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The utility of bispectral index monitoring for prevention of rocuronium-induced withdrawal movement in children

A randomized controlled trial

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Abstract

Background: This study was designed to determine whether a deep hypnotic state with a bispectral index (BIS) value less than 40 could alleviate withdrawal movement (WM) upon rocuronium injection during anesthesia induction in children.

Methods: Finally, 135 healthy children (3–12 years) scheduled for minor elective surgery were studied. Without premedication, anesthesia was induced with thiopental sodium 5 mg/kg. Patients were randomized into 2 groups (control vs experimental) and then by virtue of rocuronium injection time, patients in the experimental group were allocated into 2 groups, as follows: in the control group (group C; n = 45), rocuronium 0.6 mg/kg was administered at the loss of eyelash reflex; in the 1st experimental group, rocuronium 0.6 mg/kg was administered when BIS fell to less than 40 (group T; n = 45); however, if BIS did not fall below 40 after thiopental sodium administration, manual ventilation was provided with oxygen 6 L/minute using sevoflurane 8% and then rocuronium was administered when BIS fell below 40 (the 2nd experimental group, group S; n = 45). Rocuronium-induced WM was evaluated using a 4-point scale (no movement; movement/withdrawal involving the arm only; generalized response, with movement/withdrawal of more than 1 extremity, but no requirement for restraint of the body; and generalized response which required restraint of the body and caused coughing or breath-holding).

Results: No significant differences were found among the groups for patient characteristics including age, sex, height, and location of venous cannula. However, body weight, height, and body mass index in group S were all smaller than those in group T. The incidence of WM caused by rocuronium was 100% in group C, 95.6% in group T, and 80% in group S, and was significantly lower in group S than in group C. The grade of WM was 3.7 ± 0.6 in group C, 3.2 ± 0.9 in group T, and 2.6 ± 1.0 in group S. It was significantly lower in group T than in group C and significantly lower in group S than in groups C and T.

Conclusion: The confirmation of a deep hypnotic state with BIS values lower than 40 using BIS monitoring can reduce the grade of rocuronium-induced WMs during anesthesia induction using thiopental sodium or sevoflurane in children.

Abbreviations: BIS = bispectral index, BP = blood pressure, CI = confidence interval, DoA = depth of anesthesia, EtSevo = end-tidal concentration of sevoflurane, HR = heart rate, HRV = heart rate variation, i.v. = intravenous, TSA = thiopental sodium administration, WM = withdrawal movement.

Keywords: anesthesia, anesthesia, anesthetics, bispectral index monitor, children, general, inhalation, rocuronium, sevoflurane, thiopental

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1. Introduction

Rocuronium is a nondepolarizing muscle relaxant, which has a fast onset and is useful for rapid sequence induction. However, some anesthesiologists are reluctant to use rocuronium because its intravenous (i.v.) injection often produces withdrawal movements (WMs) associated with injection pain.[1–3] Several previous studies have been reported that the main cause of the pain generated by i.v. injection of rocuronium is the activation of nociceptors by the unphysiological osmolality or pH of the solution.[4,5]

Many studies have reported pretreatment techniques using various drugs to attenuate or eradicate WMs and pain during rocuronium injection.[6–9] However, these pretreatment techniques require additional drugs, which seems cumbersome in the clinical setting. We hypothesized that rocuronium-induced WMs might be a result of a lack of anesthetic depth. Anesthetic depth can be measured using monitoring of the bispectral index (BIS). The BIS is a processed electroencephalographic modality and is the most widely evaluated and validated device used for general anesthesia in children as well as adults.[10,11] Hwang et al[12] reported that the WM on injection of rocuronium could not be prevented with BIS monitoring in adult patients. However, they compared the 4 groups with BIS values of 85, 75, 65, and 55 (much higher than 40), and the results might be different in children. With reference to the results of the study, we sought to determine whether the confirmation of a deep hypnotic state with BIS monitoring could alleviate WMs in children. Therefore, we investigated the incidence and grade (severity) of WMs during rocuronium injection when BIS values were under 40 after thiopental sodium administration (TSA) for anesthesia induction in pediatric patients. We defined the BIS values lower than 40 (around 40) as a deep hypnotic state.[13] The aims of this study were to evaluate whether it was possible for a deep hypnotic state with BIS values lower than 40 to reduce WMs and to determine the utility of BIS monitoring for the prevention of WMs. We hypothesized that a deep hypnotic state with BIS monitoring could alleviate WMs.

2. Materials and methods

This study was a single-center prospective randomized controlled trial performed at Korea University Guro Hospital, Seoul, Republic of Korea, from April 2013 to June 2013. After obtaining approval of the Korea University Guro Hospital Institutional Review Board, the trial was registered in the UMIN clinical trials registry (unique trial number: UMIN000010545; registration number: R000012331; date of registration: April 19, 2013).

All patients were recruited from the departments of otorhinolaryngology, ophthalmology, orthopedic, genitourinary, or plastic surgery, Korea University Guro Hospital, by available research staffs. Patients were enrolled in the study at admission to the hospital the day before surgery. After an explanation on the trial, written informed consent from all parents and assent from the participants over the age of 7 were obtained.

A total of 156 patients with an American Society of Anesthesiologists physical status of 1 who were aged 3 to 12 years old and scheduled for minor elective surgery were enrolled in this study. We finally included 135 of these patients who had a 22- or 24-gauge cannula sited in the dorsal hand or wrist vein and/or to whom the exclusion criteria explained below were not applicable. Patients with a history of cardiovascular, respiratory (asthma), neurologic (seizure), kidney, or liver disease, mood disorder, prematurity, or developmental delay, the presence of upper respiratory infection, hypersensitivity to drugs, and those receiving analgesics were excluded. Patients with a vein that did not drain well or with redness, swelling, and tenderness along the vein as well as patients who had a history of difficult peripheral venous cannulation were also excluded. The i.v. cannula insertion was performed by skilled nurses on the dorsal hand or wrist of all patients in the night before surgery.

All patients were not premedicated. At the separation from their parents for entering the operating room, and during application of the BIS sensor and anesthesia mask in the operating room, an observer blinded to the group allocation evaluated the patient's face, behavior, and general response to assess anxiety on a 3-point scale (calm, asleep, cooperative, smiling, or accepting the mask readily; slight fear or anxiety; and expressing anxiety or fear by verbal response, crying, or screaming).[10] Children who expressed anxiety at level 3 or who behaved uncooperatively were excluded.

In the operating room, all patients were assessed by the Aspect A-2000® BIS monitor (version XP; Aspect Medical Systems, Newton, MA), electrocardiography, noninvasive arterial blood pressure (BP) measurement, and pulse oximetry. A pediatric BIS sensor (Aspect Medical System) was applied on the forehead of the patient. The smoothing time was set at 15 seconds and BIS values were updated every second. Initial BIS, BP, and heart rate (HR) values were recorded and the presence of any problems such as redness, swelling, or tenderness at the i.v. site was assessed. After an i.v. line was fully opened and fluid flow was confirmed to allow free administration, a 22- or 24-gauge cannula was flushed with 1 mL/kg normal saline.

Patients were randomized into 2 groups (control vs experimental) and then by virtue of rocuronium injection time following TSA, patients in the experimental group were allocated into 2 groups, as follows: in the control group (group C), rocuronium (Esmeron®, NV Organon, Oss, The Netherlands) was administered at the loss of eyelash reflex; in the 1st experimental group, it was administered when BIS values fell to less than 40 (group T); however, if BIS values did not fall below 40 after TSA, manual ventilation was provided with a tidal volume of 6 to 8 mL/kg using 8% sevoflurane (obtained by 2% increments every 3–4 breaths) at a fresh gas flow of 6 L/minute O_2 when BIS values started to increase after reaching the minimum BIS value after TSA. Manual ventilation was adjusted to maintain an end-tidal carbon dioxide pressure of 30 to 40 mm Hg. Rocuronium was then administered when BIS values fell to less than 40 (the second experimental group; group S). If the BIS value had not fallen below 40 despite manual ventilation with sevoflurane for 6 minutes or if systolic BP had fallen to less than 70% of the baseline value, manual ventilation was stopped and the case was excluded from the study. Since the ratio between the patient groups in which BIS fell below 40 or did not fall below 40 after TSA in the patients allocated to the experimental group was roughly 1:1 in the results of a pilot study, we applied the random allocation rule using the restricted randomization approach with a 1:2 ratio between the control group and the experimental group (which was then divided into the groups T and S) for randomization.[14] A single investigator was responsible for the generation of the random allocation sequence and the group assignment of patients. Random numbers from a computer-generated list in a web-site (www.randomization.com) were obtained and were kept in opaque sealed envelopes until they

were opened in the operating room by the anesthesiologist not involved in the study.

All patients did not know whether they were allocated to between the control group or an experimental group. All anesthetic procedures were carried out by 2 anesthesiologists. One independent anesthesiologist performed anesthesia induction including the administration of rocuronium or manual ventilation using sevoflurane according to the study protocol. The other independent anesthesiologist measured all outcome values throughout the induction period.

Anesthesia was induced with thiopental sodium 5 mg/kg in all patients. The patients in each group received rocuronium 0.6 mg/kg over a period of 5 seconds when the eyelash reflex was lost (group C), when the BIS value fell under 40 after TSA (group T), and when the BIS value fell under 40 not after TSA but after manual ventilation using 8% sevoflurane (group S). At that time, the elapsed time from the start of TSA and the BIS value were recorded. Next, WMs caused by rocuronium injection were observed. The incidence and grade of WMs were evaluated not by the criteria used in previous studies,[6–9,15,16] but using the following new modified criteria: no movement; movement/withdrawal involving the arm only; generalized response, with movement/withdrawal of more than one extremity, but no requirement for restraint of the body; and generalized response which required restraint of the body and caused coughing or breath-holding. As well as the BIS value and the elapsed time from TSA at the loss of eyelash reflex, the minimum BIS value after TSA and the elapsed time from TSA to the time of the minimum BIS value were also recorded. HRs before and after rocuronium injection were observed and the heart rate variation (HRV) was calculated from the difference between HRs before and after rocuronium injection using the following formula: $(HR_{after} - HR_{before})/HR_{before} \times 100$ (%). All patients were closely observed for the occurrence of adverse events during the perioperative period (until postoperative 24 hours).

The primary endpoints of this study were the incidence and grade of the WM. Secondary endpoints were the BIS values and elapsed times at each specific time point measured after TSA or at rocuronium injection during anesthesia induction, HR at rocuronium injection, and HRV during rocuronium injection.

2.1. Sample size calculation

The sample size calculation was based on the results of a pilot study performed to assess the grade of rocuronium-induced WM, a primary endpoint, with 10 cases in each group. In the pilot study, the grade of the WM (mean ± standard deviation [SD]) were 3.5 ± 0.7 in group C, 3.2 ± 1.1 in group T, and 2.8 ± 1.1 in group S, respectively. Therefore, the effect size of 3-groups was 0.276 and the total sample size was 132, calculated by 2-sided one-way analysis of variance test, a level of significance of 0.05 and a power of 0.8. Considering about 20% dropout rate, the total sample size for final enrollment was 156, including 52 patients per each group.

2.2. Statistical analysis

All results are expressed as mean ± SD, median (25th–75th percentiles [interquartile range, IQR]), or numbers of patients, and the SPSS 18 software (SPSS Inc., IBM, Chicago, IL) was used for statistical analysis.

We compared the following parameters using one-way analysis of variance (normally distributed data) or Kruskal–Wallis test (abnormally distributed data), followed by *t* test or Mann–-Whitney *U* test with Bonferroni correction: patient characteristics including age, weight, and height, the grade of WM, the BIS value and elapsed time at each time point, HR at rocuronium injection, and HRV during rocuronium injection. Sex, location of venous cannula, and the incidence of WM were compared with the chi-square test or Fisher exact test with Bonferroni correction. A value of $P < 0.05$ was considered statistically significant.

3. Results

Of the 156 patients originally enrolled in the study, 21 patients were excluded for violations of the study protocol. Thus, the results from 135 patients were evaluated and analyzed, with 45 patients finally included in groups C, T, and S, respectively (Fig. 1).

No significant differences were found among the groups for patient characteristics including age, sex, height, and location of venous cannula. However, body weight was lower in group S than in group T ($P = 0.001$), and height was smaller in group S than in group T ($P = 0.005$). Further, body mass index was lower in group S than in group T ($P = 0.005$) (Table 1).

The incidence of WM caused by rocuronium was 100% in group C, 95.6% in group T, and 80% in group S, and was significantly lower in group S than in group C ($P = 0.001$) (Table 2). The grade of WM was 3.7 ± 0.6 in group C, 3.2 ± 0.9 in group T, and 2.6 ± 1.0 in group S. It was significantly lower in group T than in group C (mean difference: −0.49, 95% confidence interval [CI]: −0.92 to −0.05, $P = 0.004$) and significantly lower in group S than in groups C and T (mean difference [group S vs group C]: −1.04, 95% CI: −1.48 to −0.61, $P < 0.001$; mean difference [group S vs group T]: −0.56, 95% CI: −0.99 to −0.12, $P = 0.009$, respectively) (Fig. 2).

The baseline BIS value was not significantly different among the 3 groups ($P = 0.777$). The BIS value and elapsed time from TSA at the loss of eyelash reflex were not significantly different among the 3 groups ($P = 0.836$, $P = 0.980$, respectively). The elapsed time from TSA to the time of minimum BIS was not different among the 3 groups ($P = 0.268$), but the minimum BIS value after TSA was lower in group T than in group C ($P < 0.001$) and higher in group S than in groups C and T ($P = 0.001$, $P < 0.001$, respectively). The elapsed time from TSA to rocuronium injection was longer in group T than in group C ($P < 0.001$) and longer in group S than in groups C and T ($P < 0.001$, $P < 0.001$, respectively). The BIS value at rocuronium injection was higher in group C than in groups T and S ($P < 0.001$, $P < 0.001$, respectively), but it was not different between groups T and S ($P = 0.106$). The BIS value 15 seconds after rocuronium injection was significantly higher in group C than in groups T and S ($P < 0.001$, $P < 0.001$, respectively) (Table 2). In group S, the end-tidal concentration of sevoflurane (EtSevo) at injection of rocuronium was 5.0% ± 0.7% and the duration of manual ventilation with 8% sevoflurane was 212 ± 56 seconds (3.5 ± 0.9 minutes).

HR at rocuronium injection was not significantly different among the 3 groups ($P = 0.218$), and neither was HRV ($P = 0.149$) (Table 2).

There were no problematic adverse events including redness and swelling at the i.v. injection site, hypotension, desaturation, or laryngospasm in all patients during the perioperative period.

4. Discussion

Rocuronium-induced pain and WM can cause injury to patients, make additional drug administration difficult, and cause

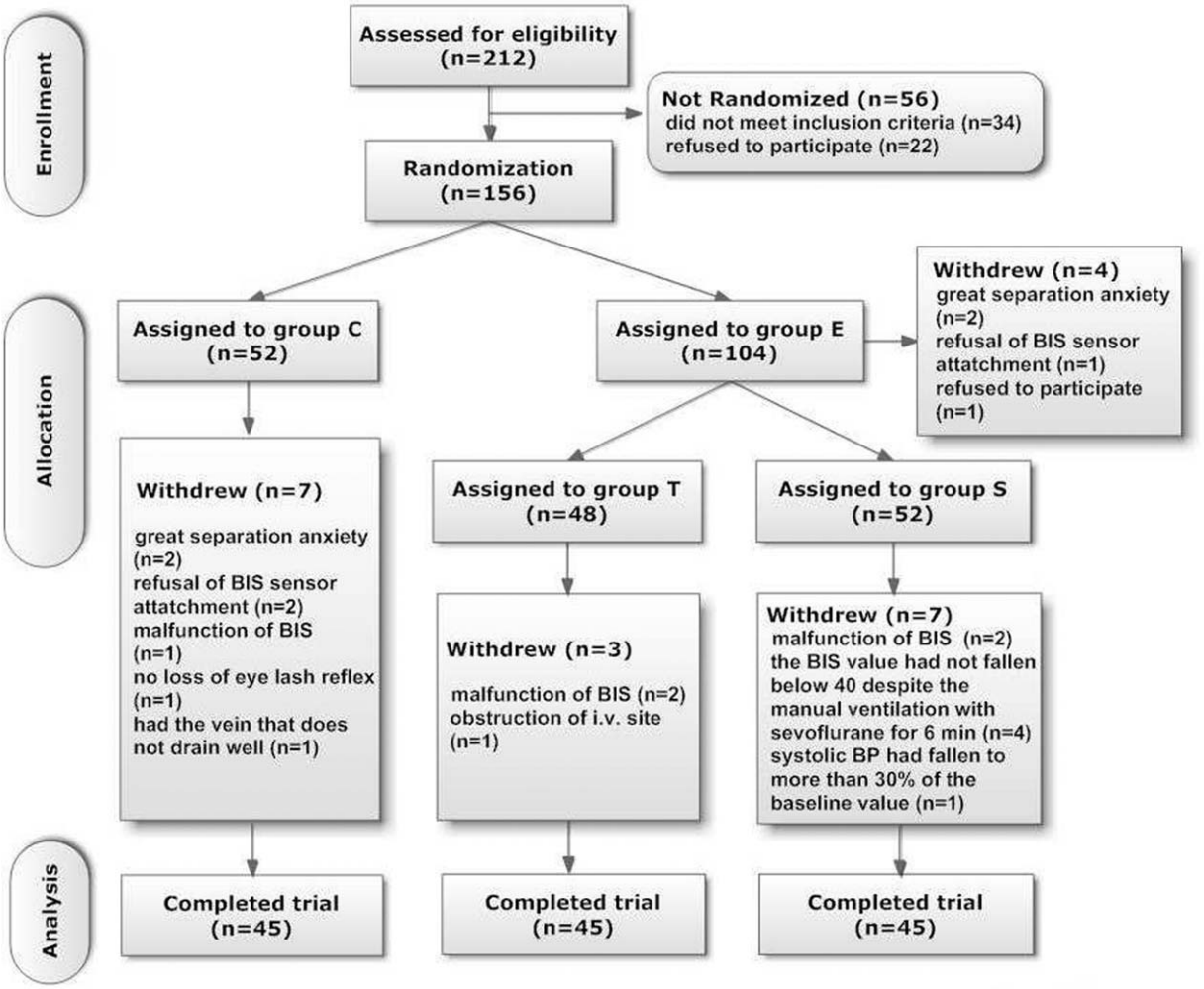

Figure 1. Flow chart of patient recruitment, randomization, and withdrawal. On the basis of the pilot study results, we applied a randomized algorithm using a 1:2 ratio between the control group and the experimental group, which was then divided into groups T and S. Group C: control group. Group E: experimental group. Group T: experimental group which received rocuronium when BIS values fell below 40 after thiopental sodium administration. Group S: experimental group which received rocuronium when BIS values fell below 40 not after thiopental sodium administration but after manual ventilation with 8% sevoflurane. Malfunction of BIS means that the BIS value of the patient did not appear on the BIS monitor or the signal quality index (SQI) showed poor signal quality (<50%) over 30 seconds during the study period. BIS = bispectral index, BP = blood pressure.

unexpected removal of the i.v. catheter, which can delay anesthesia induction and disturb rapid management for emergent problems. The incidence of WM has been reported to be 50% to 80% in adults.[1–3,17] The incidence and severity of rocuronium-induced WMs differ with age. The incidence of WM is estimated to be higher in children, where it has been reported to be 83% to 100%.[6,7,15,16] In addition, the failure rate of pretreatment for the prevention of WMs is higher in

Table 1

Patient characteristics.

	Group C (n = 45)	Group T (n = 45)	Group S (n = 45)
Age, year	7 (4–9.5)	8 (5–11)	6 (5–8.5)
Sex (M/F)	28/17	25/20	28/17
Height, cm	121.6 ± 19.1	128.2 ± 16.4	118.1 ± 16.6*
Weight, kg	25.4 (18.6–36.5)	30 (21–38.5)	21.2 (18.1–26.7)*
BMI, kg/m^2	17.5 ± 2.5	18.2 ± 3.6	16.3 ± 2.2*
Location of venous cannula (dorsal hand/wrist)	32/13	28/17	34/11

Values are expressed as mean ± SD, median (25th–75th percentiles [IQR]), or numbers of patients. Group C: control group. Group T: experimental group which received rocuronium when BIS values fell below 40 after thiopental sodium administration. Group S: experimental group which received rocuronium when BIS values fell below 40 not after thiopental sodium administration but after manual ventilation with 8% sevoflurane. BIS = bispectral index, BMI = body mass index, IQR = interquartile range, SD = standard deviation.

* $P < 0.05$ compared with group T.

Table 2

Main outcomes measured at baseline and each specific time point after thiopental sodium injection or at rocuronium injection during anesthesia induction.

	Group C (n = 45)	Group T (n = 45)	Group S (n = 45)
Baseline BIS value	95.2 ± 5.1	95.5 ± 4.2	95.0 ± 4.4
Loss of eyelash reflex			
Time, second	29.6 ± 6.5	29.8 ± 6.8	29.7 ± 7.9
BIS value	85.0 ± 13.2	83.9 ± 14.1	87.4 ± 9.5
Minimum BIS value after thiopental sodium injection			
Time, second	54.5 ± 12.2	56.5 ± 14.2	59.0 ± 10.7
BIS value	42.4 ± 13.4	32.0 ± 8.1*	50.8 ± 9.9*,†
Rocuronium injection			
Time, second	33.4 ± 6.2	52.9 ± 11.3*	212.0 ± 56.1*,†
BIS value	67.9 ± 18.1	35.0 ± 6.5*	37.0 ± 4.3*
HR, bpm	120.7 ± 16.3	116.5 ± 13.4	121.8 ± 15.8
BIS value 15 seconds after rocuronium injection	55.1 ± 17.0	36.6 ± 10.5*	36.2 ± 5.4*
HRV, %	7.5 ± 12.4	9.3 ± 13.0	12.4 ± 11.2
Incidence of withdrawal movement	45 (100%)	43 (95.6%)	36 (80.0%)*

Values are expressed as mean ± SD or numbers of patients (%). Group C: control group. Group T: experimental group which received rocuronium when BIS values fell below 40 after thiopental sodium administration. Group S: experimental group which received rocuronium when BIS values fell below 40 not after thiopental sodium administration but after manual ventilation with 8% sevoflurane. HRV during rocuronium injection (=[heart rate after rocuronium injection − heart rate before rocuronium injection]/heart rate before injection × 100%). BIS = bispectral index, HR = heart rate, HRV = heart rate variation, SD = standard deviation

* $P < 0.05$ compared with group C.

† $P < 0.05$ compared with group T.

children than in adults, since it is 7% to 35% in adults[18–20] and 27% to 46% in children.[7,15] Therefore, sudden and aggressive movement during anesthesia induction can be potentially more harmful to children than adults. In fact, there was a case report on gastric regurgitation with pulmonary aspiration following generalized spontaneous movements associated with rocuronium injection in a 5-year-old girl.[21] Therefore, it is still important for anesthesiologists to find an effective method which can reduce WMs in pediatric patients.

We noticed that anesthetic depth could be quite shallow at the point of rocuronium injection, even though rocuronium is usually injected at the loss of eyelash reflex during anesthesia induction in routine clinical practice. In this situation, there may be a risk for an episode of anesthesia awareness due to pain or stimulation of rocuronium injection and thus the use of BIS monitoring can also be effective for preventing anesthesia awareness.[22] Although no single component of anesthesia such as hypnosis can be used to define overall "anesthetic depth" considering the underlying mechanisms of general anesthesia,[23] the hypnotic depth is the primary endpoint of anesthesia and this has become the focus of contemporary depth of anesthesia monitoring.[10] Therefore, we hypothesized that rocuronium-induced WMs might be considerably suppressed if rocuronium is administered not at the loss of eyelash reflex but once a deep hypnotic state with BIS values lower than 40 has been achieved.

To our knowledge, this is the first prospective randomized study to investigate whether a deep hypnotic state with BIS values lower than 40 enables suppression of rocuronium-induced WMs and determine the utility of BIS monitoring for the prevention of WMs during anesthesia induction in pediatric patients. Therefore, we first carried out a pilot study to estimate the distribution ratio of patients in each group and select the proper randomization method, as well as to determine the sample size of this study. There were some interesting findings in the results of the pilot study. First, we confirmed that the anesthetic depth at the loss of eyelash reflex was quite shallow, judging by BIS values at this time. Second, we realized that only about 50% of children aged 3 to 12 years old could reach a deep hypnotic state with BIS values <40 after i.v. injection of thiopental sodium 5 mg/kg. The other 50% of children who could not reach BIS values <40 needed additional sedation to reach a deep hypnotic state, so we applied mask ventilation with a fresh gas flow of 6 L/minute O_2 using 8% sevoflurane (average duration: 212 ± 56 seconds) to reach BIS values lower than 40. As a result, we could assess the different

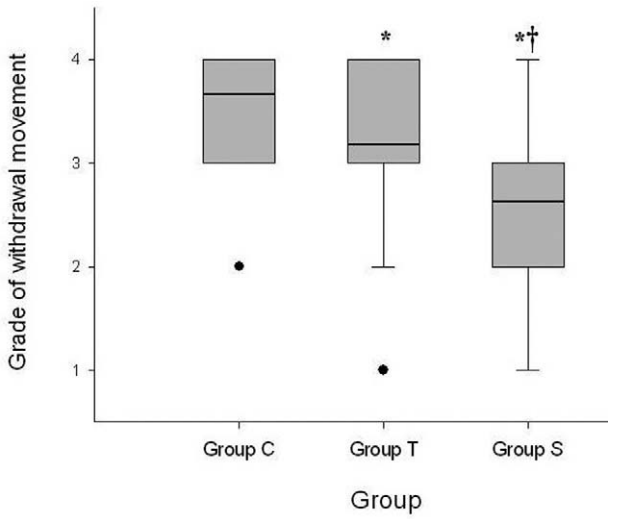

Figure 2. Grade of withdrawal movement. The graph shows a boxplot of each group with median, IQR, and range of withdrawal movement. The dots in group C and T represent the outliers. Group C: control group. Group T: experimental group which received rocuronium when BIS values fell below 40 after thiopental sodium administration. Group S: experimental group which received rocuronium when BIS values fell below 40 not after thiopental sodium administration but after manual ventilation with 8% sevoflurane. *$P < 0.05$ compared with group C. †$P < 0.05$ compared with group T. BIS = bispectral index, IQR = interquartile range.

effects of these 2 methods for reaching a deep hypnotic state on rocuronium-induced WMs. We could not randomly allocate the patients into the 3 groups investigated (the control group and the 2 experimental groups, groups T and S) because it was impossible to know if a patient would reach a BIS value <40 after TSA. However, we could randomly allocate the patients into 2 groups (the control group and an experimental group, which was then divided into groups T and S) using the randomization method of a 1:2 ratio, based on the results of the pilot study indicated a distribution ratio of patients between groups T and S of around 1:1.

We demonstrated that a deep hypnotic state with BIS values <40 could suppress WMs and that BIS monitoring for the prevention of WMs could be useful in pediatric patients. Therefore, it could be possible that WMs represent episodes of consciousness without memory consolidation. Of the 2 different treatments used to reach a deep hypnotic state, sevoflurane treatment following TSA (group S) decreased the incidence and severity of WMs, while TSA alone (group T) decreased the severity of WMs but did not decrease the incidence of WMs when compared with the control group (group C), despite allowing a deep hypnotic state with BIS values <40. In addition, sevoflurane treatment following TSA further reduced the severity of WMs when compared with TSA alone. This discrepancy between the effects of these 2 different treatments may have been caused by stronger suppression of WMs owing to the direct neuromuscular blocking effect of volatile anesthetics such as sevoflurane.[24] In our study, we observed the effect of thiopental monotherapy on BIS in groups C and T, but the effect of combined thiopental and sevoflurane therapy on BIS in group S. A combined therapy of thiopental (barbiturates) and sevoflurane may be additive for hypnosis and immobility in humans.[25] Therefore, in group S, the high minimum alveolar concentration of sevoflurane administered to the patients might suppress the grade of WMs by inducing the larger action of immobility despite the same hypnotic level with BIS values <40. Actually, in the present study, the EtSevo at injection of rocuronium was 5.0% ± 0.7% and the duration of manual ventilation with 8% sevoflurane was 3.5 ± 0.9 minutes. Yeom et al[26] showed that the 50% and 95% effective EtSevo that prevent WM at rocuronium injection are 2.9% and 4.3%, respectively. Park et al[27] also reported that inhalation induction with 8% sevoflurane can prevent the WM induced by rocuronium in children, and the sevoflurane inhalation time before rocuronium injection required to provide no withdrawal response in 50% and 95% of patients was 1.7 and 2.3 minutes, respectively. Unlike our results, they showed that inhalation of sevoflurane (required EtSevo of 5.5% ± 0.7%) with 67% nitrous oxide completely prevented WM in the short time period of 2.3 minutes. The cause of the discrepancy between the results of these studies[26,27] and our results may be related to differences in the age of the patients studied, the size of the venous cannula used, the dose of rocuronium, the application processes of anesthetics including thiopental sodium and sevoflurane, the EtSevo at injection of rocuronium, and the use of nitrous oxide between the studies.

In the present study, HRV was not different among the 3 groups. This result means that the 2 different treatments used to reach a deep hypnotic state in the experimental groups might not suppress the autonomic nervous system response evoked by pain and indicates that analgesia and areflexia other than unconsciousness as well as hypnosis may be needed to acquire an anesthetic depth which is sufficient to completely prevent rocuronium-induced WM.

In this study, age (although not statistically significant), height, weight, and BMI were lower in group S than in group T. These results indicate that the dose of thiopental sodium used as an induction agent was insufficient to cause BIS values to fall below 40 in the patients of group S and correspond to the fact that a larger volume of distribution in infants or young children results in higher dose requirements for thiopental sodium. Considering these results, rocuronium-induced WM would be attenuated if rocuronium is injected at about 56.5 ± 14.2 seconds from TSA in larger children weighing around 30 kg like the patients of group T, even in the absence of BIS monitoring. On the other hand, the similar result would be achieved if rocuronium injection is performed after TSA of more than 5 mg/kg (although the adequate dosage and injection time should be further investigated), or after mask ventilation for about 3.5 ± 0.9 minutes using 8% sevoflurane in smaller children weighing around 21.2 kg like the patients of group S.

A novel aspect of our study is the fact that the grade of WM was evaluated not by the 4-point scale used in previous studies[6–9,15,16] but by a 4-point scale with new modified criteria. We experienced a tendency for the grade of WM to be higher than 3 in most children when utilizing the scale used in previous studies. Therefore, we developed a new 4-point scale by differentiating high grades of WM and combining low grades of WM. Consequently, we could acquire a more uniform distribution of WM and assess generalized WM responses more differentially as scores of 3 or 4 in children of all groups. This also resulted in significant differences in the grade of WM among the groups. Therefore, we believe that our new 4-point scale can be effective and reasonable for the evaluation of rocuronium-induced WM in children, although further studies are needed to fully assess its effectiveness.

One limitation of this study is that BIS monitoring may not reflect actual hypnotic depth because it has a lag time, the smoothing rate of which is set to 15 seconds.[28,29] Our BIS results may have varied from actual values. For example, the BIS value observed at the loss of eyelash reflex could have been higher than the actual value. If BIS data had been recorded automatically with specific software and equipment onto a computer hard disk every 1 to 5 seconds,[28] we could have assessed hypnotic depth more precisely by predicting real-time BIS values through acquisition of the correlation curve of the recorded BIS data. Nevertheless, our results showed that the average time elapsed from the loss of eyelash reflex to the minimum BIS value was about 25 seconds in group C, while the average time during which the BIS value stayed lower than 40 was more than 20 seconds in group T. Considering these results, there is no doubt that the BIS values at rocuronium injection in groups C and T were different from each other. In fact, the BIS value measured 15 seconds after rocuronium injection was significantly higher in group C than in group T.

In conclusion, we confirmed that the BIS value at loss of eyelash reflex after TSA in children was much higher than 40. That is, anesthetic depth at the loss of eyelash reflex after TSA could not reach a deep hypnotic state indicated by a BIS value less than 40. In these situations, the patients need additional anesthesia using sevoflurane to reach a deep hypnotic state, which can be properly guided by BIS monitoring. We suggest that a deep hypnotic state with BIS values lower than 40 can reduce the grade of rocuronium-induced WMs during anesthesia induction using thiopental sodium or sevoflurane in children and thus BIS monitoring can be useful for alleviation of the WMs in children.

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