Comparison of Surgical Pleth Index–guided Analgesia with Conventional Analgesia Practices in Children

A Randomized Controlled Trial

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ABSTRACT

Background: To compare surgical pleth index (SPI)-guided analgesia with conventional analgesia by evaluating intraoperative analgesic requirements, postoperative pain, and emergence agitation in children.

Methods: This study was designed as a parallel, two-arm, double-blind, randomized controlled trial. Forty-five children undergoing elective adenotonsillectomy were randomly allocated to SPI-guided group (SPI-guided analgesia group, n = 21) or control group (conventional analgesia group, n = 24). Anesthesia was maintained with sevoflurane 2 to 3 vol% in 50% nitrous oxide and oxygen to achieve state entropy between 40 and 60. Intraoperative fentanyl 0.5 μg/kg was administered for the first event persisting 3 min and subsequent events persisting 5 min. An event was defined as an SPI over 50 (SPI-guided group) or a blood pressure or heart rate 20% above the baseline (control group). The primary outcome was intraoperative fentanyl requirement. Secondary outcomes included intraoperative sevoflurane consumption, postoperative emergence agitation and pain score, and postoperative rescue analgesic requirements.

Results: Intraoperative fentanyl requirement was lower in SPI-guided group than in control group (0.43 ± 0.53 *vs.* 1.73 ± 0.59 μg/kg; $P < 0.001$). Intraoperative sevoflurane consumption was similar. The proportion of patients with high emergence agitation scores (4 to 5) was greater in SPI-guided group (61.9 *vs.* 25.0%; $P = 0.01$). The postoperative pain score and rescue fentanyl consumption were higher in SPI-guided group (7 [4.5; 9] *vs.* 3 [2; 6.75]; $P = 0.002$; 0.50 ± 0.34 *vs.* 0.29 ± 0.30 μg/kg; $P = 0.04$).

Conclusions: As currently constructed, SPI does not appear to be valid in children. This may be due to both differences in blood vessel distensibility and baseline increased heart rates in children *versus* adults. **(ANESTHESIOLOGY 2015; 122:1280-7)**

ADEQUATE hypnosis and analgesia are essential to maintaining an adequate anesthetic depth. Several tools, including the bispectral index and spectral entropy, have been demonstrated to reflect the depth of hypnosis well.[1,2] By contrast, the administration of analgesics still depends on conventional empirical approaches based on changes in blood pressure and heart rate.

The newly developed surgical pleth index (SPI) monitors surgical stress reactions and guides proper analgesic administration during anesthesia using the pulse photoplethysmographic amplitude (PPGA) and heart rate data from pulse oximetry measurements.[3] Several studies demonstrate that SPI more reliably monitors the nociception–antinociception balance than other parameters, including heart rate, state entropy, response entropy, and PPGA.[4–6] However, there are few reports on the applicability of SPI to monitoring children,[7] and especially, no report about the usefulness of SPI to guide analgesic administration and its effect on emergence agitation, which may be affected by pain in children.

What We Already Know about This Topic

- How best to guide intraoperative analgesia remains unknown
- The surgical pleth index may help guide fentanyl administration

What This Article Tells Us That Is New

- Children assigned to surgical pleth index guidance received less intraoperative fentanyl
- However, they suffered more emergence agitation, had more postoperative pain, and required more rescue fentanyl

This article is featured in "This Month in Anesthesiology," page 1A. This article has been presented, in part, at the Top 10 Free Paper Session in the European Society for Paediatric Anaesthesiology (ESPA) Congress, which took place in Geneva, Switzerland, September 6, 2013. In the Clinical Trial Registration (UMIN000010599), the primary and secondary outcomes were changed on August 11, 2014 (during the manuscript review process). Intraoperative fentanyl requirement was designated *a priori* as the primary outcome, which was not changed during the trial and analysis. The trial registry was updated after completion to correct a mistake (that all of the outcomes were listed as "primary") in the registry.

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Therefore, we investigated the use of SPI to guide analgesic administration in pediatric anesthesia. We compared SPI-guided analgesia to conventional analgesia practices by evaluating intraoperative analgesic and anesthetic requirements, hemodynamic stability, emergence times, postoperative pain, and emergence agitation in children undergoing adenotonsillectomy during general anesthesia. We hypothesized that SPI-guided analgesia could avoid opioid overdosing and unwanted hemodynamic events by reducing intraoperative fentanyl requirement, thereby leading to postoperative conditions in aspects of emergence times, postoperative pain, and emergence agitation similar or superior to the conditions obtained from conventional analgesia practices in children.

Materials and Methods

This prospective study was approved by the Korea University Guro Hospital Institutional Review Board and registered in the UMIN clinical trials registry (unique trial number: UMIN000010599; registration number: R000012387). This study was a single-site study performed at Korea University Guro Hospital, a general hospital, Seoul, South Korea, from April 2013 to June 2013. All procedures were in accordance with the Declaration of Helsinki. All patients were recruited from the Department of Otolaryngology, Korea University Guro Hospital, by available study staffs. Patients were enrolled in the study on admission to the hospital the day before surgery. After an explanation of the trial, written, informed consent was obtained from the parents of all participants as well as assent from each child aged 7 yr or older.

In total, 58 patients aged 3 to 10 yr with the American Society of Anesthesiologists physical status I undergoing elective adenotonsillectomy were enrolled in this study. Patients with a history of cardiovascular, respiratory (asthma), neurologic (seizure), or kidney disease; prematurity; developmental delay; upper respiratory infection; fentanyl allergy; and those receiving analgesics, anticonvulsants, or psychiatric medication were excluded. After allocating patients to study groups, severely anxious or uncooperative patients, either before entering the operating room or in the operating room, were also excluded.

Patients were randomly allocated to the SPI-guided analgesia group (SPI-guided group) or the conventional analgesia group (control group) based on the criteria of analgesic administration. For randomization, random numbers from a computer-generated table were obtained and kept in opaque sealed envelopes which were opened by an independent anesthesiologist not involved in the study.

All patients received intramuscular atropine 0.01 mg/kg 30 min before anesthetic induction. Before entering the operating room, an observer blinded to the group allocation evaluated the patient's behavior and asked each patient a few questions to assess anxiety on a 3-point scale (1: calm, asleep, cooperative, smiling, or accepting the mask readily; 2: slight fear or anxiety; and 3: expressing anxiety or fear by verbal response, crying, or screaming).[8] Children who expressed anxiety at level 3 or who behaved uncooperatively were excluded. Noninvasive blood pressure monitoring, electrocardiography, pulse oximetry, end-tidal carbon dioxide, SPI, and entropy monitoring (Aisys® Carestation; GE Healthcare, Finland) were performed, and preanesthetic mean arterial pressure and heart rate were recorded for all patients. In the operating room, induction and maintenance of anesthesia and analgesic administration were performed by other independent anesthesiologists not involved in the study, and they were not blinded to the group allocation of patients.

General anesthesia was induced with intravenous thiopental sodium 5 mg/kg, intravenous rocuronium 0.6 mg/kg, and mask ventilation with sevoflurane 3 vol% and oxygen 6 l/min for 2 min, followed by intubation. Mechanical ventilation was maintained at a tidal volume of 8 to 10 ml/kg, and ventilation frequency was adjusted to maintain an end-tidal carbon dioxide between 30 to 35 mmHg. Anesthesia was maintained and continuously adjusted with sevoflurane 2 to 3 vol% (1.2 to 1.5 minimal alveolar concentration) in 50% nitrous oxide–oxygen (both at 1.5 l/min) to achieve state entropy between 40 and 60. The criteria of sevoflurane administration were the level of state entropy (40 to 60).

The analgesic administration in each group was guided using the defined criteria in a report of Chen *et al.*[9] in which an SPI value over 50 and a blood pressure or heart rate increase 20% above baseline value were set as equivalent indicators of light analgesia, and if an event occurred, then fentanyl 0.5 μg/kg was intravenously administered for the first event persisting 3 min; the same dose was repeated for any additional events persisting 5 min. In SPI-guided group, the SPI target range was 20 to 50; an event was defined as an SPI increase to greater than 50.[9–12] In control group, an event was defined as an intraoperative mean arterial pressure or heart rate increase to 120% or more of the preanesthetic baseline value (defined as hypertension and tachycardia events, respectively).[9] Mean arterial pressure and heart rate were recorded every 3 min, and in SPI-guided group, the SPI value was documented at the same interval. Sevoflurane and nitrous oxide were discontinued once the mouth gag was removed at surgical conclusion, and oxygen 6 l/min was provided. Intraoperative fluid therapy with isotonic crystalloid solution was administered based on the patient's weight according to the 4/2/1 rule.[13] After the end of surgery, a blinded, independent investigator assessed the patients during the emergence and recovery phases.

The emergence times were measured from the discontinuation of anesthetic to the recovery of spontaneous ventilation, eye opening, and extubation by the investigator blinded to the patient's assignment. When spontaneous ventilation recovered, patients received intravenous pyridostigmine 0.25 mg/kg and glycopyrrolate 0.01 mg/kg to reverse muscle relaxation, and the endotracheal tube was removed after spontaneous ventilation and muscular strength sufficiently recovered.

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In the recovery room, emergence agitation and pain were scored by the investigator blinded to the patient's assignment. Emergence agitation was assessed using a 5-point scale (1: sleeping; 2: calm/awake; 3: irritable or crying, but consolable; 4: crying inconsolably; and 5: severely restless/disoriented), and patients scoring 4 or greater were diagnosed with emergence agitation.[14] The pain score was determined using the modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS),[15] which comprises five items including crying, facial, verbal, torso, and leg status that were summed to calculate a final pain score. The maximum pain score is 10 (severe pain) and the minimum 0 (no pain). The final emergence agitation and pain scores were the highest of all the scores measured during the stay in the recovery room. Patients with an emergence agitation score 4 or greater or a modified CHEOPS score 7 or greater were administered fentanyl 0.5 μg/kg, and those whose emergence agitation score was 3 or whose modified CHEOPS score was from 4 to 6 received fentanyl 0.25 μg/kg. Patients were assessed every 10 min, and fentanyl 0.25 or 0.5 μg/kg was administered using the same criteria. Patients with emergence agitation scores 2 or less, pain scores 3 or less, and a modified Aldrete score of 10 were discharged from the recovery room. Adverse events, including respiratory depression (oxygen saturation <95%) and nausea or vomiting, were recorded. In patients experiencing respiratory depression, we applied an oxygen mask and encouraged breathing with slight stimulation. Nausea or vomiting was treated with intravenous ondansetron 0.15 mg/kg.

The SPI was calculated using methodology described in a report by *Huiku et al.*[3] SPI values range from 0 to 100, with higher scores indicating higher stress levels, and was calculated as follows. The heart beat interval (HBI) and PPGA were determined first from photoplethysmography through pulse oximetry. Of these, PPGA was measured as the distance from the pulse baseline to the pulse maximum in the plethysmographic signal.[16] It means the percentage from the light that passed the tissue at a certain heart rhythm and it is presented as an arbitrary unit using integer arithmetic so that the reading of 100 is 1% of the PPGA.[17] Then, the HBI and PPGA were normalized (HBI_{norm}; $PPGA_{norm}$) to a corresponding data distribution from a large group of adult patients using a histogram transformation.[18] Finally, the SPI was calculated using the following equation:

$$SPI = 100 - (0.33 \times HBI_{norm} + 0.67 \times PPGA_{norm})$$

A primary aim of this study was intraoperative fentanyl requirement. Secondary endpoints included the assessment of intraoperative sevoflurane consumption and hemodynamic events, emergence times, postoperative pain, and emergence agitation. Sevoflurane consumption was calculated from the difference in weight of the vaporizer before and after anesthesia,[19] using a precision weighing scale with least count of 0.1 g (PCB 10000–1; Kern, Germany).

Statistical Analysis

The primary endpoint in this study was the fentanyl dose administered during surgery. The sample size calculation was based on the results of a pilot study with five cases in each group. In the pilot study, intraoperative fentanyl doses (mean ± SD) were 1.1 ± 0.42 μg/kg in SPI-guided group and 1.6 ± 0.7 μg/kg in control group, respectively. Therefore, the effect size of two groups was 0.87. On the assumption that the allocation ratio of two groups was 1, a sample size of 22 patients was selected for each group, calculated by Student *t* test, two-sided test, a level of significance of 0.05, and a power of 0.8. We estimated a 30% dropout, resulting in the final enrollment of 29 patients in each group (total, 58 patients).

Statistical analyses were performed using SPSS software (SPSS version 20.0; IBM, USA). Student *t* test or Mann–Whitney *U* test was used to compare the mean values of the intraoperative fentanyl dose and intraoperative sevoflurane consumption, emergence times, pain scores, and the fentanyl dose administered in the recovery room between the groups. The normal distribution of the continuous data was first evaluated using the Shapiro–Wilk test ($P > 0.05$). The normally distributed data were analyzed using the Student *t* test, and the abnormally distributed data were analyzed using the Mann–Whitney *U* test. Differences in the incidence of intraoperative hemodynamic events (hypertension and tachycardia) and adverse events in the recovery room between the groups were compared using a chi-square test or Fisher exact test. Emergence agitation scores, assessed using a 5-point scale, were compared using the Mann–Whitney *U* test, and the incidence of emergence agitation was compared using a chi-square test. The data are expressed as the mean ± SD, median (25; 75 quartiles), or number of patients (%). *P* values were reported as two-tailed values, and a *P* value less than 0.05 was considered statistically significant.

Results

Of the 58 patients originally enrolled in the study, 13 patients were excluded for violations of the study protocol. Forty-five patients were evaluated, with 21 patients included in SPI-guided group and 24 patients in control group (fig. 1). There was no significant difference between the groups in age, sex, height, weight, body mass index, surgical time, anesthesia time, level of preoperative anxiety, baseline mean arterial pressure, or baseline heart rate (table 1).

Intraoperative sevoflurane consumption was similar between the groups, but the intraoperative fentanyl dose was significantly lower in SPI-guided group than in control group (0.43 ± 0.53 μg/kg *vs.* 1.73 ± 0.59 μg/kg; mean difference: 1.3; 95% CI, 0.961 to 1.640; $P < 0.001$) (table 2). Hypertension incidence, determined from the total number of measurements for all patients in each group, was significantly higher in SPI-guided group than in control group (36.1 *vs.* 24.9%; $P = 0.01$), but no difference was found in the incidence of

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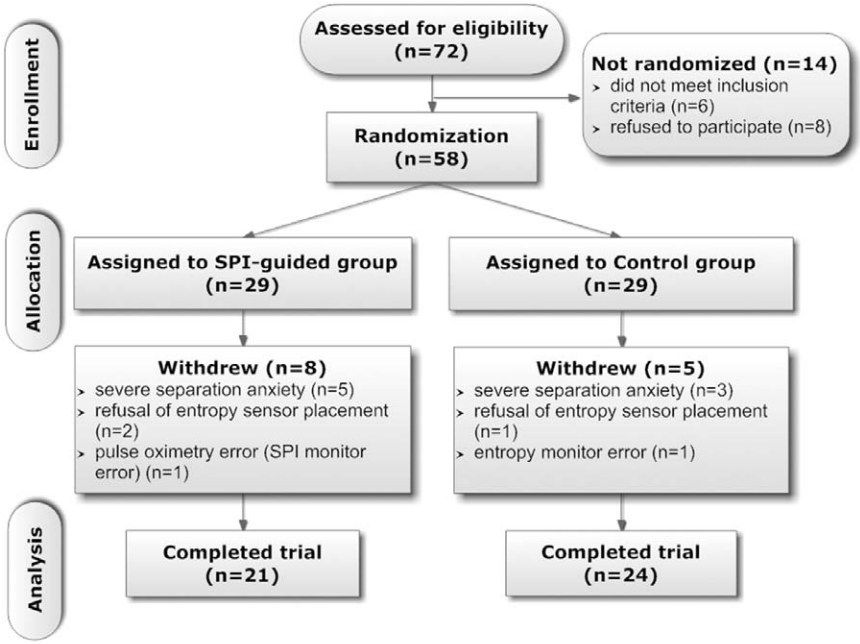

Fig. 1. A flow chart describing patient recruitment, randomization, and withdrawal. Initially, 58 patients were randomly assigned to one of two groups as follows: the surgical pleth index (SPI)-guided analgesia group (SPI-guided group) or the conventional analgesia group (control group). Finally, 45 patients (21 in SPI-guided group and 24 in control group) completed this study.

tachycardia events (63.4 *vs.* 63.5%; $P = 1.00$) (fig. 2). The emergence times from the discontinuation of anesthetic to recovery of spontaneous ventilation, eye opening, and extubation were not significantly different between the groups (table 2). State entropy was well maintained between 40 and 60 during the surgery in both groups, and there was no significant difference between the groups (fig. 3).

Table 1. Demographic and Clinical Data

	SPI-guided Group (n = 21)	Control Group (n = 24)
Age (yr)	7 (5–10)	7 (3–10)
Sex (M/F)	12/9	11/13
Height (cm)	121.2 ± 9.5	125.5 ± 12.2
Weight (kg)	24.5 ± 5.3	27.7 ± 8.3
Body mass index (kg/m^2)	16.6 ± 1.9	17.2 ± 2.9
Preoperative temperament* 1/2 (n)	14/7	13/11
Anesthesia time (min)	27.7 ± 9.8	31.1 ± 7.8
Surgical time (min)	15.3 ± 6.2	17.9 ± 6.4
Baseline mean arterial pressure (mmHg)	82.4 ± 9.4	87.1 ± 10.2
Baseline heart rate (beats/min)	95.5 ± 15.3	102.3 ± 15.1

Values are represented as mean ± SD, median (range), and number of patients. No statistically significant differences were observed between the control and SPI groups.

* Preoperative temperament was assessed using a 3-point scale (1: calm, asleep, cooperative, smiling, and accepts mask readily; 2: slight fear or anxiety; and 3: expressing anxiety or fear by verbal response, crying, or screaming), and children with a score of 3 were excluded from this study; values are represented as the number of children with each score.

Control group = the conventional analgesia group; SPI-guided group = the surgical pleth index–guided analgesia group.

The percentage of patients with an emergence agitation score 4 or greater in the recovery room was significantly higher in SPI-guided group than in control group (61.9 *vs.* 25.0%; $P = 0.01$) (table 3 and fig. 4), and the median emergence agitation score was also higher in SPI-guided group than in control group (4.0 *vs.* 1.5; $P = 0.004$) (table 3). The pain score and rescue fentanyl consumption in the recovery room were higher in SPI-guided group than in control group (7 [4.5; 9] *vs.* 3 [2; 6.75]; $P = 0.002$; 0.50 ± 0.34 μg/kg *vs.* 0.29 ± 0.30 μg/kg; $P = 0.04$, respectively) (table 3).

In SPI-guided group, adverse events that occurred in the recovery room included respiratory depression (four cases), nausea or vomiting (two cases), dizziness (one case), and mild laryngeal edema (one case). In control group, four cases of respiratory depression and two cases of nausea or vomiting were reported. Among the adverse events, one patient in SPI-guided group and two in control group had both respiratory depression and nausea or vomiting. There were no significant differences between the groups in the total incidence of adverse events or in respiratory depression, which were relatively frequent in both groups.

Discussion

In this study, SPI-guided analgesia reduced fentanyl consumption during surgery compared with conventional analgesia practices, whereas it also led to more frequent hypertension during surgery and higher emergence agitation and pain scores in the recovery room.

The SPI value was maintained within 20 to 50, consistent with previous studies.[9,11,20] In adults, the effectiveness

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Table 2. Intraoperative Sevoflurane and Fentanyl Consumption and Emergence Profiles

	SPI-guided Group (n = 21)	Control Group (n = 24)	*P* Value
Sevoflurane consumption (g)	21.0 ± 6.4	25.1 ± 14.2	0.24
Fentanyl consumption (μg/kg)	0.43 ± 0.53	1.73 ± 0.59	<0.001
State entropy at the end of surgery	50.0 ± 10.0	48.0 ± 8.5	0.48
Time to spontaneous ventilation (min)	11.7 ± 3.5	11.6 ± 3.7	0.92
Time to eye opening (min)	14.8 ± 2.6	16.3 ± 4.2	0.16
Time to extubation (min)	13.9 ± 3.0	15.2 ± 4.3	0.28

Values are represented as mean ± SD.

Control group = the conventional practice analgesia group; SPI-guided group = the surgical pleth index–guided analgesia group; Time to extubation = time from stopping the anesthetic agent to extubation; Time to eye opening = time from stopping the anesthetic agent to eye opening; Time to spontaneous ventilation = time from stopping the anesthetic agent to recovery of spontaneous ventilation.

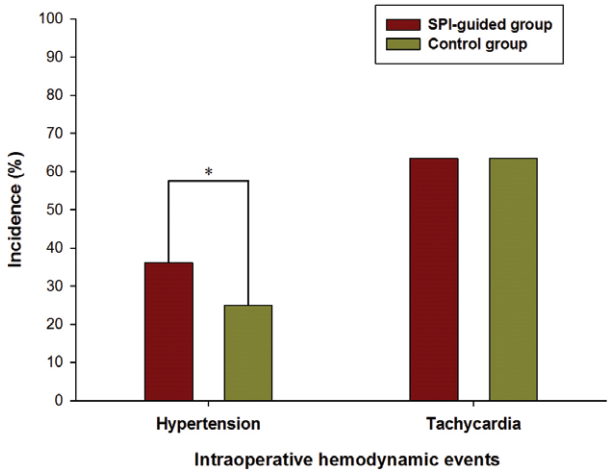

Fig. 2. Incidence of intraoperative hemodynamic events. Hypertension and tachycardia were defined as a 20% increase above the baseline blood pressure or heart rate. The total numbers of blood pressure and heart rate measurements during anesthesia were 194 in surgical pleth index (SPI)-guided group and 249 in control group. The number of hypertension events was 70 (36.1%) in SPI-guided group and 62 (24.9%) in control group. The incidence of hypertension was significantly higher in SPI-guided group than in control group ($P = 0.012$). The number of tachycardia events was 123 (63.4%) in SPI-guided group and 158 (63.5%) in control group, and there was no significant difference between the two groups. Control group = the conventional analgesia group; SPI-guided group = the SPI-guided analgesia group. *$P < 0.05$ between the two groups.

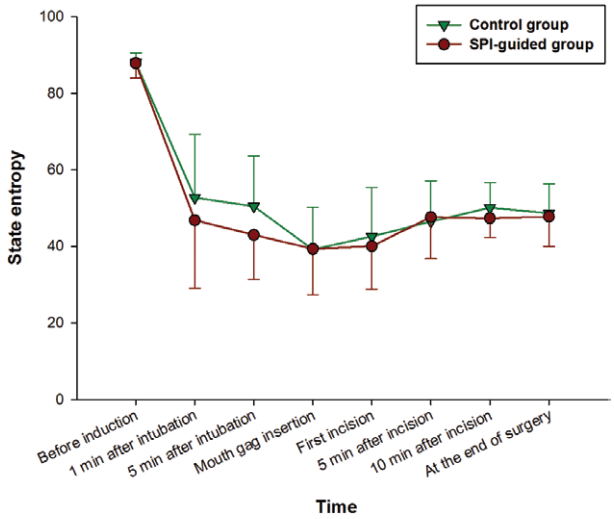

Fig. 3. Change of state entropy values in each group. State entropy values were well maintained between 40 and 60 during the surgery in both groups, and there was no significant difference between the groups. Control group = the conventional analgesia group; SPI-guided group = surgical pleth index–guided analgesia group.

of SPI for managing the nociception–antinociception balance during general anesthesia has been demonstrated in ear-nose-throat surgery and gynecological laparoscopic surgery.[9,21] Bergmann *et al.*[11] reported that adjusting the remifentanil dosage according to the SPI in outpatient anesthesia reduced both propofol and remifentanil consumption, and there was no difference between the SPI and control groups in postoperative pain intensity. In this study, although SPI-guided analgesia reduced intraoperative analgesic dosages, our findings in intraoperative hemodynamics and postoperative pain were not consistent with previous studies. This may be because the current study enrolled children unlike the other studies, which included adults. The SPI is calculated from HBI and PPGA, which are normalized to a corresponding data distribution determined from a large group of adult patients, so the application of SPI to children is a limitation. More importantly, given that the SPI-guided analgesia group showed more frequent hypertension and higher postoperative pain scores in this study, the SPI value more likely reduced the analgesic dosage by underestimating the degree of pain rather than by accurately reflecting postoperative pain. In other words, children are more likely to have lower SPI values that fail to reflect the actual level of nociception due to their different cardiovascular structure and function compared with adults. In children, the vascular walls have a lower collagen–elastin ratio and percentage of smooth muscle cells compared with adults, who show increased collagen and muscle cells with age.[22,23] Furthermore, basal catecholamine concentration (epinephrine and norepinephrine) and resting muscle sympathetic nerve activity increase in children with age, leading to enhanced stimulation of vascular smooth

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Table 3. Emergence Agitation Score, Pain Score, and Fentanyl Consumption in the Recovery Room

	SPI-guided Group (n = 21)	Control Group (n = 24)	*P* Value
Emergence agitation score	4 (2.5; 5)	1.5 (1; 3.75)	0.004
Incidence of emergence agitation	13 (61.9)	6 (25.0)	0.01
Pain score (modified CHEOPS)	7 (4.5; 9)	3 (2; 6.75)	0.002
Rescue fentanyl consumption (μg/kg)	0.50 ± 0.34	0.29 ± 0.30	0.04

Values are mean ± SD, median (25%; 75% quartiles), or number of patients (%).The incidence of emergence agitation is the number (%) of children with an emergence agitation score of 4 or 5.

Control group = the conventional analgesia group; modified CHEOPS = the modified Children's Hospital of Eastern Ontario Pain Scale; SPI-guided group = the surgical pleth index–guided analgesia group.

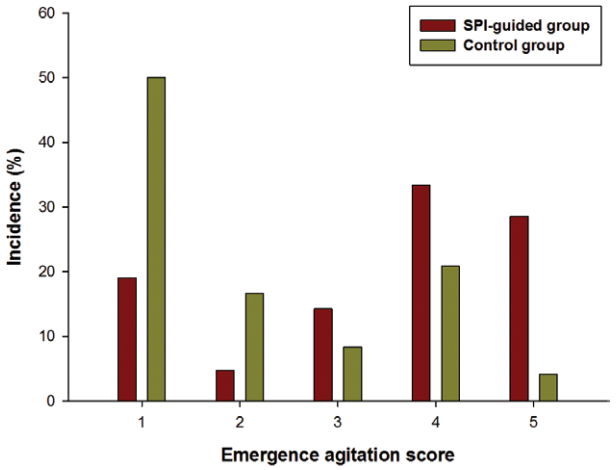

Fig. 4. Distribution of emergence agitation scores in each group. Emergence agitation was assessed using a 5-point scale. The percentage of children with each score is indicated by a *dark red* (SPI-guided group: the surgical pleth index–guided analgesia group) or *dark green bar* (control group: the conventional analgesia group). The percentage of patients with an emergence agitation score ≥4 in the recovery room was significantly higher in SPI-guided group than in control group.

muscle and vasoconstriction.[24] Sarkola *et al.*[25] demonstrated that children had lower vascular wall stress and higher distensibility compared with adolescents in an ultrasonographic investigation of vascular structures in healthy children and adolescents. They also showed that vascular changes, including thickened vascular walls, increased arterial stiffness, and increased blood pressure, occur with growth. The SPI value is determined by two factors, HBI and PPGA, and PPGA depends on vascular wall distensibility and intravascular pulse pressure.[26] Because children have a lower vascular tone and higher vascular distensibility compared with adults, they are less likely to show prominent decreases in PPGA from sympathetic stimulation, leading to an underestimation of the SPI value. Taken together, the SPI value is less likely to reflect the nociception–antinociception balance accurately in children because of their unique cardiovascular structure and physiology. Therefore, a redefinition of the target SPI for surgery under general anesthesia in children, or the development of a new formula, which calculates the SPI value while accounting for the specific pediatric cardiovascular system, is needed.

Postoperative emergence agitation is usually observed in preschool children, and rapid emergence and pain are two leading factors affecting its occurrence.[27] Because we found that there were no differences in emergence times or intraoperative sevoflurane consumption between SPI-guided group and control group, the difference in the occurrence of emergence agitation between the groups may be associated with postoperative pain. The postoperative pain score in the recovery room was significantly lower in control group. In addition, fentanyl is effective for preventing emergence agitation, and higher fentanyl dose is associated with a lower incidence of emergence agitation.[28] The intraoperative fentanyl dosage was significantly higher in control group. These findings may explain the lower incidence of emergence agitation in control group (25.0%) than in SPI-guided group (61.9%).

The current study was performed in children undergoing adenotonsillectomy, which was likely to be quite stressful and painful, leading to higher frequencies of hypertension and tachycardia. Thus, the SPI group, which received a lower dose of analgesics during surgery, was hemodynamically unstable, resulting in higher incidence of hypertension.

Opioids cause adverse events, such as respiratory depression and nausea or vomiting, in a dose-dependent manner during the postoperative period.[29] In this study, the incidence was not lower in SPI-guided group, which received lower doses of fentanyl during surgery, compared with control group. This observation reflects the inclusion of adverse events occurring after the administration of rescue fentanyl in the recovery room. The rescue fentanyl dose was higher in SPI-guided group, which showed a higher incidence of emergence agitation. Among patients experiencing adverse events, five patients from SPI-guided group and three from control group reported respiratory depression, nausea or vomiting after receiving rescue fentanyl. The association between intraoperative opioid dosage and the incidence of adverse events reported in the current study was different from those reported by Finkel *et al.*[29] This discrepancy may result from their use of acetaminophen as a rescue analgesic, whereas we used fentanyl. Use of ketorolac,[30,31] clonidine,[32] or dexmedetomidine,[33] which all have demonstrated effects on emergence agitation and postoperative pain, in the recovery room as rescue drugs might have been a better choice to reduce opioid-related complications.

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A major limitation of this study is that the SPI value is based on the data of adult patients. In addition, we did not record the SPI value in the conventional analgesia group (control group). If we had monitored the SPI value in this group during surgery, we might have determined the association between analgesic dosage and SPI, and perhaps, a target range of SPI values assessing the adequacy of analgesia during surgery in children could be investigated. Nevertheless, there is a study that evaluated the applicability of SPI to monitoring analgesia in children by Kallio *et al.*[7] They reported that both SPI and PPGA are sensitive markers of operative stress in anesthetized children undergoing strabismus surgery. Surgery was associated with a significant increase in SPI and decrease in PPGA in children. They suggested that SPI could be useful to detect autonomic responses to nociceptive stimuli in children. Based on this report, our study was designed to investigate the usefulness of SPI to guide analgesic administration in children.

Another limitation of this study may be the difficulty in differentiating primary emergence agitation and agitation due to pain using a 5-point scale instead of the pediatric anesthesia emergence delirium scale[34] for assessing emergence agitation. Pain is one of the main factor associated with emergence agitation.[35] Thus, it is considerably difficult for us to differentiate emergence agitation from pain especially after a painful surgery such as adenotonsillectomy. Lee *et al.*[36] also reported that insufficient intraoperative analgesia brought about the difficulty in discriminating between agitation caused by postoperative pain and emergence agitation in children undergoing adenotonsillectomy; we observed similar results in control group. Therefore, a more valid assessment of emergence agitation with the pediatric anesthesia emergence delirium scale incorporating cognitive-related assessment items other than agitation behaviors is needed, which will differentiate emergence agitation and pain more precisely.

The intramuscular atropine premedication is another limitation of the study. We minimized possible hemodynamic changes by administering intramuscular atropine 30 min before anesthetic induction rather than intravenous atropine immediately before induction. Nevertheless, potentially, intramuscular atropine may increase anxiety in pediatric patients and affect SPI value by increasing heart rate. To exclude any residual vagolytic effect of atropine on the results of our study, we compared the heart rates before atropine administration in the preoperative area (heart rate before atropine) with the first heart rates in the operating room (heart rate after atropine) in all patients. As a result, there was no significant difference between the two values although the heart rate after atropine (102 [92; 111]; median [25; 75 quartiles]) slightly increased compared with the heart rate before atropine (96 [88; 100]). Therefore, on the assumption that intramuscular atropine may affect HBI only rather than PPGA, we estimated how much of an error it would introduce into SPI as follows: The baseline heart rates in this pediatric population were a full 50% higher than typical heart rates in adults (table 1) and so the baseline HBIs decreased to 67% of those of adults. Because heart rates after atropine were a full 59% higher than typical heart rates in adults, the HBIs after atropine became 63% of those of adults with a 4% decrease compared with the baseline HBI. As HBI contributes to 33% of SPI, the difference in the contribution of the HBIs before and after atropine was approximately −1.3% (33% × 0.63 − 33% × 0.67). Finally, intramuscular atropine would introduce an error of approximately 1.3% increase into SPI in this study, which can be regarded as negligible.

In conclusion, SPI-guided analgesia resulted in lower intraoperative fentanyl consumption but less stable hemodynamics during surgery and increased postoperative pain and emergence agitation, resulting in higher postoperative analgesic requirements compared with conventional analgesia practices in children undergoing adenotonsillectomy under general anesthesia. SPI with a target range of 20 to 50 was inadequate for managing the intraoperative nociception–antinociception balance in children. Therefore, future research should focus on identifying appropriate SPI target ranges, and efforts should be reinforced to develop new indicators that objectively assess the degree of pain in children.

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Competing Interests

The authors declare no competing interests.

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