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Comparison of intraoperative neurophysiological monitoring between propofol and remimazolam during total intravenous anesthesia in the cervical spine surgery: a prospective, double-blind, randomized controlled trial

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Background: Although total intravenous anesthesia (TIVA) with propofol and remifentanil is frequently used to optimize intraoperative neurophysiological monitoring (IONM), the exact effect of remimazolam on IONM remains unknown. Here, we compared the effects of propofol and remimazolam along with remifentanil on IONM during TIVA.

Methods: In this prospective, double-blind, randomized controlled trial, 64 patients requiring IONM during cervical spine surgery were administered either propofol (Group P) or remimazolam (Group R). The preoperative latencies of the somatosensory-evoked potentials (SEP; N20 for the median nerve and P37 for the tibial nerve) were measured. SEP latencies and amplitudes and motor-evoked potential (MEP) amplitudes were measured 30 min after anesthetic induction (T1), 30 min after surgical incision (T2), after laminectomy or discectomy (T3), immediately after plate insertion or pedicle screw fixation (T4), and before surgical wound closure (T5). The primary outcome was the between-group difference in the N20 latency changes measured at T1 and preoperatively.

Results: The change in SEP latencies including N20 and P37 at T1 compared with preoperative time was not significantly different between Groups P and R. Except for the amplitude of the right abductor brevis, there was no significant group-by-time interaction effect for intraoperative MEP amplitudes or SEP latencies and amplitudes.

Conclusions: TIVA with remimazolam and remifentanil for cervical spine surgery yielded stable IONM, comparable to those observed with conventional TIVA with propofol and remifentanil. Further clinical trials are needed in other surgical contexts and with more diverse patient populations to determine the effects of remimazolam on IONM.

Keywords: Anesthesia, intravenous; Evoked potentials, motor; Evoked potentials, somatosensory; Intraoperative neurophysiological monitoring; Propofol; Remimazolam.

Introduction

Intraoperative neurological injuries are rare but may have catastrophic consequences in cervical spine surgeries [1]. Early detection of iatrogenic neurological compromise during the procedure is essential to avoid neurological injury and can reportedly reduce the incidence of new postoperative neurological deficits from 3.7 to 6.9% to less than 1% [2]. In this regard, intraoperative neurophysiological monitoring (IONM), such as monitoring of somatosensory-evoked potentials (SEPs) and motor-evoked potentials (MEPs), is becoming a standard intervention. Because SEP and MEP signals are unavoidably influenced by the anesthetic method or drug used, efforts are in progress to achieve optimal anesthetic management, including the use of agents that have minimal or no effects on IONM [3].

Generally, volatile anesthetics act on both γ-aminobutyric acid (GABA) and N-methyl-D-aspartate receptors, thereby significantly reducing the amplitude of cortical MEP and SEP signals as well as delaying their latency compared with intravenous (IV) anesthetics [4,5]. Thus, total intravenous anesthesia (TIVA) with little effect on MEP signals is preferred for IONM [6]. However, propofol, a representative IV anesthetic, is also associated with reduced amplitude and delayed latency of SEPs in a dose-dependent manner [3,7]. Long-term propofol infusions can cause a significant decrease in MEP amplitude [8], as well as various side effects such as delayed recovery, metabolic acidosis, platelet function decline, and hyperlipidemia [2].

Remimazolam, a newly developed benzodiazepine, is an ester-based GABAA receptor agonist that is harmless even under constant IV infusion [9,10]. Remimazolam has certain explicit benefits over conventional benzodiazepines, including a short context-sensitive half-life, rapid onset, conversion to an inactive metabolite by tissue esterase independent of hepatic or renal function, and presence of an antidote [11,12]. Recently, few case reports have shown that TIVA with remimazolam may have minimal effect on the MEPs of patients undergoing cervical spine surgery [13–15] and SEPs of those undergoing neurosurgery [16]. However, no systematic studies have specifically addressed the usefulness of remimazolam in IONM, and clinical trials are required to establish whether TIVA with remimazolam is comparable to conventional TIVA with propofol. Therefore, in the present study, we aimed to compare the effects of IV remimazolam and IV propofol on IONM in patients undergoing cervical spine surgery with SEP and MEP monitoring in all four extremities.

Materials and Methods

Participant enrollment and assignment

This study was a prospective, double-blind, randomized clinical trial and performed at a tertiary hospital in compliance with the 2013 Declaration of Helsinki. Our protocol was approved by the Institutional Review Board and hospital research ethics committee of Gangnam Severance Hospital, Yonsei University Health System (IRB No. 3-2021-0189) on June 23, 2021, and registered at ClinicalTrials.gov (NCT04968054) on July 13, 2021, before patient enrollment. The present study included patients (20–70 years of age) with an American Society of Anesthesiologists physical status of I–III scheduled for elective cervical spine surgery requiring IONM due to musculoskeletal diseases requiring IONM, such as cervical spondylotic myelopathy or ossification of the posterior longitudinal ligament, in the Department of Neurosurgery at a single institution between July 2021 and May 2023. Exclusion criteria for the study included patients who had tolerance or hypersensitivity to benzodiazepines, dependence on or addiction to psychotropic drugs or alcohol, previous brain-related neurosurgery, pacemaker or intracranial device, received steroid pulse therapy recently (within one month), or refused consent. Written informed consent was obtained from all the participants.

After obtaining informed consent, patients were randomly allocated (1:1 ratio) to either Group P (propofol) or Group R (remimazolam). The randomization sequence was determined via computer-generated block randomization with a block size of four by a researcher who was not involved in the study. Each generated code was hidden in a numbered opaque envelope. On the day of surgery, another researcher opened the envelope, and each patient was assigned to the study group according to the code in the envelope. All patients, surgeons (one attending surgeon with over 30 years of experience and his surgical team), and outcome assessors were unaware of the patient group assignment.

Preoperative SEP examination

Before admission to the hospital, a preoperative SEP (preopSEP) examination was conducted on all enrolled patients by an experienced physiatrist in an electromagnetically shielded room using Medelec™ Synergy electromyogram equipment (Oxford Instrument Medical) at the outpatient clinic. Bilateral median and tibial SEP latencies were obtained by stimulating the median nerves at the wrists or the tibial nerves at the ankles (intensity, 12–20 mA; pulse width, 0.3 ms; frequency, 4.7 Hz; sweep numbers per average, 300), recording at C3 (right median), C4 (left

median), and Cz (right and left tibial nerves), and referencing FPz according to the international 10–20 electroencephalography (EEG) system. The latency was recorded as N20 for median SEPs and P37 for tibial SEPs.

Anesthesia and intervention

All patients entered the operating room without any benzodiazepine premedication, and their vital signs were monitored using non-invasive blood pressure, pulse oximetry, and electrocardiography measurements. Depth of anesthesia was assessed via the Patient Status Index (PSI) value using a SedLine® sensor (Masimo) attached to the forehead. Intraoperative body temperature was monitored using an esophageal stethoscope, and continuous arterial blood pressure was measured via radial arterial catheterization.

In Group P, TIVA was performed with an effect-site target-controlled infusion (TCI) of 2% propofol (Fresofol 2% injection 50 ml vial; Fresenius Kabi) and 20 μg/ml remifentanil (Ultian™ injection 1 mg vial; Hanlim). A commercially available TCI pump (Agilia® Connect; Fresenius Kabi) was used. The effect-site TCI for propofol was based on Schnider's pharmacokinetic model and that for remifentanil was based on Minto et al.'s model [17,18]. Anesthesia was induced with 3 μg/ml propofol and 3 ng/ml remifentanil initially, and the doses were subsequently titrated depending on the patient's PSI and vital signs. In Group R, TIVA with remimazolam–remifentanil was performed via a previously described method [9,10]. Remimazolam (ByFavo™; Hana Pharmaceutical) was initially administered at 6–12 mg/kg/h during anesthetic induction and maintained at 0.5–2 mg/kg/h after the patient lost consciousness.

In both groups, 0.6 mg/kg rocuronium (Esmeron™, N.V. Organon) was administered as a neuromuscular blocking agent (NMBA) for intubation, and no additional infusion was used for MEP monitoring during surgery (except in cases when the patient moved to an extent of spontaneous breathing that interfered with the operation). In addition, the response of the adductor pollicis brevis muscle to train-of-four (TOF) stimulation of the ulnar nerve using a neuromuscular transmission module (M-NMT Modulew, Datex-Ohmeda Inc.) was measured every 15 min. Continuous end-tidal carbon dioxide ($EtCO_2$) tension was maintained at 30–40 mmHg. The depth of anesthesia was adjusted by PSI from 25 to 50, with a mean arterial pressure (MAP) within 20%–30% of the baseline value (minimum 65 mmHg over). Acetaminophen (1 g) and nefopam (20 mg) were administered intravenously to reduce postoperative pain, and 75 μg of palonosetron was injected to prevent postoperative nausea and vomiting during surgery. Patient-controlled analgesia was formulated with 10 μg/kg of fentanyl, 2 mg/kg of nefopam, and 0.6 mg of ramosetron for an IV route. At the completion of the operation, all administered anesthetic agents were terminated; further, neuromuscular blockade (NMB) was reversed by using 0.07 mg/kg neostigmine with 0.05 mg/kg of glycopyrrolate. After confirming spontaneous breathing and recovery of consciousness in the patient, extubation was performed. Patients were then transferred to the post-anesthesia care unit (PACU).

Acquisition of IONM

IONM was conducted using the Cascade® IONM system (Cadwell Industries) by a skilled technician under the direct supervision of a professional physiatrist blinded to the group allocation of patients. Intraoperative SEP waves were acquired continuously throughout the surgical procedure, following a protocol similar to that used for preopSEPs. The initial waveform was acquired immediately after completion of the IONM setup that occurred after anesthesia induction. Intraoperative MEPs were obtained from the bilateral deltoids (Del), abductor pollicis brevis (APB), tibialis anterior (TA), and abductor hallucis (AH) muscles using transcranial electrical consisting of six squared stimuli (intensity, 200–400 mV; pulse duration, 0.5 ms; interstimulus interval, 5 ms). Interhemispheric stimulation was applied using a subdermal needle electrode placed at C3 and C4 according to the international 10–20 EEG system. Montages C3 and C4 were used to obtain the MEPs of the right and left extremities, respectively.

Both intraoperative SEP and MEP waves were obtained at the following time intervals in sequence: T1, 30 min after anesthetic induction; T2, 30 min after the surgical incision (approximately 60 min after administering an NMBA for intubation); T3, after laminectomy or discectomy; T4, immediately after the insertion of plates or fixation of the pedicle screw; and T5, before closing the surgical wound. The warning criteria for SEPs were defined as either a latency prolongation of more than 10% compared with the baseline (T1) latency, or a decrease in peak-to-peak amplitude of more than 50% compared with the baseline amplitude on any side, of any examined nerve [19]. The warning criterion for MEPs was defined as a decrease in amplitude greater than 50% compared with the baseline (T2) amplitude [19]. As T2 was approximately more than 60 min after NMBA administration for endotracheal intubation, the time point at which MEP comparisons relied on anesthetic effects rather than NMB effects was considered. When MEP was measured at T2, the range of TOF (%) values was over 0.5 in both the groups. Any alterations in SEPs or MEPs beyond the warning criteria were promptly relayed to the surgeons

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and attending anesthesiologist during surgery. To ascertain the intergroup differences in the coefficient of variation (CV) of the MEP amplitudes, the MEP wave was recorded three times, with at least 30-s intervals, at both T1 and T2. Since NMB is known to increase the CV of MEP amplitude [20], repeated measurements were performed at T1 and T2. However, at T3–T5, we refrained from repeated transcranial electrical stimulation for MEP acquisition because this could induce patient movement and potentially interfere with critical surgical procedures.

Outcome assessment

Our primary outcome was to confirm any significant differences in the change in the SEP latency of the median nerve (N20) obtained before and after anesthesia that was defined as the ratio (percentage) of the value measured after anesthetic induction (T1) divided by the value measured before anesthesia (preopSEP) between the two groups. The secondary outcome was to determine any differences in the change in SEP latency of the tibial nerve (P37) before and after anesthesia between the groups. Temporal changes in the latency and amplitude of SEPs and the amplitude of MEPs obtained during surgery were compared between the groups. We also collected information on the total consumption of anesthetics and vasopressors administered during anesthesia, hemodynamic data and PSI values, duration of stay in PACU, length of postoperative hospital stays, and postoperative adverse events, including neurological dysfunction. Neurological examinations were conducted one day before and one day after the surgery by a neurosurgeon using the Japanese Orthopedic Association (JOA) scoring system within a range of 0–17, encompassing motor functions of the upper and lower extremities, sensory functions of the upper and lower extremities and trunk, and bladder function [21].

Statistical analysis

A previous study [2] comparing two anesthesia methods showed a significant difference in the SEP latency between the two groups when the mean difference was 1.6. Based on this result, 27 subjects per group were required for calculating a 0.05 type 1 error (α) and 80% power (1-β). However, considering a dropout rate of 20%, 33 participants per group were required (66 in total). G*Power version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf) was used to determine the sample size.

The Shapiro–Wilk test was used to confirm the normal distribution of all variables. Continuous variables are presented as the mean ± SD or median (Q1, Q3) and were compared using an independent two-sample t-test or Mann–Whitney test, as appropriate, according to the normality distribution. Categorical variables are indicated as the percentages of the total number of patients and were compared using the chi-squared test or Fisher's exact test, as appropriate. The standardized difference was calculated using the mean ± SD or the proportion of each group based on a commonly used formula [22]. Linear mixed models were applied to continuous outcomes, such as SEPs, MEPs, and hemodynamic data with repeated measures. We evaluated the effect of the anesthetic intervention on each outcome between the groups at each time point in terms of (1) between-group differences (group effects), (2) within-group changes over time (time effects), and (3) between-group differences in changes over time (group-by-time interaction effects). Post hoc analyses with Bonferroni correction were performed for multiple comparisons when variables with repeated measures showed significant differences between the groups. After applying the Bonferroni correction, the adjusted P value was found to be less than 0.05/3. All statistical analyses were conducted using SAS (version 9.4; SAS Institute) with two-sided P values < 0.05 indicating statistical significance.

Results

Of the 66 patients assessed for eligibility and randomly assigned, IONM could not be performed for two patients. Finally, 64 patients (Group P, 33; Group R, 31) completed the study and were included in the final analysis (Fig. 1). Patient demographic data are presented in Table 1. The preoperative neurological function was assessed using the JOA scoring system.

The SEP latencies (N20 and P37) measured before surgery (at preoperative time and T1) are listed in Table 2. The change (%) in bilateral N20 latency 30 min after anesthetic induction compared with preoperative time did not differ between the groups (right: 100.3% for Group P vs. 99.8% for Group R, P = 0.688; left: 100.7% for Group P vs. 93.7% for Group R, P = 0.098). Additionally, the changes in the bilateral P37 latencies at T1 did not differ from those preoperatively between the groups.

Changes in intraoperative bilateral N20 latencies and amplitudes, including those of P37, with each parameter transformed as a percentage of the values based on T1 (baseline) are shown in Fig. 2. No significant differences in group-by-time interaction effects were observed. Intraoperative changes in MEP amplitudes are shown in Fig. 3. Among the eight MEP amplitudes, each parameter was transformed as a percentage of the values based on T2 (baseline), and a significant group-time interaction effect was observed only in the right APB (P = 0.015, Fig. 3C). All variables related to SEP latencies and amplitudes and MEP amplitudes are

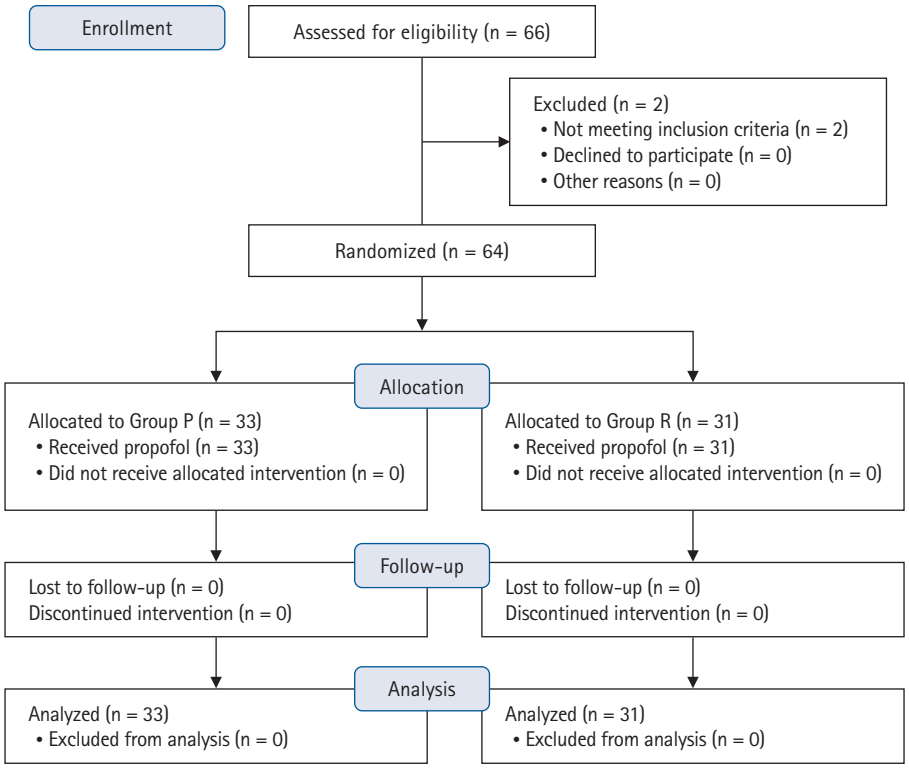

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. P: propofol, R: remimazolam.

presented in Supplementary Tables 1 and 2, and Supplementary Material, respectively.

The intraoperative NMBA level increased over time in TOF (%) that was the first and fourth twitch response to TOF stimulation in both groups, and no significant group-time interaction effect was observed between Groups P and R (Supplementary Fig. 1). In addition, the CV (%) of MEP amplitudes at T1 and T2 did not differ significantly between the groups (Supplementary Table 3).

The intraoperative parameters and postoperative recovery profiles are presented in Table 3. The total consumption of phenylephrine was significantly lower in Group R than in Group P (280 [90–1,300] μg vs. 880 [320–3,020] μg, respectively; P = 0.030). Intraoperative PSI values and perioperative hemodynamic parameters are shown in Supplementary Fig. 2. Group R had a significantly smaller range of heart rate changes over time than Group P (P = 0.003). Moreover, the PSI values showed a significant group-by-time interaction effect (P < 0.001) and were significantly higher in Group R than in Group P, except before anesthesia induction.

One patient in each group experienced intraoperative movement to the extent of spontaneous breathing that interfered with the operation, thus requiring additional muscle relaxants. In both cases, the additional administration of NMBA had little effect on surgery or IONM; therefore, these patients were not excluded from the study. The postoperative total JOA score increased in both groups compared with those measured before surgery, and no significant differences in motor and sensory function according to JOA scores were observed between Groups P and R. Regarding postoperative complications, there were no significant differences between the groups; one case of myodesopsia and one case of urinary tract infection in Group P were observed that were resolved before discharge. Two patients in Group R experienced wound problems (oozing, dehiscence), but no sequelae were observed upon discharge.

Discussion

This study found no significant difference in the change in SEP latencies between Groups P and R preoperatively and after anesthetic induction, suggesting that remimazolam administration itself had no influence on SEP latencies in any muscle group due to anesthesia. Furthermore, no significant group-by-time interaction effect on SEP latency/amplitude or MEP amplitude during the operation, except in the right APB, was observed.

IONM is widely used because of its safety and effectiveness in detecting nerve injuries during surgery [23–25]. This allows immediate corrective actions to preserve neurological function and decreases the incidence of new-onset postoperative neurological

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Table 1. Patient Characteristics

Variable	Group P (n = 33)	Group R (n = 31)	Absolute standardized difference
Demographic characteristics			
Sex (M/F)	21/12	18/13	0.114
Age (yr)	54.8 (33–69)	58 (33–70)	0.362
Height (cm)	167.1 ± 8.6	164.3 ± 9.4	0.317
Weight (kg)	71.6 ± 12.9	67.4 ± 11.7	0.340
BMI (kg/m^2)	25.5 ± 3.0	24.8 ± 2.7	0.231
Comorbidities			
Hypertension	16 (48.5)	12 (38.7)	0.198
Diabetes mellitus	4 (12.1)	5 (16.1)	0.115
Cardiac	4 (12.1)	3 (9.7)	0.078
Respiratory	3 (9.1)	4 (12.9)	0.122
Hepatologic	3 (9.1)	4 (12.9)	0.122
Renal	1 (3.0)	1 (3.2)	0.011
Neurologic	1 (3.0)	1 (3.2)	0.011
ASA physical status			
I	6 (18.2)	5 (16.1)	0.054
II	19 (57.6)	21 (67.7)	0.211
III	8 (24.2)	5 (16.1)	0.203
JOA score, preoperative			
Total	14.9 ± 1.5	14.3 ± 1.8	0.206
Motor function, upper extremity	3.2 ± 0.6	3.1 ± 0.7	0.625
Motor function, lower extremity	3.6 ± 0.6	3.5 ± 0.6	0.325
Sensory function, upper extremity	1.6 ± 0.6	1.4 ± 0.7	0.437
Sensory function, trunk	1.9 ± 0.4	1.9 ± 0.3	0.800
Sensory function, lower extremity	1.9 ± 0.3	1.9 ± 0.3	0.632
Bladder function	2.8 ± 0.5	2.6 ± 0.7	0.329
Surgical characteristics			
Diagnosis			
OPLL	21 (63.6)	25 (80.7)	0.386
Myelopathy	7 (21.2)	6 (19.4)	0.046
Spinal stenosis	5 (15.6)	0	0.598
Methods			
ACDF	11 (33.3)	6 (19.4)	0.321
LMSF	10 (30.3)	6 (19.4)	0.255
Laminoplasty	4 (12.1)	10 (32.3)	0.500
ACCF	5 (15.1)	5 (16.1)	0.027
Others	3 (9.1)	4 (12.9)	0.122
Levels			
1–2	14 (42.4)	13 (41.9)	0.010
3–4	9 (27.3)	13 (41.9)	0.312
≥ 5	10 (30.3)	5 (16.1)	0.341
Position (supine/prone)	16/17	11/20	0.266

Values are presented as mean ± SD, except for age (mean [range]), or number (%). P: propofol, R: remimazolam, BMI: body mass index, ASA: American Society of Anesthesiologists, JOA: Japanese Orthopedic Association, OPLL: ossification of the posterior longitudinal ligament, ACDF: anterior cervical discectomy and fusion, LMSF: lateral mass screw fixation, ACCF: anterior cervical corpectomy and fusion.

Table 2. Comparison of SEP Latencies between Groups

Variable	Group P (n = 33)	Group R (n = 31)	Mean difference (95% CI)	P value
N20 (right)				
Preop (mV)	19.87 ± 1.59	19.51 ± 1.26	0.36 (−0.36 to 1.08)	0.364
T1 (mV)	19.98 ± 1.33	19.42 ± 1.19	0.56 (−0.07 to 1.19)	0.082
T1/Preop (%)	100.3 ± 5.5	99.8 ± 5.3	0.5 (−2.5 to 3.5)	0.688
N20 (left)				
Preop (mV)	19.75 ± 1.46	19.75 ± 1.66	0.01 (−0.78 to 0.79)	0.992
T1 (mV)	19.86 ± 1.09	18.55 ± 3.67	1.31 (−0.03 to 2.65)	0.388
T1/Preop (%)	100.7 ± 6.0	93.7 ± 19.7	7.0 (−1.3 to 15.3)	0.098
P37 (right)				
Preop (mV)	43.24 ± 3.69	42.66 ± 3.90	0.59 (−1.31 to 2.48)	0.573
T1 (mV)	41.69 ± 4.14	39.71 ± 8.60	1.98 (−1.37 to 5.32)	0.253
T1/Preop (%)	96.0 ± 6.7	96.9 ± 10.6	0.9 (−4.1 to 5.9)	0.743
P37 (left)				
Preop (mV)	43.07 ± 4.14	42.44 ± 3.97	0.63 (−1.40 to 2.66)	0.570
T1 (mV)	40.92 ± 8.44	40.31 ± 8.83	0.61 (−3.71 to 4.92)	0.779
T1/Preop (%)	93.5 ± 19.8	98.9 ± 9.3	5.4 (−3.1 to 13.9)	0.208

Values are presented as mean ± SD. The bilateral latencies of the median (N20) and tibial (P37) SEPs measured 30 min after anesthetic induction (T1) were compared to those of the SEPs measured preoperatively (Preop) and are expressed as a proportion (T1/Preop, %). SEP: somatosensory-evoked potential, P: propofol, R: remimazolam.

deterioration by detecting intraoperative spinal cord compromise early during spinal surgery [14,26]. Generally, anesthetics adversely affect the ability to record evoked potential responses in a dose-dependent manner that may reduce the efficacy of detecting compromised spinal function [3,27,28]. Consequently, it is crucial to preserve the quality of SEPs and minimize the effects of anesthetic agents on neurological monitoring.

Compared with other anesthetic agents, both propofol and benzodiazepines have exhibited fewer effects on SEP latency and amplitude and MEP amplitude. TIVA with propofol and remifentanil is a typical anesthetic method frequently used to optimize IONM [29,30], although dose-related adverse effects may occur with propofol anesthesia depending on the infusion duration [31–33]. A similar effect is observed with benzodiazepine use. Previous studies have reported mild and moderate decreases in N20 and later components of the cortical amplitude wave with the administration of 0.1–0.25 mg/kg diazepam [34]. Administration of 0.2 mg/kg midazolam, followed by an infusion at 5 mg/h, has been reported to produce a depression in the cortical SEP amplitude without alterations in latency [35]. A significant amplitude depression of electrical transcranial MEP, up to 23% of the baseline value, was observed following one injection of 0.05 mg/kg midazolam [35]. However, it is unclear whether remimazolam suppresses SEP or MEP owing to the lack of control data without remimazolam use. Only few cases of successful SEP or MEP monitoring with intraoperative remimazolam infusion have been reported [13–15]. To determine whether the effects of remimazolam and propofol are comparable, the impact of intraoperative remimazolam infusion on SEP and MEP should be evaluated to ensure appropriate IONM monitoring.

Prolonged exposure to anesthetics because of long operative duration can depress MEP responses that is called 'anesthetic fade' [36]. In contrast, we found that MEP amplitudes increased slightly over time under general anesthesia in both groups, with similar levels of NMBA between the groups. These findings may be attributed to the recovery effect over time due to NMBA administration during induction. Although partial NMB, such as 1–2 twitches or at T1 between 5% and 50% of the baseline in a TOF electrical stimulation of the ulnar nerve, did not make a significant difference for proper MEP monitoring, the allowable degree of NMB for MEP monitoring remains controversial. In our study, we observed that even NMB levels below approximately 80% of the TOF slightly deteriorated MEP amplitudes.

In addition to the use of anesthetics, intraoperative variables that may affect evoked potentials include blood pressure, temperature, acid-base balance, oxygen and carbon dioxide tensions, and hematocrit [37]. Consequently, our efforts kept the vital signs stable and maintained the body temperature intraoperatively. Moreover, we investigated the arterial blood gases and estimated blood loss including that in blood transfusion. No significant differences in the factors that may affect evoked potentials were observed between the two groups, and these similar conditions may

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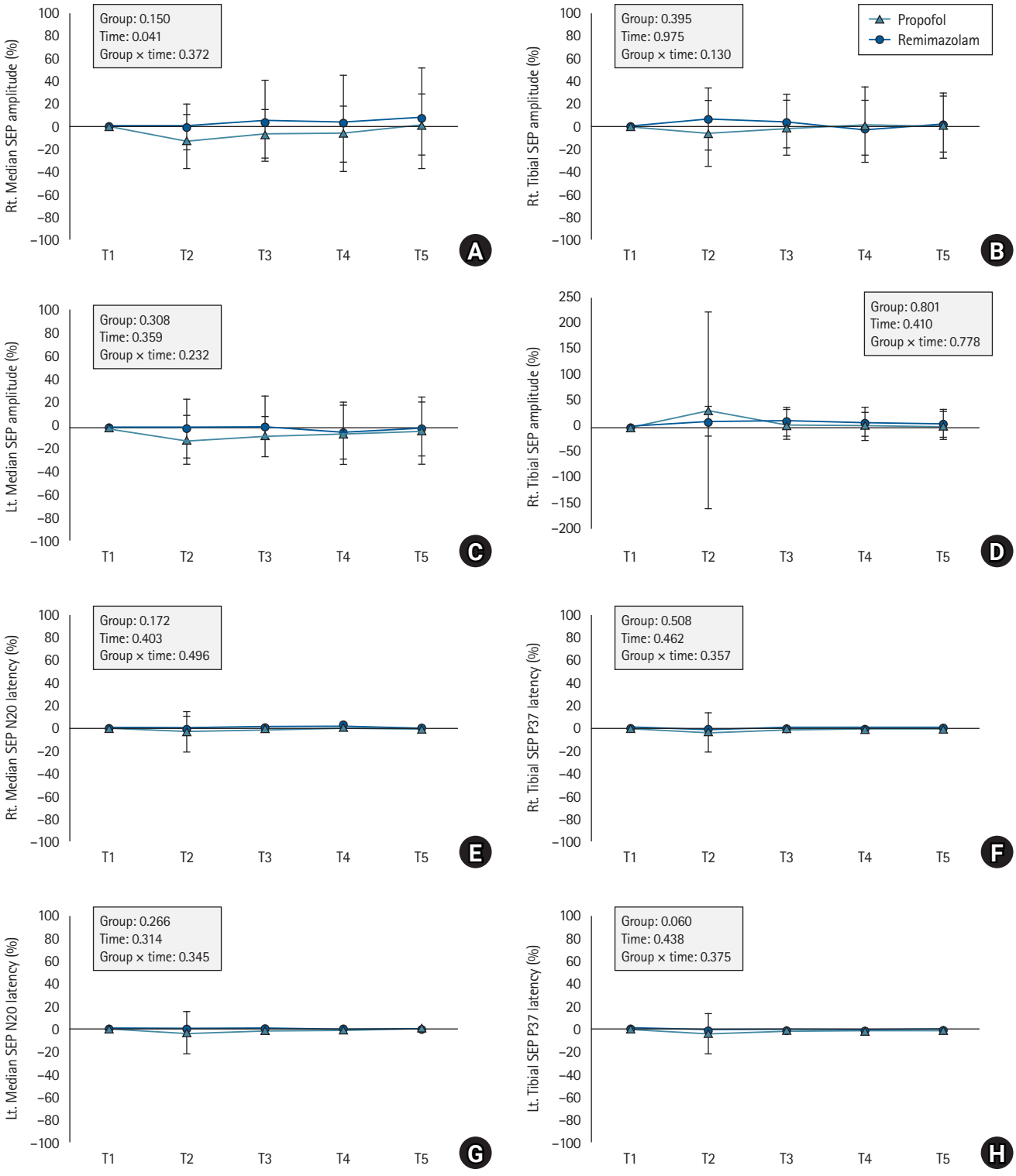

Fig. 2. Intraoperative changes in SEP latencies and amplitudes. Group P vs. Group R and their group-by-time interaction effects are shown using a linear mixed model. Graphs of SEP latency and amplitude were plotted for each parameter transformed as a percentage of the values based on T1 (baseline). The amplitudes of the right (A) and left (B) N20 as well as the right (C) and left (D) P37 showed no significant intergroup differences over time. There were no significant intergroup differences in the right (E) and left (F) N20 latencies or right (G) and left (H) P37 latencies over time. Values are presented as mean ± SD. P: propofol, R: remimazolam, SEP: somatosensory-evoked potential, T1: 30 min after anesthetic induction, T2: 30 min after surgical incision, T3: after laminectomy or discectomy, T4: immediately after the insertion of plates or fixation of pedicle screws, T5: before closing the surgical wound, N20: SEPs of the median nerve, P37: SEPs of the tibial nerve.

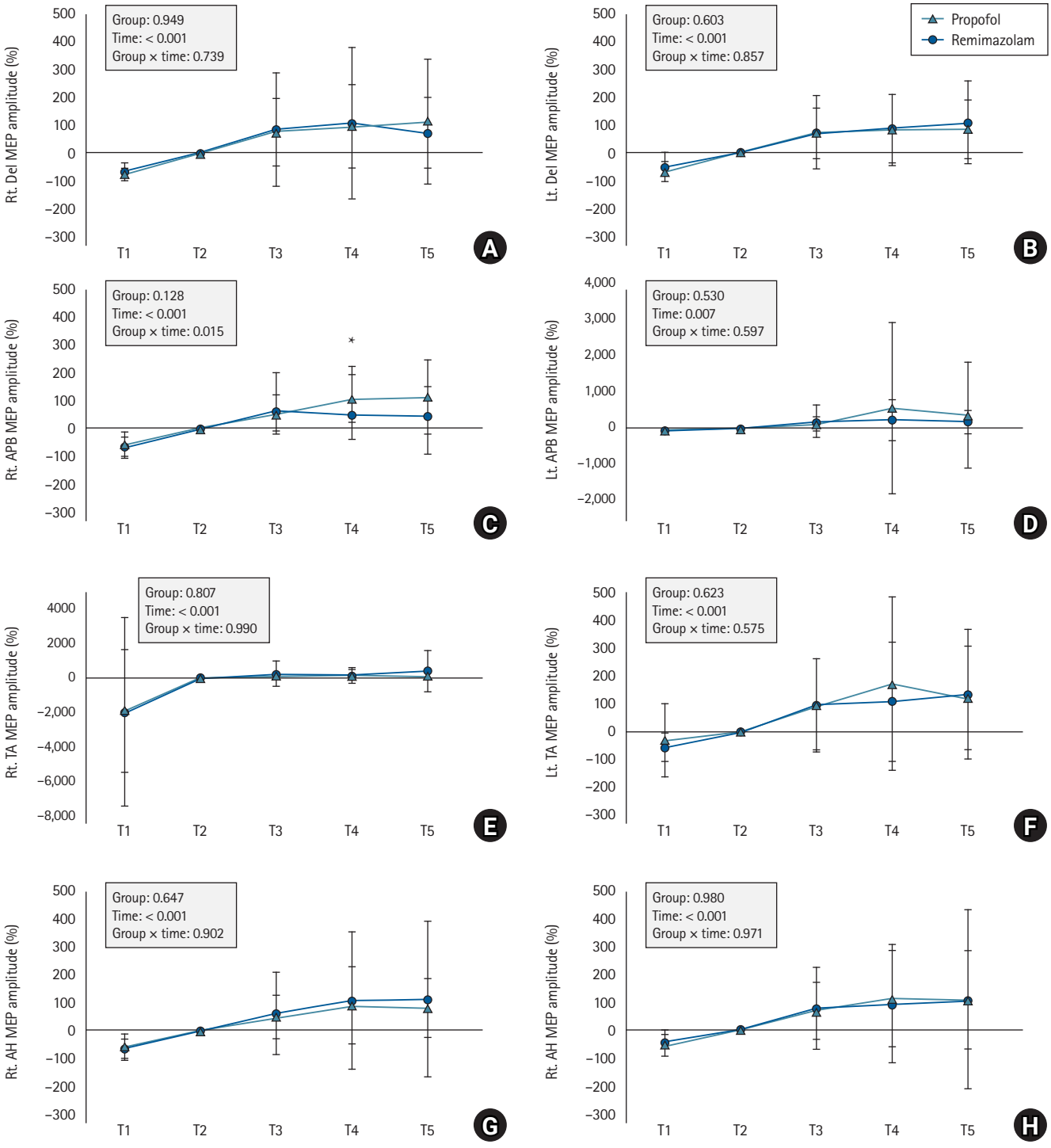

Fig. 3. Intraoperative changes in MEP amplitudes. Group P vs. Group R and their group-by-time interaction effects are shown using a linear mixed model. Graphs of the MEP amplitude were plotted from each parameter transformed as a percentage of the values based on T2 (baseline). Amplitudes of the right (A) and left (B) Del, right (C) and left (D) APB, right (E) and left (F) TA, and right (G) and left (H) AH muscles were not significantly different in intergroup differences over time, whereas the right (C) APB showed a significant intergroup difference over time (P = 0.015). Values are presented as mean ± SD. *P = 0.049 between Groups P and R (T4 of Rt. APB). P: propofol, R: remimazolam, MEP: motor-evoked potential, T1: 30 min after anesthetic induction, T2: 30 min after surgical incision, T3: after laminectomy or discectomy. T4: immediately after the insertion of plates or fixation of pedicle screws, T5: before closing the surgical wound, NMB: neuromuscular blockade, DEL: deltoid, APB: abductor pollicis brevis, TA: tibialis anterior, AH: abductor hallucis.

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Table 3. Intraoperative Parameters and Postoperative Recovery Profile

Variable	Group P (n = 33)	Group R (n = 31)	P value
Intraoperative characteristics			
Duration of operation (min)	185 (145, 230)	155 (120, 240)	0.211
Duration of anesthesia (min)	245 (210, 295)	230 (185, 305)	0.485
Input and output			
Administered fluid (ml)	1,900 (1,600, 2,600)	2,100 (1,500, 2,800)	0.747
Urine output (ml)	650 (400, 1,500)	500 (220, 780)	0.099
Estimated bleeding (ml)	450 (250, 800)	550 (250, 900)	0.835
Transfusion (n)	2 (6.1)	0	0.493
Arterial blood gas analysis			
pH	7.398 ± 0.025	7.391 ± 0.029	0.300
PO_2 (mmHg)	216.8 (204.0, 235.5)	214.5 (192.0, 246.8)	0.851
PCO_2 (mmHg)	35.2 (33.8, 36.8)	34.5 (33.0, 36.8)	0.582
Hematocrit (%)	35.4 ± 4.4	35.6 ± 3.4	0.777
Administered agents			
Total consumption			
Propofol (mg)*	1,791 (1,476, 2,016)	0	< 0.001
Remimazolam (mg)*	0	194 (139, 296)	< 0.001
Remifentanil (μg)	1,890 (1,562, 2,498)	2,294 (1,612, 3,488)	0.158
Phenylephrine (μg)*	880 (320, 3,020)	280 (90, 1,300)	0.030
Ephedrine (mg)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.370
Norepinephrine (μg)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.174
Population (n)			
Phenylephrine	32 (97.0)	26 (83.9)	0.099
Ephedrine	3 (9.1)	1 (3.2)	0.614
Norepinephrine	2 (6.1)	0	0.493
Additional rocuronium	1 (3.0)	1 (3.2)	> 0.999
Postoperative characteristics			
LOS in PACU (min)	30 (30, 40)	30 (30, 40)	0.394
LOS in a hospital (d)	7.4 ± 3.8	7.4 ± 4.9	0.973
JOA score, postoperative			
Total	15.1 ± 1.7	14.6 ± 1.8	0.304
Motor function, upper extremity	3.1 ± 1.1	3.2 ± 1.0	0.684
Motor function, lower extremity	3.7 ± 0.6	3.6 ± 0.6	0.559
Sensory function, upper extremity	1.6 ± 0.6	1.4 ± 0.7	0.352
Sensory function, trunk	1.9 ± 0.3	1.8 ± 0.4	0.403
Sensory function, lower extremity	1.9 ± 0.3	1.8 ± 0.4	0.403
Bladder function	2.9 ± 0.4	2.7 ± 0.6	0.197
ΔJOA scores†			
ΔTotal	0.2 ± 1.6	0.3 ± 1.8	0.858
ΔMotor function, upper extremity	−0.1 ± 0.9	0.1 ± 0.9	0.417
ΔMotor function, lower extremity	0.1 ± 0.5	0.1 ± 0.6	0.626
ΔSensory function, upper extremity	0.0 ± 0.5	0.0 ± 0.3	0.747
ΔSensory function, trunk	0.0 ± 0.3	0.0 ± 0.3	0.65
ΔSensory function, lower extremity	0.1 ± 0.2	0.0 ± 0.4	0.268
ΔBladder function	0.1 ± 0.3	0.1 ± 0.6	0.816
Postoperative complications	2 (6.1)	2 (6.4)	> 0.999

Values are presented as median (Q1, Q3), number (%) or mean ± SD. P: propofol, R: remimazolam, PO_2: partial pressure of oxygen, PCO_2: partial pressure of carbon dioxide, LOS: length of stay, PACU: postanesthesia care unit, JOA: Japanese Orthopedic Association. *P < 0.05 between Groups P and R. †ΔJOA scores refers to the difference between the JOA scores measured before and after surgery.

lend further credibility to our finding that remimazolam and propofol showed comparable IONM. Further, Group P showed a significant decrease in heart rate intraoperatively and was administered a larger amount of phenylephrine (a vasoactive drug) than Group R. These findings suggest that remimazolam can provide a more hemodynamically stable anesthetic environment than propofol, a premise supported by a previous study [38]. To the best of our knowledge, the present study is the first double-blind, randomized controlled trial to compare the effects of propofol and remimazolam during TIVA for IONM.

For reliable detection of neurological injury by monitoring MEP amplitude changes, the amplitude should be larger, although the CV must be smaller, meaning that the MEP amplitude variability (measured by the CV) should decrease. Selner et al. considered that a CV greater than 40% is inadequate for MEP interpretation [39]. We found that the CV of MEP amplitudes during anesthesia was below 40% in all muscles except the right TA (41.8%) in Group R. Similar to that observed in our study, previous studies have also found that the variability in MEP responses in the leg is commonly greater than that in the arm [40,41]. Accordingly, our MEP CV values suggest that MEP amplitudes are reliable and appropriate when interpreted during both remimazolam and propofol infusions.

Our study has some limitations. First, PSI monitoring was used as a guide to compare the depth of anesthesia between Groups P and R. However, the equivalent PSI value may not indicate the equivalent depth of anesthesia, especially when drugs other than propofol are used [42]. Ideally, the actual plasma concentrations of propofol and remimazolam should be measured and compared intraoperatively; however, this was not possible in this study. Moreover, the PSI showed a significant intergroup difference over time, even though both groups maintained a general anesthesia depth range of 25–50. Given the controversy regarding monitoring the depth of anesthesia with benzodiazepines, including remimazolam, a clear interpretation of the differences in PSI is difficult. Second, because of the small sample size, it was difficult to fully verify the significance of the secondary outcome and distinctively prove the reliability of IONM for actual neurological deficits. Therefore, it is challenging to clearly define true or false positives in relation to evoked potential monitoring and neurological deterioration. Third, some of the results were difficult to interpret. A significant group-time interaction effect on MEP amplitude was observed only in the right APB ($P = 0.015$); in particular, larger amplitudes were observed in Group R than in Group P immediately after plate insertion or pedicle screw fixation ($P = 0.049$). A previous study has reported that performing spinal surgery in the prone position may compress the brachial plexus, resulting in abnormal unilateral MEP results [43]; however, this does not fully explain the reason for observing MEP amplitude differences only in the right APB. Additionally, although the difference between the two groups was statistically significant, it is difficult to assert its clinical significance. Therefore, further studies on the effects of remimazolam on MEPs in specific muscle areas are warranted.

In conclusion, as the TIVA combination of remimazolam–remifentanil showed no significantly different effects on IONM compared with conventional TIVA based on propofol–remifentanil, remimazolam can be used as an alternative to propofol for evoked potential monitoring. Additionally, our research broadens the range of options for anesthetics and their combinations when performing IONM during spinal surgery. Remimazolam can provide a safe anesthetic environment, especially for high-risk patients who have difficulty using propofol or are hemodynamically unstable. To corroborate our findings, additional clinical trials are required in other surgical contexts and in more diverse patients to determine the effects of remimazolam on evoked potentials.

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

Author Contributions

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Supplementary Materials

Supplementary Table 1. Profiles of intraoperative latency and amplitude of SEPs between groups.
Supplementary Table 2. Profiles of intraoperative amplitude of MEPs between groups.
Supplementary Table 3. The CV (%) of MEP amplitude .
Supplementary Fig. 1. Intraoperative levels in NMB changes.
Supplementary Fig. 2. Changes in perioperative parameters.
Supplementary Material. Original tracings of IONM obtained during anesthesia.

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