461–4
26. Staniek M, Lehnertz K: Symbolic transfer entropy. Phys Rev Lett 2008; 100:158101
27. Storey JD: The positive false discovery rate: A Bayesian interpretation and the q-value. Ann Stat 2003; 31:2013–35
28. Soehle M, Ellerkmann RK, Grube M, et al.: Comparison between Bispectral Index and patient state index as measures of the electroencephalographic effects of sevoflurane. Anesthesiology 2008; 109:799–805
29. Lee DK: Alternatives to P value: Confidence interval and effect size. Korean J Anesthesiol 2016; 69:555–62
30. Schuttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H: Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: Part I. Pharmacokinetics and clinical pharmacodynamics. Anesthesiology 2020; 132:636–51
31. Purdon PL, Sampson A, Pavone KJ, Brown EN: Clinical electroencephalography for anesthesiologists: Part I: Background and basic signatures. Anesthesiology 2015; 123:937–60

32. Vijayan S, Ching S, Purdon PL, Brown EN, Kopell NJ: Thalamocortical mechanisms for the anteriorization of alpha rhythms during propofol-induced unconsciousness. J Neurosci 2013; 33:11070–5
33. Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ: Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness. Proc Natl Acad Sci U S A 2010; 107:22665–70
34. Klimesch W: Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 2012; 16:606–17
35. Halgren M, Ulbert I, Bastuji H, et al.: The generation and propagation of the human alpha rhythm. Proc Natl Acad Sci U S A 2019; 116:23772–82
36. Alamia A, VanRullen R: Alpha oscillations and traveling waves: Signatures of predictive coding? PLoS Biol 2019; 17:e3000487
37. Kallionpaa RE, Valli K, Scheinin A, et al.: Alpha band frontal connectivity is a state-specific electroencephalographic correlate of unresponsiveness during exposure to dexmedetomidine and propofol. Br J Anaesth 2020; 125:518–28
38. Duclos C, Nadin D, Mahdid Y, et al.: Brain network motifs are markers of loss and recovery of consciousness. Sci Rep 2021; 11:3892
39. Kim H, Hudetz AG, Lee J, Mashour GA, Lee U, Re CSG: Estimating the integrated information measure phi from high-density electroencephalography during states of consciousness in humans. Front Hum Neurosci 2018; 12:42
40. Kumral D, Sansal F, Cesnaite E, et al.: BOLD and EEG signal variability at rest differently relate to aging in the human brain. Neuroimage 2020; 207:116373
41. Biggs D, Boncompte G, Pedemonte JC, Fuentes C, Cortinez LI: The effect of age on electroencephalogram measures of anesthesia hypnosis: A comparison of BIS, alpha power, Lempel–Ziv complexity and permutation entropy during propofol induction. Front Aging Neurosci 2022; 14:910886
42. Phabphal K, Chisurajinda S, Somboon T, Unwongse K, Geater A: Does burst-suppression achieve seizure control in refractory status epilepticus? BMC Neurol 2018; 18:46
43. Zhao TY, Chen D, Xu ZX, Wang HL, Sun H: Comparison of Bispectral Index and patient state index as measures of sedation depth during surgeries using remimazolam tosilate. BMC Anesthesiol 2023; 23:208
44. Rampil IJ: A primer for EEG signal processing in anesthesia. Anesthesiology 1998; 89:980–1002
45. Sackey PV, Radell PJ, Granath F, Martling CR: Bispectral Index as a predictor of sedation depth during isoflurane or midazolam sedation in ICU patients. Anaesth Intensive Care 2007; 35:348–56
46. Noh GJ, Kim KM, Jeong YB, et al.: Electroencephalographic approximate entropy changes in healthy volunteers during remifentanil infusion. Anesthesiology 2006; 104:921–32