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Association between the Depth of Sevoflurane or Propofol Anesthesia and the Incidence of Emergence Agitation in Children: A Single-Center Retrospective Study

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In the present study, we investigated the hypothesis that the depth of general anesthesia affects emergence agitation (EA) in children in the early postanesthetic period. We retrospectively examined male and female children (aged 1-9 years) who underwent ambulatory surgery that lasted < 2 h. Various parameters, including the modified Yale Preoperative Anxiety Score (mYPAS) before anesthesia induction, the Pediatric Anesthesia Emergence Delirium (PAED) score at recovery time, and the value of the patient state index (PSI), were extracted from our electronic anesthesia database. The relationships between the PAED score and the mean PSI values were examined with univariate analyses. We also investigated the associations among the mean PSI, propofol anesthesia, age, mYPAS, the type of surgery, and the total amount of fentanyl divided by body weight with the PAED score using multiple regression analysis with interaction terms. There were 32 and 34 patients in the sevoflurane and propofol groups, respectively. The PAED scores (all patients: $r = -0.34$, $p = 0.0048$; sevoflurane group: $r = -0.37$, $p = 0.036$) were negatively correlated with the mean PSI, whereas the PAED score in the propofol group [$r = 0.31$ (−0.03, 0.59), $p = 0.073$] did not show a significant positive correlation with the mean PSI in the univariate analysis. The multiple linear regression analysis outcomes revealed that the mean PSI value was an independent clinical factor associated with the PAED score. Intraoperative electroencephalogram monitoring may be proved as one of the useful tools for the assessment of EA risks in children.

Keywords: electroencephalogram; emergence agitation; patient state index; propofol; sevoflurane
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Introduction

The incidence of emergence agitation (EA) in children reaches rates as high as 80% in some studies (Dahmani et al. 2014). EA is often an unpleasant experience for patients and caregivers, including parents. Therefore, preventing EA is an important goal for anesthesiologists who take care of pediatric patients. Some studies in adults have shown that light general anesthesia was associated with a decrease in postoperative delirium (Radtke et al. 2013; Jin et al. 2020; Li and Zhang 2020). Therefore, the depth of general anesthesia may affect EA. However, the etiology of EA remains unknown.

To avert EA, estimating risk is very crucial. One of the simple and easy ways to monitor anesthetic depth and brain function is the utilization of an electroencephalogram. An observational study by Faulk et al. (2010) found that the duration under a deep hypnotic state (bispectral index, BIS < 45) appears to be neither predictive nor related to the incidence of EA. A randomized controlled trial by

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Frederick et al. (2016) found that there was no significant effect of BIS-guided deep anesthesia (BIS < 45) versus light anesthesia (BIS = 55-60) on severe EA. However, neither study examined the relation of EA with the BIS value above these ranges and indicated that they should thoroughly explore the association between BIS values and EA. This is not necessarily a definitive solution because the study protocol limited the anesthetic method in these studies. Prior research demonstrated that the patient state index (PSI) might possess greater sensitivity and/or specificity and better discriminatory performance than the BIS (Chen et al. 2002). Therefore, it is necessary to assess the association between PSI values and EA.

In this pilot study, we performed a retrospective cohort study to investigate the hypothesis that the depth of general anesthesia affects EA by analyzing the relationship between various depths of general anesthesia and the incidence of EA.

Materials and Methods

After obtaining approval from the institutional review board at the Sendai Medical Center on November 9, 2020 (IRB: 20-74), we conducted a retrospective cohort study. Owing to the retrospective nature of the study using de-identified data from electronic medical records, it was exempted from the requirement for written informed consent. We used an electronic anesthesia database (Mirrel, FUKUDA DENSHI, Tokyo, Japan) to identify all children aged 1-9 years who had undergone < 2 h of ambulatory surgery from March to October 2020 without postoperative radiographic confirmation at our hospital.

No premedication or other concomitant anesthetics were used before the induction of general anesthesia. Briefly, while accompanied by a parent or guardian, children were induced with high concentrations of sevoflurane. In the propofol group, anesthesiologists administered propofol after induction. Anesthesia management, including the use of sevoflurane or propofol and adjusting anesthetic depth, was performed under the instructions of board-certified attending anesthesiologists assigned to the respective patients. All the patients were extubated when they were awake. No special treatment for EA was conducted. The criteria for discharging a patient from the operation room in our hospital include adequate ventilation, stable vital signs, and regaining consciousness. End-tidal sevoflurane concentrations (EtSevo) in the sevoflurane group, PSI values, and 95% spectral edge frequency: left (SEFL) or right (SEFR) (obtained from the SedLine® monitor, Masimo Corporation, Irvine, CA, USA) were supposed to be recorded at 1-min intervals from the beginning until the end of surgery. We included several different types of ambulatory surgeries, whereas all surgeries were similar and minor surgeries. We subdivided the ear–nose–throat (ENT) surgery group because ENT surgery constitutes a risk factor for EA, as demonstrated in previous reports (Galinkin et al. 2000), and we attempted to minimize the confounding effects of several different procedures. We obtained the following information from the electronic anesthesia database: age, height, weight, type of surgery (ENT surgery group: stroboscopic surgery, epiblepharon surgery, or tonsillectomy; non-ENT surgery group: plastic surgery or minor urological surgery), total amounts of fentanyl and rocuronium bromide divided by body weight, modified Yale Preoperative Anxiety Score (mYPAS) before anesthesia induction in the operating room (Kain et al. 1997), time of surgery, time of anesthesia and the Pediatric Anesthesia Emergence Delirium (PAED: range from 0 to 20) score immediately after extubation, which is considered as one of the most reliable scales of EA (Sikich and Lerman 2004). The exclusion criteria were as follows: a) American Society of Anesthesiologists physical status scores of > 2; b) patients who had undergone mask ventilation without endotracheal intubation or laryngeal masks during surgery and who had been extubated with general anesthesia; or c) patients with incomplete data. The mean values of PSI recorded during surgery were calculated.

In several studies, the diagnosis of EA was considered when the PAED scores were ≥ 10 during recovery from anesthesia (Sikich and Lerman 2004; Lin et al. 2018; Nakamura et al. 2018). However, the cut-off value of 10 was not necessarily definitive because some studies showed that PAED scores of > 12 appeared to provide greater sensitivity and specificity than PAED scores of ≥ 10 (Bajwa et al. 2010; Hino et al. 2017). In addition, whether EA occurred could not show the severity of EA. Therefore, we used the raw data of the PAED score as an objective variable in the present study.

The relationships between the PAED score and the mean PSI value, SEFL, or SEFR were examined in univariate analysis. Furthermore, we analyzed these relationships separately for the sevoflurane and propofol anesthesia groups. In addition, we investigated various clinical factors (the mean PSI, propofol anesthesia, age, mYPAS and type of surgery, and fentanyl/body weight) associated with the PAED score with multiple regression analysis containing interaction terms. The interaction term between the mean PSI value and type of anesthesia was also tested (propofol = 1, sevoflurane = 0). We classified the types of surgeries into two groups, namely, the ENT surgery group and the non-ENT surgery group because ENT surgery constitutes a high-risk factor for EA (Kanaya 2016).

Data were expressed as mean ± standard deviation and absolute numbers. We used Spearman's rank correlation coefficient in univariate analyses. For all tests, a p-value of < 0.05 was considered statistically significant. The R programming environment was used for statistical data analyses (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

After the inclusion and exclusion criteria were applied, 32 patients were identified in the sevoflurane group and 34

in the propofol group. No notable complications, such as episodes of hypotension or hypoxia, were noted in our study. Table 1 shows the characteristics of the patients. Fig. 1 shows the linear correlations and correlation coefficients between the PAED score and the mean PSI value. The PAED scores [all patients: $r = -0.34$ (−0.54, −0.11), $p = 0.0048$; sevoflurane group: $r = -0.37$ (−0.64, −0.03), $p = 0.036$] were negatively correlated with the mean PSI, whereas the PAED score in the propofol group [$r = 0.31$ (−0.03, 0.59), $p = 0.073$] did not show a significant positive correlation with the mean PSI in the univariate analysis. In addition, the PAED scores were not correlated with the mean SEFL [all patients: $r = -0.08$ (−0.32, 0.16), $p = 0.52$; sevoflurane group: $r = 0.11$ (−0.25, 0.44), $p = 0.55$; propofol group: $r = 0.19$ (−0.16, 0.50), $p = 0.27$] or the mean SEFR [all patients: $r = -0.06$ (−0.29, 0.19), $p = 0.65$; sevoflurane group: $r = -0.33$ (−0.61, 0.02), $p = 0.06$; propofol group: $r = 0.21$ (−0.13, 0.51), $p = 0.23$].

The relationship between the mean PSI value and mean EtSevo in the sevoflurane group was statistically significant [$r = -0.72$ (−0.85, −0.50), $p < 0.0001$].

A multiple linear regression analysis containing interaction terms was also performed to adjust for the mean PSI value, anesthesia method, age, mYPAS, and type of surgery (Table 2). The interaction term between the mean PSI and the type of anesthesia was significant. This indicated that

Table 1. Summary of patient characteristics.

Parameter	
Age (years)	4.8 ± 2.1
Sex (Male/Female)	31/35
Height (cm)	107 ± 15
Weight (kg)	18.5 ± 5.7
BMI	15.9 ± 2.1
Anesthesia (Sevoflurane/Propofol)	32/34
ENT surgery or not	39/27
Operation time (min)	40.4 ± 21
Anesthesia time (min)	90.2 ± 25
Intraoperative fentanyl (μg/kg)	4.5 ± 3.0
Intraoperative rocuronium bromide (mg/kg)	0.8 ± 0.4
Mean EtSevo (%)/Mean propofol administration (mg/kg/hr)	3.0 ± 2.1/5.1 ± 0.6

Data are expressed as mean ± standard deviation.
BMI, body mass index; ENT, ear–nose–throat; EtSevo, end-tidal sevoflurane concentration.

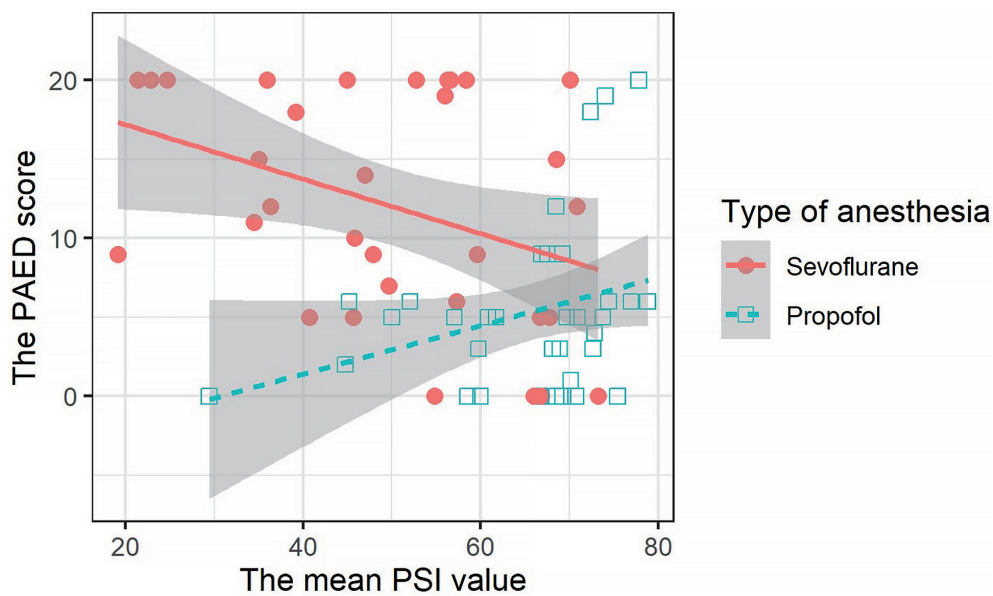

Fig. 1. Scatterplot of Pediatric Anesthesia Emergence Delirium score and the mean value of patient state index for all subjects according to the type of anesthesia.
All patients: $r = -0.34$, $p = 0.0048$; Sevoflurane group: $r = -0.37$, $p = 0.036$; Propofol group: $r = 0.31$, $p = 0.073$
●, Sevoflurane anesthesia; □, Propofol anesthesia.

Table 2. Results of multiple linear regression analysis for the Post Anesthesia Emergence Delirium scale and clinical factors.

Factor	Mean difference	*p*-value
Mean PSI value (/10)	−1.52 (−2.87, −0.17)	0.031*
Mean PSI value (/10): type of anesthesia (propofol = 1, sevoflurane = 0)	2.78 (0.57, 4.98)	0.017*
Propofol anesthesia	−21.60 (−35.60, −7.61)	0.0037*
Age	−0.30 (−1.17, 0.58)	0.51
mYPAS	0.07 (0.01, 0.14)	0.026*
ENT surgery	−0.26 (−4.19, 3.68)	0.9
Fentanyl (μg)/Body weight (kg)	−0.54 (−1.07, 0.00)	0.055

The table reports the mean difference and their 95% confidence intervals. :refers to the interaction term. *$p <$ 0.05, based on multiple linear regression analysis.
PSI, patient state index; mYPAS, modified Yale Preoperative Anxiety Score; ENT, ear–nose–throat.

the relationship between the mean PSI value and PAED score differed depending on the type of anesthesia. In sevoflurane anesthesia, the PAED score decreased by 1.52 for every 10-point increase in the mean PSI value. Conversely, in propofol anesthesia, the PAED score increased by 1.26 for every 10-point increase in the mean PSI value. The results revealed that the mean PSI value and the interaction term between the mean value of PSI and type of anesthesia and propofol anesthesia were independent clinical factors associated with the PAED score.

Discussion

We conducted this retrospective cohort study to determine whether the depth of general anesthesia affected EA based on the mean PSI value during surgery. Our results suggest that lower mean PSI values (sevoflurane anesthesia) and higher mean PSI values (propofol anesthesia) were associated with a higher PAED score (favors the incidence of EA) in multivariate analyses, although the correlation coefficient was small in the univariate analysis. Furthermore, our study confirmed that EA occurred less frequently with propofol anesthesia than with sevoflurane anesthesia in children.

Thus far, few reports have shown a relationship between EA and the depth of anesthesia for both sevoflurane and propofol. The new finding reported here is that the relationship between the mean PSI value and PAED score differed depending on the type of anesthesia. We found that lower mean PSI values in sevoflurane anesthesia tended to be associated with a higher PAED score, whereas higher mean PSI values in propofol anesthesia tended to be associated with a higher PAED score. Mean PSI values in the propofol group were high compared to the sevoflurane group. Children exhibit relatively greater power in the high-frequency bands, which may cause the PSI value to be high in propofol anesthesia (Yuan et al. 2020). Thus, higher PSI values may not necessarily suggest light anesthetic states. Additionally, our findings demonstrated that no significant difference was observed between SEF and PAED scores. Hence, PSI value might be beneficial to evaluate the risk of EA by using the depth of anesthesia during surgery. Sevoflurane is a well-known risk factor for EA and has an excitatory effect on the central nervous system (Kuratani and Oi 2008). Moreover, several studies have suggested that the epileptogenicity of sevoflurane is dose-dependent and may be a contributing factor to EA in children (Komatsu et al. 1994; Constant et al. 2005). However, the mechanism of EA remains unclear. Our results showed that lower mean PSI values tended to be associated with a higher PAED score in sevoflurane anesthesia; this may be consistent with the previous reports on adult patients administered with light anesthesia (higher BIS values) reducing the risk of postoperative delirium (Radtke et al. 2013; Jin et al. 2020; Li and Zhang 2020). In contrast, the results of the present study indicated that higher mean PSI values in propofol anesthesia tended to be associated with a higher PAED score. The dose-dependent effect of EA in propofol anesthesia is unclear, but it is possible that these results in propofol anesthesia might be associated with the propofol's effect of reducing the incidence of EA (Bryan et al. 2009; Pieters et al. 2010).

Previous studies found that a higher EA incidence was observed in preschool-aged children (Aono et al. 1997) and in children who were overanxious upon their entry into the operating room (Kain et al. 2004). We used the mYPAS score (Kain et al. 1997) to assess the preoperative anxiety levels in the operating room. This score yielded a significant relationship with the PAED score like a previous study. In the present study, propofol anesthesia was associated with a lower PAED score, which was in agreement with findings from previous reports (Kanaya et al. 2014). Therefore, propofol anesthesia reduces EA and may be an optimal option for general anesthesia in children.

Faulk et al. (2010) showed that the length of time in a deep hypnotic state (BIS < 45) and the incidence of EA exhibited no significant differences. A prospective, controlled analysis by Frederick et al. (2016) suggested that there was no significant effect of BIS-guided deep anesthesia (BIS < 45) versus light (BIS = 55-60) anesthesia on the occurrence of EA. However, these authors only reported the relationship between a limited depth of anesthesia and EA. The present study investigated the relationship

between a wide range of depths of anesthesia and EA in sevoflurane or propofol anesthesia. Therefore, our results may be important in clinical practice.

Novel SedLine® electroencephalography (EEG) monitor that uses a symmetrical bilateral array that provides four-channel data has been recently introduced in clinical practice for the administration of pediatric anesthesia in Japan. The SedLine® presents PSI values after advanced artifact rejection (Lee et al. 2015). This novel PSI monitor seems to be a more sensitive monitor for measuring small changes at the level of consciousness than the BIS monitors used in the elderly (Kurup et al. 2004). Therefore, PSI measured by SedLine® may be one of the optimal EEG monitors in the perioperative periods. Accordingly, we retrospectively used the PSI data in the present study. Based on the relationship between the mean PSI value and mean EtSevo in the sevoflurane group, the correlation between these values is relatively strong in pediatric patients.

The present study had several limitations. First, the study had a retrospective design, and the anesthesia methods used in the study were not primarily designed to compare the occurrence of EA and the depth of anesthesia. Although we used multiple regression analyses to identify several confounding factors that contained interaction terms, not all relevant factors were extracted. For example, the electronic anesthesia database at our hospital did not include electroencephalography. In addition, the method of anesthesia and administration of drugs differed based on the attending anesthesiologists. Their EtSevo was almost zero value after surgery, although slow sevoflurane induction was employed for patients in the propofol group. Second, the sample size calculation was difficult because there was no previous report that examined the relationship between the PAED score and the mean PSI value. Thus, the sample size calculation was conducted as a post hoc analysis. Analysis of the relationship between the PAED scale and PSI in all patients in this study revealed that the sample size of 64 was sufficient based on our power analysis ($\alpha = 0.05$, $\beta = 0.20$, $r = 0.34$) for the univariate analysis. However, the β error may increase owing to the small sample size in the multivariate analysis. Therefore, no significant differences might be identified for various studied factors, including age, ENT surgery, and fentanyl administration in the multivariate analysis conducted in the present study. Third, this research has ENT surgery. Although the PSI value was computed after advanced artifact rejection, surgical procedures might influence the PSI value.

This retrospective study using data from 66 pediatric patients who underwent minor ambulatory surgery at a single center demonstrated that the mean PSI value during maintenance of general anesthesia and preoperative anxiety may be associated with the PAED scale during recovery. We showed that propofol anesthesia is associated with a lower EA incidence. It is possible that EEG monitoring may be proved to be one of the useful tools for the assessment of EA risks.

Author Contributions

Conceptualization: A.K. and T.W.; Formal analysis and investigation: A.K., S.T., and T.W.; Writing-original draft preparation: A.K. and T.M.; Writing-review and editing: M.M. and T.W.; Supervision: M.Y.

Conflict of Interest

The authors declare no conflict of interest.

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