Comparing the effect between continuous infusion and intermittent bolus of rocuronium for intraoperative neurophysiologic monitoring of neurointervention under general anesthesia

Myoung Jin Ko, MD[a], Beomjin Oh, MD[a], Jae-Wook Jung, MD[a], Dae Seok Oh, MD[a], Sung Chul Jin, MD[b], Eunsu Kang, MD[a], Yong Han Kim, MD[a], Se Hun Kim, MD[a], Hyojoong Kim, MD[a],*

Abstract

Background: Medical researchers have been reluctant to use neuromuscular blocking drugs (NMBD) during the use of intraoperative motor evoked potential (MEP) monitoring despite the possibility of patient movement. In this study, we compared the effects of no NMBD and continuous rocuronium infusion on the incidence of patient involuntary movement and MEP monitoring.

Methods: In this study, 80 patients who underwent neuro intervention with MEP monitoring were randomly assigned into 2 groups. After an anesthetic induction, bolus of rocuronium 0.1 mg/kg was injected when it was needed (for patient involuntary movement or at the request of the surgeon) in group B, and 5 mcg/kg/min of rocuronium were infused in group I study participants. The incidence of patient involuntary movement and spontaneous respiration, the mean MEP amplitude, coefficient of variation (CV), the incidence of MEP stimulus change and train-of-four (TOF) count were compared.

Results: The incidence of involuntary movement and spontaneous movement were measured as significantly lower in group I ($P < .05$). The incidence of undetectable MEP did not differ as measured in both groups. The means and CVs of MEP amplitude in all limbs were significantly lower in group I. The mean TOF counts from 30 to 80 min of operation were significantly higher in group B.

Conclusion: We conclude that the continuous infusion of rocuronium effectively inhibited the involuntary movement and spontaneous respiration of the patient while enabling MEP monitoring.

Abbreviations: BIS = bispectral index, CV = coefficients of variation, IOM = intraoperative neurophysiologic monitoring, MEP = motor evoked potential, NMB = neuromuscular blockade, NMBD = neuromuscular blocking drugs, SSEP = somatosensory evoked potential, TOF = train-of-four.

Keywords: intraoperative neurophysiologic monitoring, motor evoked potential, neuromuscular blocking drug

1. Introduction

Endovascular neurointervention has grown into a good therapeutic approach to the maintenance of blood vessels and abnormalities in the central nervous system, including intracranial aneurysm, arteriovenous malformation and vascular stenosis. Most of these procedures are performed under general anesthesia, as they require limited patients movement to obtain high-resolution images and patient comfortable status. In this situation, the use of intraoperative neurophysiologic monitoring (IOM), including somatosensory evoked potential (SSEP) and motor evoked potentials (MEP) has become more common and is often considered a predictor of neurologic functional outcomes.[1,2]

SSEP has been used in the discipline of neurointervention since the 1980s, but was reported to be vulnerable to detect motor damage of the patient, and the limit has been improved with the development of MEP.[1,3–5] However, neuromuscular blocking drugs (NMBD) used in general anesthesia can produce muscle relaxations that are too deep to measure with the MEP. Although most institutions do not use NMBD during MEP as NMBD can disturb monitoring, some surgeons and anesthesiologists still prefer using the NMBD to maintain partial neuromuscular block.[6–8] A more profound block reduces the MEP excessively and a less profound block is associated with excessive patient movement.[8] In this case, when partial neuromuscular blockade is used with IOM, the goal is to minimize patient movement in order that it is not distracting or hazardous and still allow reliable MEP or electromyography recording. Achieving both of these goals requires monitoring as much as the blocking of the nerve muscles with a peripheral nerve stimulator as possible. Conventional studies have reported that patients with normal neurological function and baseline responses with sufficient amplitude, partial neuromuscular blockade with T1 reduced to 10% to 20% of baseline or train-of-four (TOF) count with 2 is acceptable.[9]

There are 2 ways to give NMBD, which are by prolonged infusion and intermittent bolus injection. The bolus administration of NMBD can be performed easily on demand, but the plasma concentration of it not constant. While continuous infusion has advantage to maintaining constant plasma concentration, in general, the use of prolonged infusion of NMBD with moderate to high elimination half-life was limited due to the delayed recovery due to accumulation. But it is noted that rocuronium has similar recovery index (the time required for the first twitch of TOF to recovery from 25% to 75% of baseline) between bolus and 2 h infusion.[10] So, rocuronium seems to be suitable for prolonged infusion. However, research is lacking on which of the above 2 methods can help achieve a smoother operation without disturbing MEP measurements. Therefore, it is noted in this study, which compares the effect of prolonged infusion and bolus injection of rocuronium on the progress of neurointervention and MEP monitoring.

2. Methods

This study was approved by the Institutional Review Board of the Haeundae Paik Hospital and registered at https://cris.nih.go.kr (protocol number KCT0002829). All patients signed an informed consent. This prospective randomized study has proceeded between December 2017 and April 2018. Total 80 patients who were undergoing elective coil embolization or stent insertion under general anesthesia with MEP monitoring after diagnosis of cerebral aneurysm in our hospital were enrolled in this study. The patients were excluded if they had an American Society of Anesthesiologists physical status IV or higher, severe cardiopulmonary disorders with hemodynamic instability, significant hepatic disease, end-stage renal disease, neuromuscular disease or motor neuron disease.

We randomly assigned the patients into 1 of 2 groups and administered rocuronium intravenously either continuous infusion (Group I, 40 patients) or intermittent bolus manner (Group B, 40 patients). The blocked randomization was performed by using computer software generation. In this context, only the attending anesthesiologist was informed about the study group before administering the anesthesia. The patients entered the operation room without premedication. The use of an electrocardiography, pulse oxymetry, capnography, noninvasive blood pressure and bispectral index (BIS) were monitored intraoperatively. In this case, the neuromuscular transmission module (Intellivue NMT, Philips, USA) was adjusted to monitor degree of muscle relaxation. An arterial catheter was also placed in all of the patients for the direct measurement of blood pressure after an anesthetic induction.

Anesthesia was induced by intravenous propofol (effect-site concentration 2–5 μg/ml, Schneider model) with remifentanil (effect-site concentration 2–4 ng/ml, Minto model) through a target-controlled infusion pump (Orchestra, Fresenius kabi, USA). After the induction, a tracheal intubation was facilitated with rocuronium (0.6 mg/kg). Remifentanil was titrated to control the change of blood pressure to the surgical procedure within a 20% range of its preoperative value, if blood pressure raised or fell more than 10% of the preoperative value, the target concentration was raised or lowered. And propofol was infused at a dose range of 2 to 4 mcg/ml to maintain BIS between 40 and 60. In this case, phenylephrine was infused intravenously when hypotension occurred. It is noted that hypotension was defined as a decrease in the mean arterial pressure of more than 20% of preoperative baseline, or below 60 mmHg.

Twenty minutes after induction, the patients in group I were administered rocuronium infusion by 5 mcg/kg/min. Likewise the patients in group B were injected rocuronium 0.1 mg/kg as needed. The bolus rocuronium administration was needed when spontaneous breathing or movement was detected, or when the surgeon requested such action or procedure.

The response of the adductor pollicis brevis muscle to the TOF stimulation of the ulnar nerve was monitored every 5 min. At that time, the MEP amplitude was measured by a neurophysiologist who was blinded to the study group. MEP was recorded by paired subdermal needle electrodes inserted into all four limb muscles (abductor pollicis brevis, vastus lateralis, extensor hallucis longus and abductor hallucis). The MEPs were triggered by an electrical stimulation of the scalp with Nim-eclipse system IOM machine (Medtronic, USA). It delivered electrical stimulus pulse trains (pulse width = 50 mcs, n = 5, interpulse interval = 2 ms, 500 Hz) between the 2 electrodes placed over the motor cortex region at C3 and C4 (International 10–20 System).[11] The optimal amplitude was obtained by adjusting the MEP stimulus intensity in intervals of 50 to 100 V from a starting value of 400 V, and a change of stimulus intensity was recorded. The MEP was checked through every insertion of each coil, or when the surgeon decided and the amplitudes of MEP or change of stimulus intensity were recorded by neurophysiologist. To estimate within the patient variability, we compared the mean MEP amplitudes and the coefficients of variation (CVs, %) of all measured MEP amplitudes in four limbs between groups.[12,13] When the MEP alteration occurred, such as a loss of MEP or a sudden decrease of MEP amplitude by more than 50%, the neurophysiologist recorded that measurement as an undetectable MEP.

After the surgery, propofol, remifentanil, and/or rocuronium were discontinued. At a TOF count 2 or more, a single bolus dose of sugammadex 2 mg/kg was administered, and at a TOF count less than 2, sugammadex 4 mg/kg was administered. When the patient's status reached consciousness and spontaneous respiration were restored, at that time the endotracheal tube was removed.

In this study, our primary outcomes were incidence of spontaneous respiration, involuntary movement and amplitude of MEP. The spontaneous respiration was noted by attending anesthesiologist when curare cleft of capnography was appeared and the involuntary movement was noted by attending neurosurgeon. Patient movements included acceptable movement (movement that not excessive and not interrupt the surgery including mild cough), unacceptable movement (movement that interrupt surgery including head or limbs elevation) and no movement. In these terms, we also recorded total dose of anesthetics, phenylephrine, sugammadex during surgery, TOF, and emergence time (defined as a time interval between the discontinuation of anesthetics and a tracheal extubation).

2.1. Statistical analysis

We determined that the sample size for this study following a pilot study. Our primary outcome was the involuntary movement difference between both groups, and there was a 10% difference in a pilot study. We expected that there would be a 10% difference of involuntary movement between group B and group I. It is particularly important that a power analysis (α = 0.05, β = 0.20) showed that a total 70.640 patients would be required, as well as considering 10% of dropouts, we thus enrolled 80 patients in the study. The data are presented for the frequency with a noted percentage for the categorical variables and mean ±

Table 1

The patient's demographic variables.

	Group I (n = 39)	Group B (n = 40)	P value
Sex			
male	12 (30.8)	9 (22.5)	.41[1]
female	27 (69.2)	31 (77.5)	
Age (years)	58.9 ± 9.8	62.0 ± 9.3	.15[2]
Weight (kg)	63.7 ± 9.2	62.2 ± 11.0	.28[3]
Height (cm)	161.0 ± 8.0	158.4 ± 7.1	.13[2]
BMI (kg/m^2)	24.6 ± 3.2	24.7 ± 3.0	.78[3]
ASA			
1	15 (38.5)	13 (32.5)	.86[4]
2	22 (56.4)	25 (62.5)	
3	2 (5.1)	2 (5.0)	

ASA = American society of anesthesiologists classification, BMI = body mass index.
[1] P values were derived from chi-square test.
[2] P values were derived from independent t test.
[3] P values were derived from Mann-Whitney U test.
[4] P values were derived from Fisher exact test.
Shapiro-Wilk test was employed for test of normality assumption.

standard deviation for continuous variables. The differences in the study participant's characteristics were compared across subgroups with chi-square test or Fisher exact test for categorical variables and independent test or Mann-Whitney U test for continuous variables as appropriate. To check if its distribution is normal, we used the Shapiro-Wilk test. All statistical analyses were carried out using SPSS 24.0, and p values less than 0.05 was considered as statistically significant.

3. Results

We enrolled a total 80 patients in this study, and 1 patient in group I was dropped because of the malfunction of MEP monitoring device. The patient's demographic data are presented in Table 1. In fact, the variables in Table 1 showed no considerable differences as reviewed. The perioperative clinical data are shown in Table 2. The mean anesthesia time and operation time did not differ between the 2 groups. It is noted that the mean propofol and remifentanil doses did not differ between the 2 groups, but the total administered rocuronium doses are significantly higher in infusion group. Because of this, it is noted that higher doses of sugammadex were needed to reverse neuromuscular blockade in group I, and time of emergence from

Table 2

Perioperative clinical data.

	Group I (n = 39)	Group B (n = 40)	P value
Anesthesia time (min)	95.4 ± 19.8	88.9 ± 18.4	.08[1]
Operation time (min)	62.5 ± 17.1	56.7 ± 18.8	.08[1]
Emergence time (min)	12.1 ± 3.6	11.6 ± 3.3	.49[1]
Total infused propofol (mg)	603.1 ± 173.4	527.2 ± 117.9	.09[1]
Total infused remifentanil (mcg)	553.9 ± 171.3	500.5 ± 193.9	.11[1]
Incidence of hypotension			
Yes	27 (69.2)	28 (70.0)	.94[2]
No	12 (30.8)	12 (30.0)	
Total injected phenylephrine (mcg)	743.45 ± 758.2	1092.8 ± 1742.9	.73[1]
Total injected rocuronium (mg)	54.5 ± 13.6	39.7 ± 7.6	< .001[1]
Total injected sugammadex (mg)	169.8 ± 71.0	122.5 ± 27.9	.006[1]

[1] P values were derived from Mann-Whitney U test.
[2] P values were derived from chi-square test.
Shapiro-Wilk test was employed for test of normality assumption.

Table 3

Comparisons of MEP variables.

	Group I (n = 39)	Group B (n = 40)	P value
Mean stimulus intensity (V)	406.8 ± 22.1	403.7 ± 32.7	.51[1]
Mean MEP amplitude (mV)			
Right Arm	1483.9 ± 1213.5	2608.0 ± 1646.2	< .001[1]
Left Arm	1383.1 ± 1219.9	2798.3 ± 2059.9	< .001[1]
Right Leg	780.3 ± 571.8	1502.2 ± 1182.7	.007[1]
Left Leg	1050.1 ± 1063.1	1521.8 ± 1235.9	.03[1]
CV of MEP amplitude (mV)			
Right Arm	33.1 ± 22.9	53.3 ± 26.8	.001[1]
Left Arm	30.0 ± 23.1	55.3 ± 29.8	< .001[1]
Right Leg	35.4 ± 21.7	51.6 ± 28.6	.01[1]
Left Leg	39.5 ± 24.4	54.4 ± 33.8	.03[1]
Increase of stimulus intensity			
Yes	4 (10.3)	3 (7.5)	.71[2]
No	35 (89.7)	37 (92.5)	
Decrease of stimulus intensity			
Yes	0 (0.0)	1 (2.5)	.999[2]
No	39 (100.0)	39 (97.5)	
Incidence of spontaneous respiration			
Yes	0 (0.0)	6 (15.0)	.03[2]
No	39 (100.0)	34 (85.0)	
Incidence of involuntary movement			
Yes	2 (5.1)	12 (30)	.006[3]
No	37 (94.9)	28 (70)	
Incidence of undetectable MEP			
Yes	3 (7.7)	5 (12.5)	.71[2]
No	36 (92.3)	35 (87.5)	

CV = coefficient of variation, MEP = motor evoked potential.
[1] P values were derived from Mann-Whitney U test.
[2] P values were derived from Fisher exact test.
[3] P values were derived from chi-square test.
Shapiro-Wilk test was employed for test of normality assumption.

anesthesia did not differ. The overall incidence of hypotension and total amount of administered phenylephrine doses were not different between the 2 groups.

Table 3 shows the MEP parameters. The mean stimulus intensity was not different between the 2 groups. The incidences of changing stimulus intensity were 4 in each group. Both mean MEP amplitudes and CVs of all limbs were significantly smaller in group I. The undetectable MEP were noted to have occurred in 3 patients in group I and 5 patients in group B, but it did not show significant difference as measured. There was no spontaneous respiration of patients as noted and exhibited in group I, whereas 6 cases were occurred in group B (P = .26). The incidence of involuntary movement of patients was also significantly lower in group I (P = .006).

Figure 1 shows mean TOF counts checked every 10 min in both groups. The TOF counts were significantly higher in group B from 30 min. In group B, the TOF counts were maintained between 1 and 2.

The unacceptable movement that can interrupt the process of neurointervention did not occur in group I, whereas it was noted to have occurred during 4 cases in group B. Broadly speaking, it could not show significant difference (P = .116).

When we separated the procedures into long and short duration of procedure based on 60 min, the incidence of involuntary movement in long duration procedure was significantly high in group B (Table 4).

No patient showed significant a MEP change during the procedures, and no motor deficit was found postoperatively in all patients.
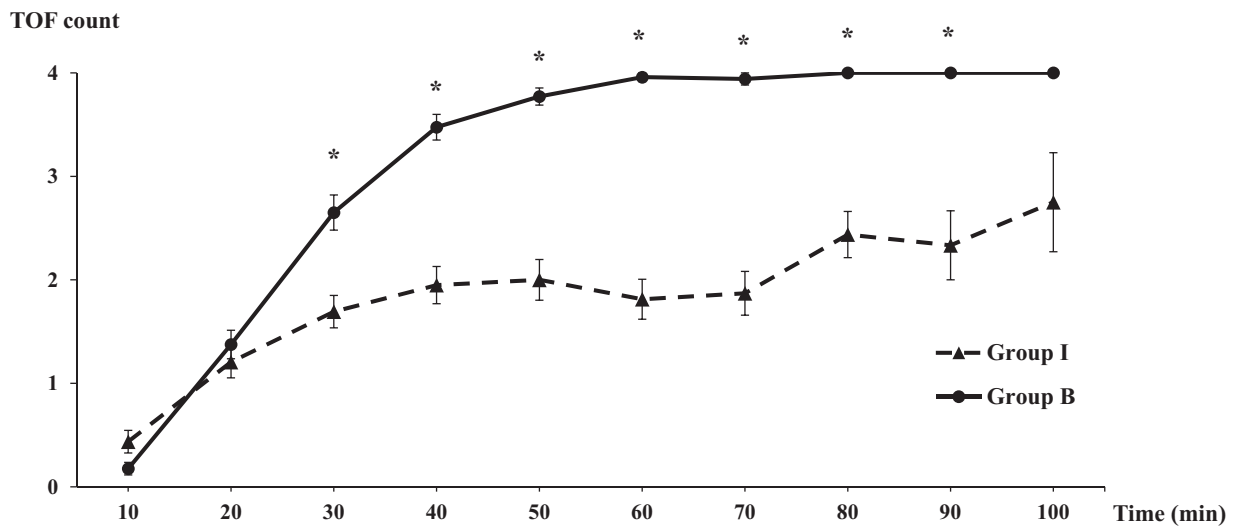
Figure 1. Comparison of TOF count between infusion and bolus group (Bonferroni-corrected p value). TOF = train-of-four. The error bars indicate standard error of mean.

4. Discussion

Intraoperative neurophysiologic monitoring is widely used for brain or spine surgery to detect complications early. Especially, the MEP monitoring is used as a supplementary technique to detect perforating vessel compromise, which may lead to motor impairment not detected by SSEP.[14]

Intraoperative MEP is usually characteristic of a recording of compound muscle action potential of peripheral muscle (eg, abductor pollicis brevis muscle, tibialis anterior muscle) in a patient, and it requires the transmission of a neural signal through the neuromuscular junction. In other words, the use of NMBD during surgery can significantly affect the amplitude of MEP and raise inter-trial variability of MEP amplitudes.[15,16] In line with this data, the amplitude of MEP is decreasing with increasing neuromuscular blockade (NMB), and is not able to be detected from more propound NMB. Likewise, it is important to note that in reviewing the complexity of using NMBD, Sloan advised avoiding NMBD during MEP monitoring.[17] By the same token in this case, Kothbauer also worried that a partial NMB could add an uncontrolled variable to this measurement when interpreting the available MEP data, and this factor can worsen the specificity of MEP in a patient.[18] In these terms, no NMB during surgery is related to problems such as a limited exposure of surgical field and involuntary patient movement.[6–8] Patient movement during the MEP monitoring may interfere with

surgery and raise serious safety concerns.[19] Hemmer et al reported that 3.2% of the patients with no NMB exhibited unacceptable movement during craniotomy for aneurysm clipping.[20] Some studies that reported that the incidence of spontaneous movement did not differ between partial and no NMB groups.[12,21] It is noted that in our study, the incidence of involuntary movement and spontaneous respiration were significantly lower in the infusion group.

In the observance of 'no NMBD use methods' for preventing unexpected movement, more anesthetics may be needed in that case, and it can cause unwanted deep anesthesia in the patient. One consequence of this is that deep anesthesia is associated with some problem such as hypotension, shock and delayed emergence. Although the relation between anesthetic depth and long-term survival is inconclusive, many literature reviews suggest an association between deep anesthesia and poorer outcomes.[22–24] Leslie and Short recommend maintaining optimal anesthetic depth; and it is defined as deep enough to avoid intraoperative responsiveness and postoperative recall, but light enough to avoid intraoperative hypotension and postoperative side effect in the patient.[25] In present study, we titrated anesthetics to keep BIS values between 40 and 60, and administered a low amount of NMBD to prevent involuntary patient movement. To keep the BIS values consistent, the target concentrations of anesthetics might be lower and the incidence of

Table 4

Incidence of involuntary movement and unacceptable movement over time of procedure.

	Long duration of operation			Short duration of operation		
Variable	Group I (n=23)	Group B (n=16)	P value	Group I (n=16)	Group B (n=24)	P value
Incidence of involuntary movement						
yes	2 (8.7)	6 (37.5)	.045	0 (0)	3 (12.5)	.26
no	21 (91.3)	10 (62.5)		16 (100)	21 (87.5)	
Incidence of unacceptable movement						
yes	0 (0)	3 (18.8)	.06	0 (0)	1 (4.2)	1.00
no	23 (100)	13 (81.3)		16 (100)	23 (95.8)	

Long: over 60 min; short: less than 60 min.
P values were derived from Fisher exact test.

patient movement seemed to be higher than previous studies, but additional trials are needed to support this conclusion.

In previous studies, an excessive movement was observed in 6% to 10% of the patients undergoing MEP monitoring without NMB.[14,26] We have also shown that in about 10% of patients in group B, an involuntary movement was recorded. However, the degree of movement was not considered in former studies. In another study, the intraoperative movement during MEP was classified as either nociception induced movement (defined as "coughing" or reflexive limb movement temporally elicited by MEP stimulation), or excessive field movement (defined as grossly visible head movement as determined by surgical and anesthesia team), and the incidences were measured as 1% and 2.2%, respectively.[20] In these terms, those studies did not classify the movement from the point of view of a surgeon. This brings us to understand that we classified the patient movements into unacceptable and acceptable movement, as noted according to the degree of disturbing the procedure. When rocuronium is administered in repeated dosages, its serum profiles show a sawtooth pattern. So, when the plasma concentration of rocuronium is high, the patient movement can be suppressed, but when that is low, not only does the patient movement occur more, but it can be more severe enough to interfere the surgery. On the other hand, when the plasma concentration is kept constant by continuous infusion of rocuronium, even if patient movement occurs, it is expected the occurrence of unacceptable movement would be suppressed. And in this study, although the difference did not show statistical significance, no unacceptable movement was reported in group I, whereas 4 were reported in group B. This was equivalent to 5%, and the small dose of NMBD was injected to resume the operations for the study at that time. Some researchers showed that the elimination half-life of rocuronium administered as a bolus followed by continuous infusion was not significantly different with elimination half-life of single bolus dose of rocuronium.[27,28] But there is lack of data describing the pharmacokinetics of intermittently injected rocuronium.

The prevailing discipline for successful MEP monitoring includes the procedure to first, proper waveform and amplitude, which are needed. In the meantime, because the propound NMB can excessively suppress the amplitude of MEP, the use of proper NMBD is important in this case. Some literature reported that successful MEP monitoring was performed when they kept the TOF count 1 to 2.[7–9] However, there are few studies that suggested a dose of NMBD for the proper MEP monitoring of a patient. In the present study, we could maintain that the TOF count between 1 to 2 with the rocuronium infusion rate of 5 mcg/kg/min was sufficient (Fig. 1). Monitoring of the MEPs were successful in both groups, and the MEP variability that were calculated by CV were significantly lower in the infusion group. The other condition for successful MEP monitoring was shown to have decreased in terms of a false-positive and false-negative rate. The stimulus intensity is an important variable for these factors.[21] This brings us to understand that as the stimulus intensity increases, especially over 500 V, it is noted that the false-negative rate can also experience increases. Guo et al study suggested that to lower the stimulus intensity, and reported 150 V of stimulus intensity could be sufficient when measuring in upper limbs.[29] In this study, the baseline stimulus intensity was 400 V and the mean stimulus intensity did not differ between groups, and there was no case requiring over 500 V of stimulation.

Essentially, it is noted that the continuous infusion of NMBD can be a cause of delayed emergence and remaining paralysis after reversal of NMBD, and these factors can threaten the patient safety. Additionally, it is evident that an incomplete reversal from NMBD can lead to severe hypoventilation and hypoxia after extubation in the patient. These could be the main reasons why anesthesiologists do not prefer the infusion of NMBD when working with patients. But, after sugammadex was introduced, the rapid and complete reversal from NMB became possible. Sugammadex is an antagonist of steroidal NMB, as noted especially with rocuronium, and doses are determined by the degree of muscle relaxation noted in the patient.[30] In the present study, individualized dose of sugammadex as determined by the TOF count, made no difference in the measured emergence time between the 2 groups. And any adverse events such as recurarization and hypoxia were not observed in patients who were in the recovery room during the period of study.

There are some limitations to the present study. First, it is small sample size of this study. Despite no unacceptable movement was occurred in group I, the occurrence of it in group B was not enough to make statistically valid result. If the larger study groups were involved, significantly different incidence of the unacceptable movement could have drawn. Second, only a single infusion rate of rocuronium was used in this study. Although favorable results were drawn in this study, more studies which use various infusion rates of rocuronium are required for a more positive outcome. Third, relatively short duration procedures were enrolled in this case. Because it is noted that the TOF count was seen to increase over time, the infusion rate of 5 mcg/kg/min may not be sufficient to prevent patient movement in long-duration procedure.

In conclusion, continuous infusion of rocuronium effectively inhibited the involuntary movement and spontaneous respiration of the patient, without disturbing the MEP monitoring. Additionally, it was noted that the MEP variability was more favorable when rocuronium was continuously infused.

Author contributions

Conceptualization: Myoung Jin Ko, Hyojoong Kim.
Data curation: Beomjin Oh, Jae-Wook Jung, Dae Seok Oh, Eunsu Kang.
Investigation: Myoung Jin Ko, Jae-Wook Jung, Dae Seok Oh, Sung Chul Jin, Yong Han Kim, Se Hun Kim.
Methodology: Myoung Jin Ko, Sung Chul Jin, Se Hun Kim.
Supervision: Yong Han Kim, Hyojoong Kim.
Visualization: Eunsu Kang.
Writing – original draft: Hyojoong Kim.
Writing – review & editing: Myoung Jin Ko, Hyojoong Kim.

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