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Effect of low-dose volatile anesthetics on intraoperative neurophysiological monitoring during anesthesia with remimazolam

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Background: Remimazolam is a novel short-acting benzodiazepine. We investigated the effects of low doses of volatile anesthetic agents on motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) during remimazolam-remifentanil anesthesia.
Methods: Thirty-nine patients undergoing cervical spine surgery were randomly assigned to either the sevoflurane (n = 20) or desflurane (n = 19) groups. Volatile anesthetic agents were administered at 0.3, 0.6, and 0.8 minimum alveolar concentrations (MACs) during remimazolam-remifentanil anesthesia. Significant changes were considered as more than 50% amplitude suppression and more than 10% latency increase from baseline values. The primary outcome was MEP amplitude change. Secondary outcomes included MEP latency, SSEP amplitude and latency, and group comparisons.
Results: The MEP amplitudes were slightly reduced at 0.3 MAC; however, a suppression of more than 50% from baseline values at 0.3 MAC, particularly in the upper limbs, was observed in a notable proportion of participants; 30.0% and 47.4% in the sevoflurane and desflurane groups, respectively. The corresponding percentages for the lower limbs were 15.0% and 15.8%, respectively. MEP amplitude suppression was more than 50% in the majority of participants at 0.6 and 0.8 MAC. No significant difference was observed between the groups. SSEPs exhibited no significant amplitude suppression or latency prolongation across all MAC levels.
Conclusions: Notable MEP amplitude suppression was observed in many patients when 0.3 MAC volatile anesthetics were used as adjuncts. Therefore, even low doses of volatile anesthetics must be added cautiously to remimazolam-based anesthesia to prevent confounding. The SSEPs were relatively preserved, regardless of MAC.

Keywords: Cervical vertebrae; Desflurane; Evoked potentials; Intraoperative neurophysiological monitoring; Remimazolam; Sevoflurane.

Introduction

Intraoperative neurophysiological monitoring (IONM) is conducted during neuro, spinal, and spinal cord surgery to preserve neurological function and prevent the incidence of postoperative neurological deficits and iatrogenic damage [1]. The most commonly used modalities in IONM include somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs), and electromyography [2].

General anesthetic agents that inhibit neurotransmission exert a significant effect on the evoked potential (EP). Volatile anesthetic agents suppress EP in a dose-dependent

manner [3]. Low concentrations (0.5–1.0 minimum alveolar concentration [MAC]) of volatile anesthetic agents have been used successfully for monitoring SSEPs [3,4]. However, MEP monitoring is more sensitive to general anesthetic agents, and lower concentrations (up to 0.5–0.6 MAC) of volatile anesthetic agents are considered suitable for effective monitoring [5]. Thus, the use of propofol-opioid infusion is preferred because its depressive effect on IONM is less pronounced than that of volatile anesthetic agents [5]. Nevertheless, concerns regarding hemodynamic instability and the dose-dependent suppression of MEPs following propofol infusion persist [6]. These limitations have led to increasing research on combining intravenous (IV) anesthetic agents with volatile anesthetic agents [7–10] or other agents, such as dexmedetomidine [11] and lidocaine [12], as anesthetic adjuvants. Anesthesiologists aim to mitigate undesirable effects and achieve synergistic effects through such combinations.

Remimazolam, a novel ultrashort-acting benzodiazepine, exhibits a high clearance rate, a small volume of distribution, and rapid recovery [13]. Furthermore, it provides greater hemodynamic stability, thereby facilitating its use as an alternative to propofol for the induction and maintenance of general anesthesia [13,14]. Remimazolam has been reported to allow adequate monitoring of both SSEPs and MEPs [15–17]. A recent prospective study compared the effects of total IV anesthesia using remimazolam and propofol on IONM [18], finding results comparable to those with propofol. However, data on the interaction between IONM and the combination of remimazolam with volatile anesthetic agents are scarce.

Commonly used volatile anesthetic agents, such as sevoflurane and desflurane, suppress MEP amplitude in a dose-dependent manner; however, discrepancies between these agents have been reported [9,10]. Therefore, we aimed to evaluate the effects of the addition of volatile anesthetic agents during remimazolam-remifentanil anesthesia under concurrent MEP-SSEP monitoring. The changes in MEP amplitude with the increase in the dose of volatile anesthetic agents were assessed. Furthermore, we compared IONM responses between sevoflurane and desflurane.

Materials and Methods

This double-blinded, parallel-group, randomized controlled trial was conducted at a tertiary educational hospital in South Korea between January 2023 and December 2023. The study protocol was approved by the Asan Medical Center Institutional Review Board (Approval number: 2022-0725) and was registered at the Clinical Research Information Service (https://cris.nih.go.kr/: KCT0007534) in South Korea before patient enrollment. The study protocol adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the principles of the Declaration of Helsinki of 2013. Written informed consent was obtained from all patients before inclusion.

Study population and design

Patients aged 20–79 years with an American Society of Anesthesiologists physical status of grade I–III who underwent elective cervical spine surgery at our institution and received IONM were eligible for inclusion in the study. The exclusion criteria were as follows: tolerance or hypersensitivity to benzodiazepines, dependence or addiction to psychotropic drugs or alcohol, history of brain-related neurosurgery, presence of an intracranial device or pacemaker, pregnant and lactating women, history of acute narrow-angle glaucoma, moderate hypersensitivity to dextran 40, history or susceptibility to malignant hyperthermia, and history of hypersensitivity to halogenated inhalational agents.

An internet-based randomization program (sealedenvelope.com) was used to create a randomization list with an un-stratified block size of four. Patients were assigned to the desflurane (n = 20) and sevoflurane (n = 20) groups at a 1:1 ratio. Data collection and interventions were performed by the first investigator (W.K.). The first investigator received the enrollment data and a random number from the second investigator (H.S.P.) on the day of the surgery. The neurologist, trained technologists, and all patients were blinded to the type of volatile anesthetic agents and the inspiratory concentration used during data collection and analysis.

The baseline values were obtained before commencing the administration of each inhalational agent (Baseline, Fig. 1) after completing the main procedure with IV anesthesia using remimazolam and remifentanil. Age-adjusted MAC was applied in the present study. The first concentration (0.3 MAC) of the volatile anesthetic agent was introduced and the MAC was increased from 0.6 to 0.8 in an incremental manner. A five-minute steady-state was maintained at each time point before the IONM data were obtained. After each recording, each volatile anesthetic was washed out using a fresh gas flow over 8 L/min. Washout was considered in this study when the end-tidal concentration of the volatile anesthetic approached 0.0%. Final MEPs and SSEPs data were then obtained (End).

Anesthesia protocol

Monitoring, including a noninvasive blood pressure monitor, pulse oximeter, three-lead electrocardiogram, and a SedLine® EEG-sensor (Masimo Corp.), was commenced on entering the

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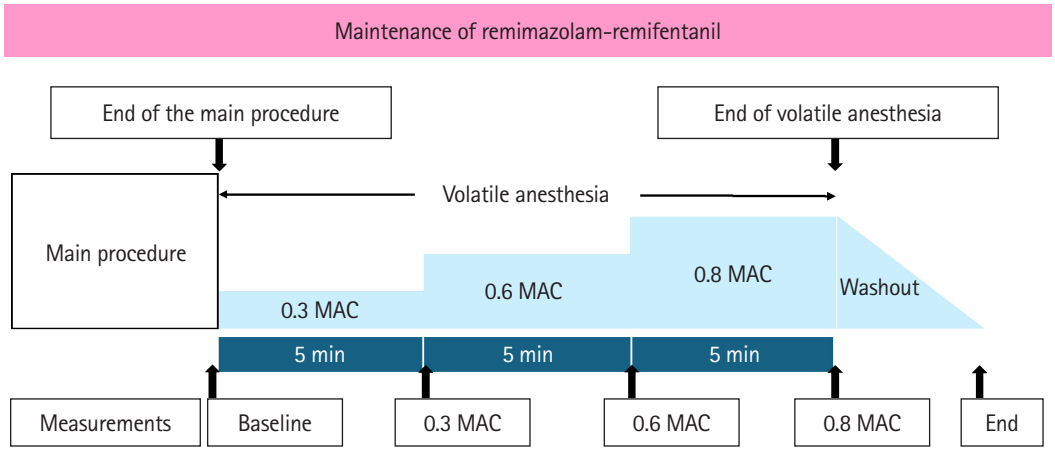

Fig. 1. Flow diagram of the intervention. MAC: minimum alveolar concentration.

operating room. The core body temperature was measured and maintained at 35.5°–37.0°C. Remimazolam (Byfavo Inj, Hana Pharm Co., Ltd.) was infused continuously at a rate of 6 mg/kg/h until the patient lost consciousness to induce general anesthesia. Remimazolam was infused continuously at a rate of 0.9–1.5 mg/kg/h at the discretion of the attending anesthesiologists and within the range of the approved maintenance dose [13]. Remifentanil was administered via target effect-site concentration-controlled infusion [19] and maintained at an effect-site concentration of 3–5 ng/ml. A bolus dose of rocuronium (0.6 mg/kg) was administered to facilitate endotracheal intubation. An arterial line catheter was inserted following intubation to monitor invasive arterial pressure. In addition, a bite block was inserted to protect the teeth and tongue during IONM. Additional doses of rocuronium were not administered during surgery. The administration of sugammadex at a dose of 2–4 mg/kg is permitted when the train-of-four (TOF) ratio is maintained at less than 0.8 after vertebral body exposure to achieve adequate electrical stimulation intensity for MEPs. Notably, this intervention was not required in any case in the present study. The study intervention was initiated when the surgeons started to close the surgical field after confirming the final IONM results (Fig. 1). A single IV bolus dose of flumazenil (0.2 mg) was administered after the surgery to reverse the effects of remimazolam.

IONM

Trained neurophysiological monitoring technologists at our institution performed IONM, under the supervision of neurologists. The IONM data were analyzed by a neurologist and the second investigator (H.S.P.). Neuromaster MEE-1000, MEE-2000 (Nihon Kohden), and CADWELL cascade (Cadwell Laboratories) were used to perform neurophysiological monitoring. Transcranial electrodes were used as stimulation electrodes at stimulation sites C3 (cathode) and C4 (anode) in accordance with the International 10–20 system [20]. The stimulus waveform was a constant current with a rectangular pulse of electrical stimulus intensity (100–500 V). The first EP stimulation was performed after the completion of general anesthesia induction and electrode placement to examine the electrode positions and assess the signal while under the influence of neuromuscular blocking agents. The stimulation was gradually increased upon exposure of the vertebral body and attaining a TOF of more than 0.8 until a reproducible MEP was elicited. Following determination, the individual stimulation intensity was maintained without alteration for the duration of the surgery. Transcranial MEPs were recorded from the abductor pollicis brevis (APB) and abductor hallucis longus (AHL) for the upper and lower limbs, respectively. All sites were monitored bilaterally. The parameters for MEP electrical stimulation were as follows: stimulus duration, 0.05–0.075 ms; interstimulus interval, 2.0 ms; trains of three to six stimuli; bandpass filter, 10–30 Hz and 2000–3000 Hz; and recording time, 100 ms. The MEPs were manually monitored at intervals of 5–15 min; in addition, monitoring was performed intermittently to prevent unwanted patient movement during surgery.

Cortical SSEP stimulations were elicited at the bilateral median nerve of the wrist and posterior tibial nerve of the internal malleolus. A single-pulse stimulation with a pulse duration of 0.1–0.5 ms, intensity of 10–30 mA, and frequency of 4.7 Hz was applied to elicit SSEP. The bandpass filter setting was maintained at 20–1000 Hz (high-cut, 2–3 kHz; low-cut, 10–30 Hz). SSEPs, monitored continuously by a computer or at intervals of 1–2 min throughout the procedures, were averages of 200–1000 sweeps. These stimulation conditions were maintained before and after changing the anesthetic agents.

The peak-to-peak amplitudes and onset latency were measured during the study intervention. A decrease of more than 50% in the amplitude or an increase of more than 10% in latency was defined as an alarm sign in this study [5,8].

Outcome variables

The primary outcome of this study was the change in MEP amplitude in response to increasing concentrations of inhalational agents during the background infusion of remimazolam-remifentanil. At each MAC, we calculated the percentage change in amplitude relative to the baseline measurement obtained before the administration of inhalational agents (Baseline). The secondary outcome measures included the changes in the latency of MEPs and the amplitude and latency of SSEPs, as well as comparison between the sevoflurane and desflurane groups in terms of these variables.

Sample size and statistical analysis

A previous study revealed that desflurane at a MAC of 0.5 achieved a MEP amplitude suppression of 1 039.22 μV to 607.4 μV, with a standard deviation of 701.0 μV [9]. Thus, assuming a power of 0.8 and an alpha level of 0.1, at least 17 participants were required to observe a statistically significant change in the amplitude from the baseline value. Twenty participants were evenly allocated between the two groups to account for a dropout rate of 20%, thereby facilitating exploratory intergroup comparisons.

The Shapiro–Wilk test was used to assess the distribution of continuous variables. Student's t-test or the Mann–Whitney *U* test was used as appropriate to compare continuous variables between the groups. Chi-square test or Fisher's exact test was used as appropriate to compare categorical variables between the groups. Data are presented as mean ± standard deviation (MD), median (Q1, Q3), or n (%). The effects of inhalational agents repeatedly measured over time were analyzed using the linear mixed-effects model as it accounts for repeated measures, missing data, and unequal sample sizes (sevoflurane group = 20, desflurane group = 19). The patients were designated as random effects while modeling the data to account for inter-individual differences. Unstructured covariance was used to maintain flexibility in the relationships between repeated measurements. The concentration of the inhalational agent (MAC) and anesthesia grouping (including the interaction term) were defined as the fixed effects [21]. Quantitative analysis was performed to analyze the percentages of differences in amplitude and latency values from the baseline values. The compared data are presented as the least square means (LSMs) ± standard error (SE). LSMs account for group and time imbalances, as well as missing data; thus, it varies from raw means. This approach facilitated valid intergroup comparisons of the outcomes, as well as comparison between the outcomes at specific time points (the concentration of the inhalational agent), even with missing observational data. Pairwise comparisons of the LSMs were conducted to assess the intra-group and inter-group differences at each time point (MAC). Statistical significance was set at $P = 0.05$ for all comparisons.

Results

Among the 40 participants enrolled, one participant withdrew from the study. Thus, the final analysis included 39 participants (Fig. 2). No significant differences were observed between the two groups in terms of the baseline demographic or clinical characteristics (Table 1). IONM was completed without adverse events in all cases. No postoperative neurological deficits were observed in any of the participants.

Changes in MEP amplitudes in response to increment MAC

The percentage change in the amplitude at 0.3 MAC revealed a slight reduction in both groups (Fig. 3). The percentage change observed in the upper limb in the desflurane group was higher than that in the sevoflurane group (22.2% vs. 43.4%); however, this difference between the inhalational groups was not significant at 0.3 MAC ($P = 0.147$). The percentage change in amplitude was more than 50% of the baseline value as the MAC increased to 0.8 (Fig. 3). However, the amplitude suppression did not recover to levels close to the baseline at the end time-point. The remaining amplitude changes were comparable between the two groups.

The suppression rates (proportion of participants with significant amplitude changes) at 0.3 MAC were 6/20 (30.0%) for the upper limbs in the sevoflurane group and 9/19 (47.4%) in the desflurane group (Table 2). The corresponding rates for the lower limbs were 3/20 (15.0%) in the sevoflurane group and 3/19 (15.8%) in the desflurane group. Differences between the groups in terms of the suppression rates were not statistically significant throughout the study. The MEP amplitude signal disappeared in four of the 20 participants when the concentration of sevoflurane increased from 0.3 MAC to 0.6 MAC (Table 2). On the other hand, the MEP amplitude signal disappeared in one of the 19 participants in the desflurane group at 0.8 MAC. Signal reappearance after the discontinuation of the administration of volatile anesthetics (End) was observed in these participants. The LSM value

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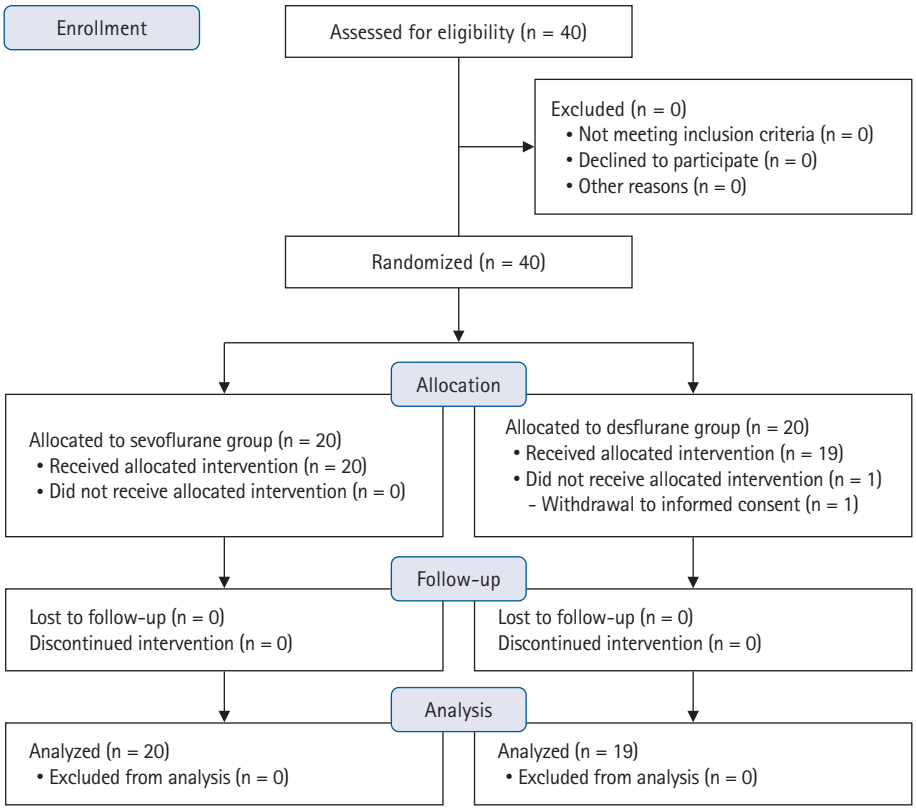

Fig. 2. CONSORT flow diagram illustrating the participant enrollment and allocation during the study period.

Table 1. Demographic and Clinical Characteristics among the Study Groups

Variable	Sevoflurane group (n = 20)	Desflurane group (n = 19)	P value
Age (yr)	57.3 ± 12.8	57.3 ± 13.3	0.987
Sex (M/F)	14/6 (70.0/30.0)	10/9 (52.6/47.4)	0.432
Height (m)	1.66 ± 0.09	1.62 ± 0.12	0.262
Weight (kg)	70.6 ± 12.8	67.7 ± 12.9	0.478
Body mass index (kg/m^2)	30.0 ± 3.3	30.4 ± 3.4	0.745
Diabetes	3 (15.0)	0	0.248
Hypertension	10 (50.0)	5 (26.3)	0.231
Chronic kidney disease	0	0	
Liver disease	0	0	
Cerebrovascular disease	1 (5.0)	2 (10.5)	0.963
ASA-PS			0.940
I or II	17 (85.0)	15 (79.0)	
III	3 (15.0)	4 (21.1)	
Anesthesia time (min)	167.4 ± 40.2	163.3 ± 32.4	0.730
Remimazolam (mg)	190.0 (168.5, 255.0)	187.0 (177.5, 230.0)	0.736
Remifentanil (μg)	2460.0 ± 994.8	2360.5 ± 882.6	0.744

Values are presented as mean ± SD, median (Q1, Q3), or number (%). ASA-PS: American Society of Anesthesiologists physical status.

of the amplitude decreased significantly as the MAC increased in the upper and lower limbs in both groups ($P < 0.001$, Supplementary Table 1). No significant interaction was observed between the inhalational groups and each time-point ($P = 0.136$ for the upper limb, 0.065 for the lower limb).

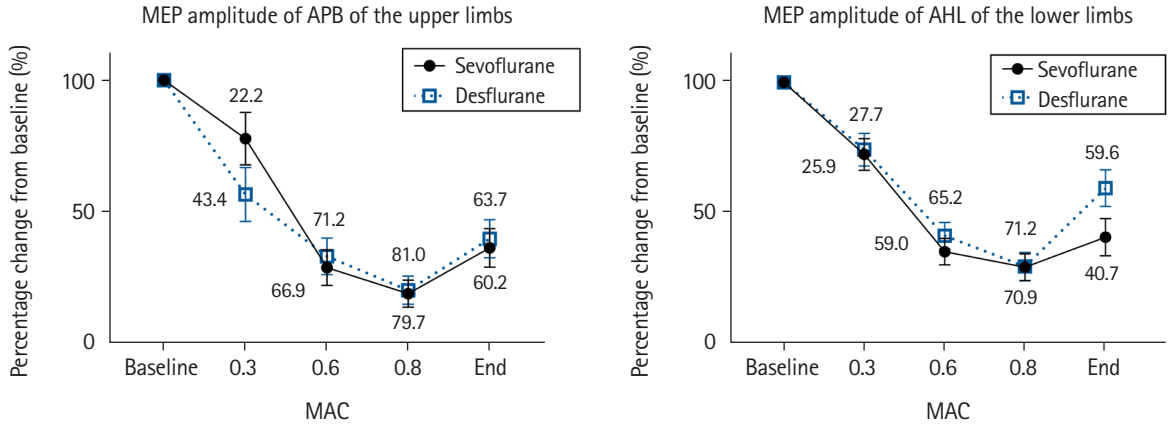

Fig. 3. Percentage change in amplitude from baseline of MEPs. The amplitudes were measured from the APB muscle and AHL muscle across increasing MAC in the sevoflurane and desflurane groups. No significant intergroup differences were observed at any level. MEPs: motor evoked potentials, APB: abductor pollicis brevis, AHL: abductor hallucis longus, MAC: minimum alveolar concentration.

Table 2. Proportion of MEP Amplitude Suppression of ≥ 50% of the Baseline or Total Suppression at Each MAC Level

Variable	Sevoflurane group (n = 20)	Desflurane group (n = 19)	P value
APB			
0.3 MAC	6 (30.0)	9 (47.4)	0.268
0.6 MAC	16 (80.0)	14 (73.7)	0.828
0.8 MAC	17 (85.0)	16 (84.2)	0.946
End	14 (70.0)	13 (68.4)	0.994
Total suppression of APB			
0.3 MAC	0	0	
0.6 MAC	4 (20.0)	0	
0.8 MAC	4 (20.0)	1 (5.3)	
End	0	0	
AHL			
0.3 MAC	3 (15.0)	3 (15.8)	0.946
0.6 MAC	16 (80.0)	10 (52.6)	0.084
0.8 MAC	18 (90.0)	15 (78.9)	0.303
END	15 (75.0)	8 (42.1)	0.080
Total suppression of AHL			
0.3 MAC	0	0	
0.6 MAC	0	0	
0.8 MAC	0	0	
End	0	0	

Values are presented as number (%). MEPs were measured at the APB of the upper limbs and the AHL of the lower limbs in the sevoflurane and desflurane groups. MEP: motor evoked potential, MAC: minimum alveolar concentration, APB: abductor pollicis brevis, AHL: abductor halluces longus, P value, group comparison.

Changes in MEP latency, SSEP amplitudes, and SSEP latency

The LSM of the MEP latency was not significantly prolonged and the percentage changes were less than 10% from the baseline value in the upper and lower limbs as the MAC increased (Supplementary Table 1). The latency changes in the sevoflurane and desflurane groups were comparable.

The LSM of the SSEP amplitude in the lower limb decreased significantly in a dose-dependent manner in the desflurane group (P = 0.023, Supplementary Table 2). No changes were observed in the upper limb; however, the percentage change in amplitude at any time point was within 50% in the upper and lower limbs. In the sevoflurane group, the LSM of the SSEP amplitude in both the upper and lower limbs did not differ significantly (P = 0.396 for the upper limb and P = 0.227 for the lower limb, Supplementary Table 2). No significant interaction was observed between the groups and each time point (P = 0.537 for the upper limb and P = 0.060 for the lower limb).

SSEP latency of the upper limbs increased significantly as the MAC was increased in an incremental manner in both groups (P < 0.001, Supplementary Table 2). However, the percentage change was less than 10% of the baseline value. The latencies of the lower limbs were not prolonged in either group (P = 0.594 and P = 0.103, respectively). A significant interaction between the groups and each time-point was observed for the upper limb (P = 0.020); however, no significant interaction was noted for the lower limb (P = 0.330). The changes in the latency and amplitude of SSEP were comparable between the two groups (Supplementary Table 2).

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Discussion

The present study evaluated the effects of adding volatile anesthetic agents to remimazolam on the intraoperative MEP and SSEP monitoring during general anesthesia. To the best of our knowledge, this is the first study to investigate the impact of this combination on MEP responses during cervical spine surgery. Although the mean percent change was not statistically significant, a considerable proportion of participants exhibited significant MEP amplitude suppression–particularly in the upper limbs–even at a low dose (0.3 MAC), with greater suppression observed at concentrations more than 0.6 MAC. In some cases, no MEP reproducible signal was detected. In contrast, the SSEPs were minimally affected throughout the study. No significant differences were observed between the sevoflurane and desflurane groups in terms of MEPs and SSEPs. These findings suggest that caution is warranted when using volatile anesthetic agents for MEP monitoring with a background infusion of remimazolam.

The findings of the present study are consistent with previous studies indicating that sevoflurane and desflurane suppress MEP amplitudes in a dose-dependent manner. However, in contrast to these studies that suggested that a limited concentration ($\leq$ 0.5 MAC) of volatile anesthetic agents enables the reliable monitoring of transcranial MEPs when used in combination with remifentanil or propofol [5,7–10,22,23], the present study could not confirm this effect at such low concentrations of volatile anesthetic agents. Both propofol and volatile anesthetic agents bind with the gamma-aminobutyric acid type A ($GABA_A$) receptor; however, their effects on EP response vary. Rather than inhibiting the excitability of the motor neurons in the spinal cord, propofol predominantly inhibits the supra-spinal motor pathways, resulting in gradual suppression of the MEP amplitudes during prolonged infusion [24]. Volatile anesthetic agents suppress SSEPs by acting on the sensory neurons in the thalamus and sensory cortex, whereas they affect the MEPs via the corticospinal tract through the alpha motor neuron synapses [25]. Midazolam, a conventional benzodiazepine that acts on the benzodiazepine site on the $GABA_A$ receptor, can be used for SSEP monitoring due to its minimal suppressive effect [3,26,27]. Its mild to moderate suppressive effect on MEP amplitude can be mitigated by adjusting the electrical stimulation parameters [28–30]. Remimazolam may produce effects similar to those of propofol or midazolam when combined with volatile anesthetic agents. However, previous studies have not studied such interactions. Thus, the findings of the present study provide new insights into this area.

The findings of the present study suggest that the suppression of MEP amplitudes induced by the combination of remimazolam and volatile anesthetic agents was more pronounced than that observed with the combination of propofol or opioids and volatile anesthetic agents [8]. According to the alarm criteria for IONM employed at our institution which generally define significant reduction as an amplitude decrease of more than 50% of the baseline MEP values [5], a notable proportion of participants exhibited such suppression even at 0.3 MAC: 30% in the sevoflurane group and 47.4% in the desflurane groups, based on upper limb monitoring. However, the alarm criteria and their interpretation exhibit mild variations across different institutions [31], as they are influenced by factors such as anesthetic parameters (e.g., temperature, depth of anesthesia, blood pressure, and the use of neuromuscular blockade), pre-existing neurological deficits, and the intensity of electrical stimulation [32,33]. Thus, these findings suggest that a higher alarm threshold may be required when adding volatile anesthetics to remimazolam infusion. Future studies to examine the neurological outcomes are warranted.

The present study could not confirm whether remimazolam exhibits 'anesthetic fade' with prolonged infusion [6] or dose-related adverse effects. Notably, a loading dose of remimazolam suppressed MEP amplitude in a case report [17]. A continuous infusion rate of 2.0 mg/kg/h has been deemed reproducible for MEP amplitude monitoring [16]. Differences in the plasma concentration of remimazolam may have also contributed to variability in the MEP responses. However, the infusion rate and accumulated dose of remimazolam at the time of MEP measurements were not recorded in the present study. Kim et al. [18] reported a slight increase in the MEP amplitudes over time in the remimazolam and propofol groups. However, this may be attributed to the decreased effect of neuromuscular blocking agents. Thus, further studies must be conducted to determine the effects of the plasma concentration of remimazolam on MEP response and accurately estimate its effect.

Discrepancies were observed between the MEP responses of the upper and lower limbs in the present study. MEP amplitude of the upper limbs was relatively lower than that of the lower limbs, and the suppression rate of the APB muscle was higher than that of the AHL muscle at 0.3 MAC for both volatile anesthetics. These findings contradict the findings of previous studies that reported that the lower limbs were generally more sensitive to anesthetic-induced depression [34,35]. This discrepancy may be attributed to the differences between the corticospinal tract response of the upper and lower limbs such as D wave refractory periods and anatomical factors (e.g., the length of the electrode needle and its distance from the target muscle) [34,35]. The preoperative motor strength state may have contributed to the variations in the MEP responses, as a motor strength of less than 3 is

associated with reduced MEP recordings [36]. This study did not include participants with significant motor weakness (< 3–4); however, cervical myelopathy in the participants may have contributed to the lower amplitude values in the upper extremities. A previous study found that MEP monitorability tended to be lower in cervical spine surgery compared to lumbar spine surgery, particularly with the use of inhalational anesthetic agents [37].

The SSEP amplitudes and latencies were minimally affected by anesthesia. These findings are consistent with those of previous studies that reported that the administration of low concentrations of up to 0.3–1.0 MAC is permitted for reliable SSEP monitoring [4,7,8,10]. The latency of MEPs and SSEPs that are more resistant to suppression by anesthesia also remained largely unchanged. This finding is also consistent with those of previous reports on midazolam [28] and volatile anesthetics [10].

No significant differences were observed between the two inhalational groups. Two previous studies comparing the effects of sevoflurane and desflurane at 0.3 MAC revealed differing results [9,10]; thus, which inhalational agent had a greater inhibitory effect on EP was unclear. The findings of the present study indicate that stronger suppression of MEP amplitudes was observed in the desflurane group; however, this effect was limited to the upper limbs. This variability between the agents may be attributed to inter-individual differences in terms of the response to volatile anesthetics and differences in the degree of synaptic inhibitions they induce [10].

This study has several limitations. First, the sample size was calculated to detect the changes in MEP amplitudes in response to volatile anesthetics. The sample size calculation did not specifically account for the effect size required to detect intergroup differences; consequently, this limitation primarily affects the secondary outcome and does not compromise the validity of the primary finding. Nevertheless, the adoption of the randomized controlled trial design was necessary to address the secondary outcome that aimed to compare the effects of two volatile anesthetics on IONM. Second, this study measured the final IONM values (End) after ceasing the administration of the volatile anesthetic agents. The blood concentration of desflurane and sevoflurane are known to decrease to clinically insignificant levels approximately 20 min after discontinuation [38,39]. Although the exact washout duration was not recorded in the present study, the End values were measured approximately 10 min after stopping volatile anesthetic agents, based on the end-tidal concentration. However, due to the dilution effect in the lung, the end-tidal concentration of the anesthetics tends to decrease earlier than the corresponding reduction in the blood concentration. As a result, significant amplitude suppression was still observed at the End time-point (Fig. 3). Furthermore, the persistence of substantial amplitude reduction suggests that once suppression occurs, a sufficient recovery period is required due to residual effects of volatile anesthetic agents. A previous study compared MEP amplitudes measured 35 min after desflurane cessation between a group receiving desflurane followed by a propofol infusion and a standard propofol infusion group [23]. The results showed that a mean MEP amplitude similar between the two groups. Notably, the 95% CI was wider in the desflurane group, leading the authors to suggest that this variability was possibly due to the residual effects of desflurane. Third, the addition of inhalational anesthetics to IV anesthesia may lead to an abrupt decrease in the mean arterial pressure (MAP) that may affect autoregulation [31]. Reduced autoregulation decreases the blood flow to the neurons and produces IONM response variability [31,40]. A MAP of ≥ 65 mmHg was targeted during the study period; however, some patients have higher lower limits of autoregulation [33]. Furthermore, interventions such as reducing the infusion rate of IV anesthetics or administering vasopressors (e.g., phenylephrine or ephedrine) may have affected the MEP amplitude by elevating the excitability of motor neurons [41]. These factors were not analyzed in the present study. Fourth, the remimazolam-remifentanil dose was titrated based on the patient state index from SedLine; however, PSI was not strictly maintained within a refined range. Anesthetic depth is correlated with MEP monitoring [42]; thus, equivalent anesthetic depth is critical for evaluating the effects of different agents. Lastly, volatile anesthetic agents provide immobility and amnesia even at low doses [7,43]; however, the present study focused solely on assessing changes in MEP and SSEP response, and did not comprehensively evaluate the clinical outcomes of adding volatile anesthetic agents.

In conclusion, the use of volatile anesthetic agents with a background infusion of remimazolam resulted in MEP amplitude suppression even at 0.3 MAC. Thus, volatile anesthetic agents must be used cautiously in conjunction with remimazolam during MEP monitoring. Further dose-finding studies of volatile agents combined with remimazolam and remifentanil anesthesia must be conducted to optimize MEPs during spinal surgery.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the cur-

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rent study are available from the corresponding author on reasonable request.

Author Contributions

Hee-Sun Park (Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)
Wonho Choi (Investigation; Methodology; Writing – review & editing)
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Supplementary Materials

Supplementary Table 1. Motor evoked potentials (MEPs). The amplitude and latency were measured at the APB of the upper limbs and the AHL muscle of the lower limbs in the sevoflurane and desflurane groups.
Supplementary Table 2. Somatosensory evoked potentials (SSEPs). The amplitude (μV) and latency (ms) were measured at the median nerve of the upper limbs and posterior tibial nerve of the lower limbs in the sevoflurane and desflurane group.

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