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Propofol reduces the incidence of emergence agitation in preschool-aged children as well as in school-aged children: a comparison with sevoflurane

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Abstract
Purpose. Young age is considered as one of the factors associated with emergence agitation (EA) following sevoflurane anesthesia. The relationship between EA following propofol anesthesia and young age has not yet been examined. This study was designed to compare the incidence of EA in younger children and older children following either propofol or sevoflurane anesthesia.
Methods. Ninety-six preschool-aged (2–5 years) children and 90 school-aged (6–11 years) children (American Society of Anesthesiologists [ASA] I or II) scheduled to undergo otorhinolaryngological surgery were randomly assigned to receive either propofol or sevoflurane. These children were divided into the following four groups: propofol-preschool (P-pre), sevoflurane-preschool (S-pre), propofol-school (P-school), and sevoflurane-school (S-school) groups. Recovery times and incidence of EA were compared among the four groups.
Results. We observed that the recovery times were similar in the four groups. After extubation, the incidence of EA in the S-pre group was significantly higher than that in the other groups. After eye opening, the incidence of EA in the S-pre and S-school groups was significantly higher than that in the P-pre or P-school groups. At all recovery times, no difference was observed in the incidence of EA between the P-pre and P-school groups.
Conclusion. Propofol, in comparison with sevoflurane, resulted in a lower incidence of EA, with no relation to age.

Key words Emergence agitation · Sevoflurane · Propofol · Children · Age

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Introduction

Emergence agitation (EA) in children after sevoflurane anesthesia has been well described. Rapid recovery from sevoflurane anesthesia in psychologically immature preschool-aged children has been associated with an increased incidence of EA [1]. Similarly, in a cohort study by Voepel-Lewis et al. [2], otorhinolaryngological surgery, young age, short time to awakening, and use of sevoflurane or isoflurane were found to be the major factors predicting EA. In their study, however, volatile anesthetics were mainly used, apart from a few cases in which propofol was used. Propofol anesthesia, which also provides rapid recovery, has been associated with a lower incidence of EA when compared to sevoflurane [3–5]. However, no studies have specifically evaluated differences in the incidence of EA after propofol based on age. Our hypothesis was that propofol anesthesia would reduce the incidence of EA in preschool-aged children. Therefore, we performed this study to compare the incidence of EA in preschool-aged children and school-aged children following either propofol or sevoflurane anesthesia.

Patients and methods

After obtaining informed parental consent and the approval of the institutional committee, 186 children, ranging in age from 2–11 years (American Society of Anesthesiologists [ASA] I or II), who were to undergo otorhinolaryngological surgery under general anesthesia were studied prospectively. The study group consisted of 96 preschool-aged (2–5 years) and 90 school-aged (6–11 years) children. They were randomly assigned to the following four groups to receive either propofol or sevoflurane anesthesia: propofol-preschool (P-pre), sevoflurane-preschool (S-pre), propofol-school (P-school), and sevoflurane-school (S-school) groups.

No premedication was given. Children with a history of known allergy to the study drugs, sleep apnea, developmental delay, or psychological disorders were excluded.

Prior to their entering the operating room, an intravenous (i.v.) catheter was inserted in all the children. On entering the operating room, routine monitors were applied and 0.01 mg·kg^{-1} atropine was administered before the induction of anesthesia. In the propofol groups, anesthesia was induced with a bolus injection of 3 mg·kg^{-1} propofol and maintained with 6–10 mg·kg^{-1}·h^{-1} propofol infusion. An intravenous injection of 10 mg lidocaine was administered to minimize the pain due to propofol injection. In the sevoflurane groups, anesthesia was induced with 8% sevoflurane via a facemask and maintained with 1.5%–3% sevoflurane. Orotracheal intubation was facilitated by 0.1 mg·kg^{-1} vecuronium. All the children were ventilated with 65% nitrous oxide in oxygen to maintain normocapnia. After intubation, 2 μg·kg^{-1} fentanyl was administered intravenously to all the children. The dose of propofol or the concentration of sevoflurane was adjusted to maintain the heart rate and blood pressure within 20% of the preinduction values. At the completion of surgery, 1 mg·kg^{-1} flurbiprofen axetil, a prodrug of the nonsteroidal anti-inflammatory drug flurbiprofen, was administered for postoperative analgesia. Subsequently, anesthetic agents were discontinued, and the trachea was extubated when the gag reflex had returned and the patients were breathing spontaneously. After extubation, all the children received 100% oxygen via a facemask. The children were discharged from the operating room when they satisfied the following criteria: stable vital signs, patent airway without any manipulation, and oxygen saturation more than 95% with 3 l·min^{-1} oxygen flow via the facemask. The children were then transferred to the recovery room. In the recovery room, all the children were breathing oxygen via a facemask and the oxygen saturation was monitored continuously. The children were left undisturbed, with the exception of calling out their names every minute until they first opened their eyes. The children would be transferred to the ward only if they were fully awake, able to take deep breaths, and maintain oxygen saturation at more than 95% in room air. All the children who reported pain during the recovery period and those who required the use of analgesics within 1 h after returning to the ward were excluded from the study.

The following time intervals were recorded: duration of surgery, time to extubation (time from the discontinuation of anesthetics to extubation), time to discharge from the operating room (time from the discontinuation of anesthetics to discharge from the operating room), emergence time (time from the discontinuation of anesthetics to spontaneous eye opening), and time to discharge from the recovery room (time from the discontinuation of anesthetics to discharge from the recovery room).

EA was assessed on a four-point scale as follows: 1, calm; 2, not calm but could easily be calmed; 3, not easily calmed, moderately agitated or restless; and 4, combative, excited, or disoriented [1].

Grades 1 or 2 were considered as no agitation, and grades 3 or 4 were considered as presence of agitation. Emergence behavior during the postoperative period was measured 5 min after extubation, 5 min after the children opened their eyes, and 1 h after they had been transferred to the ward. The incidence of adverse events such as nausea, vomiting, laryngospasm, and bronchospasm was also noted. During the recovery period, an independent anesthesiologist, who was blinded to the anesthetic used, recorded all the observations and measurements.

Data values are presented as means ± SD. Continuous variables with a normal distribution were compared among the groups, using one-way analysis-of-variance tests. If significance was detected, Scheffe's *F*-test was applied for comparisons between the groups. Categorical data were analyzed using the χ^2 test and Fisher's exact test, as required. A value of $P < 0.05$ was considered significant. The sample size was designed to evaluate the difference in the incidence of EA during recovery. A previous study had demonstrated that the incidence of EA after halothane anesthesia in preschool-aged children was 10%, as compared to 40% after sevoflurane anesthesia [1]. We assumed that the incidence of EA in preschool-aged children after propofol anesthesia would be reduced to 10%, the same as that after halothane. Thus, we calculated that a sample size of 32 patients per group would have at least 80% power at a significance level of 5% to detect a difference of 30% in the incidence of EA. As we expected that some patients would be excluded from the study, we increased the number per group to 40.

Results

We excluded ten children (four in the P-pre group; three in the S-pre group; two in the P-school group; and one in the S-school group) from the study because of insufficient analgesia. There were no significant differences in age, weight, sex distribution, or duration of surgery between the two anesthetic groups for each age group (Table 1). Among the four groups, there were no significant differences in the time to extubation, time to discharge from the operating room, time to eye opening, or time to discharge from the recovery room (Table 2).

Figure 1 shows the percentages of children with EA during recovery. At 5 min after extubation, the inci-

Table 1. Patient demographics and duration of surgery

	S-pre group (n = 45)	P-pre group (n = 44)	S-school group (n = 44)	P-school group (n = 43)
Age (years)	3 ± 1	3 ± 1	8 ± 1	8 ± 1
Weight (kg)	18 ± 4	17 ± 5	26 ± 6	25 ± 7
Sex (M/F)	25/20	28/16	26/18	23/20
Duration of surgery (min)	52 ± 21	51 ± 20	48 ± 25	47 ± 18

Values are means ± SD or numbers

Table 2. Recovery data

Time intervals (min)	S-pre group	P-pre group	S-school group	P-school group
Time to extubation	11 ± 4	12 ± 5	9 ± 4	10 ± 5
Time to discharge from operating room	16 ± 5	15 ± 4	14 ± 5	14 ± 3
Emergence time	18 ± 10	19 ± 12	17 ± 7	16 ± 7
Time to discharge from recovery room	26 ± 7	29 ± 9	25 ± 9	25 ± 6

Values are means ± SD

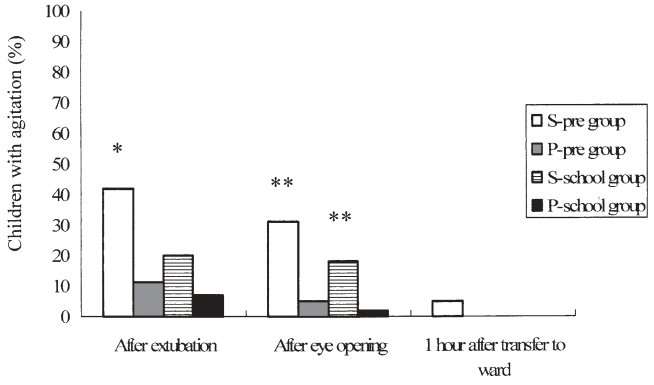

Fig. 1. Percentage of children with emergence agitation at the time points shown. *$P < 0.05$, compared with the three other groups; **$P < 0.05$, compared with both propofol-preschool (*P-pre*) and propofol-school (*P-school*) groups. *S-pre*, sevoflurane-preschool; *S-school*, sevoflurane-school

dence of EA in the S-pre group (42%) was significantly higher than that in the other groups. At 5 min after the children opened their eyes, the incidence of EA in the S-pre group (31%) and S-school group (18%) was significantly higher than that in the P-pre group (5%) or the P-school group (2%). At 1 h after the children were transferred to the ward, no difference was observed in the incidence of EA among the four groups. At all recovery times, no significant difference was observed in the incidence of EA between the P-pre and P-school groups. Systolic blood pressure and heart rate in the S-pre group were higher than those in the P-pre group 5 min after extubation and 5 min after eye opening (Table 3).

Adverse events during the perioperative and recovery periods are summarized in Table 4. Neither laryngospasm nor bronchospasm was observed. The incidence of postoperative vomiting was comparable in the four groups. No major complications such as severe hypotension, bradycardia, or oxygen desaturation were observed.

Discussion

The present study showed that propofol was associated with a lower incidence of EA as compared to sevoflurane, and no significant difference in the incidence of EA was observed between the preschool-aged and school-aged groups who received propofol.

Sevoflurane, in particular, has been associated with an increased incidence of EA in children. The proposed theoretical explanations for this phenomenon include rapid awakening in an unfamiliar environment [1,2,6,7]; immaturity [1,2,6,8]; variable recovery, resulting in a dissociative state [3,9]; and pain sensation [10,11]; however, the etiology remains unclear.

Rapid awakening has been proposed as one of the causative factors of EA [1,2,6,7]. However, recent studies showed that the incidence of EA was lower in children after propofol anesthesia than after sevoflurane anesthesia, despite similar recovery times [3,4]. Our results were also consistent with these findings. Therefore, our results and these previous findings question the relationship between rapid awakening and EA.

Previous studies have found that younger children are prone to develop EA after sevoflurane anesthesia [1,6,8]. Aono et al. [1] observed a greater incidence of

Table 3. Hemodynamic characteristics during recovery period

Time intervals (min)	S-pre group	P-pre group	S-school group	P-school group
After extubation				
HR (bpm)	142 ± 12*	120 ± 18	95 ± 12	87 ± 8
SBP (mmHg)	104 ± 13*	89 ± 11	102 ± 10	93 ± 7
DBP (mmHg)	45 ± 5	42 ± 6	51 ± 9	45 ± 7
After eye opening				
HR (bpm)	134 ± 15*	115 ± 17	95 ± 12	87 ± 8
SBP (mmHg)	98 ± 13*	85 ± 10	100 ± 14	92 ± 12
DBP (mmHg)	44 ± 4	42 ± 5	50 ± 9	48 ± 8
After transfer to ward				
HR (bpm)	104 ± 13	102 ± 15	85 ± 12	83 ± 9
SBP (mmHg)	85 ± 7	76 ± 11	102 ± 10	93 ± 7
DBP (mmHg)	43 ± 4	43 ± 4	50 ± 7	46 ± 6

* $P < 0.05$ versus P-pre group
Values are means ± SD
HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 4. Adverse events

	S-pre group	P-pre group	S-school group	P-school group
Laryngospasm	0	0	0	0
Postoperative vomiting				
In recovery room	3 (7%)	1 (2%)	0	0
During first 24 h	7 (16%)	5 (11%)	6 (14%)	5 (12%)

Values are expressed as numbers (%)

EA after sevoflurane anesthesia in preschool-aged children (40%) than in older children (11.5%). In addition, Beskow and Westrin [8] observed that EA after sevoflurane anesthesia decreased with age, and did not occur in children above 7 years of age. More recent studies have found that approximately 40% of preschool-aged children anesthetized with sevoflurane developed postoperative agitation [3–5,10,12]. Our result showing the frequent incidence (42%) of EA after sevoflurane anesthesia in preschool-aged children is consistent with those of these studies. One of the reasons for this increased incidence of EA may be related to the intrinsic central nervous system effect of sevoflurane [13]. Cohen et al. [3] have speculated that a variable rate of neurological recovery, resulting in a dissociative state, occurs in children anesthetized with sevoflurane. In this condition, younger children are more likely to demonstrate increased sensitivity and reactivity to their environment. The increased sensitivity to outside stimuli, combined with the dissociative state, may cause impaired cognition. Therefore, rapid emergence from sevoflurane does not always provide a smooth neurological recovery, particularly in preschool-aged children.

Unlike sevoflurane, studies of the use of propofol in children have consistently shown its association with a low incidence of EA [3–5]. When comparing the incidence of EA in preschool-aged children, Uezono et al. [5] found an incidence of 0% with propofol and 38% with sevoflurane. Our study also confirmed the association of propofol and a reduced incidence of EA in preschool-aged children. The decreased incidence of EA could be accounted for by the residual sedative effect of propofol. Viitanen et al. [14], in their study of children aged 1–3 years, showed that the induction of sevoflurane anesthesia with propofol resulted in a calmer state during the recovery period, but did not delay discharge as compared with sevoflurane alone. They speculated that propofol had some residual effect in the early recovery period after short-duration anesthesia. In addition, propofol has been shown to produce a positive mood or euphoric state postoperatively in adults [15,16]. These effects may also occur in young children. These sedative and euphoric effects of propofol would lead observers to grade the EA with a lower score. Based on our results, it seems that young age and immaturity cannot completely explain the origin of EA.

Pain sensation and the use of opioid analgesia have been shown to contribute to the incidence of EA [10,11,17]. We excluded these confounding factors as much as possible. Firstly, we excluded children with insufficient analgesia and those who reported pain during the recovery period. Secondly, fentanyl was administered to all the children before surgery. It has

been shown that fentanyl administration during the induction of anesthesia does not affect the incidence of EA [18].

Postoperative nausea and vomiting (PONV) is a common complication of anesthesia in children [19]. Several recent studies have demonstrated that choosing propofol may help to reduce the incidence of PONV [5,20,21]. In this study, however, in the propofol groups, the incidence of PONV was similar to that in the sevoflurane groups, probably due to the use of fentanyl in combination with nitrous oxide in all the study groups [19]. It should be noted that we obtained a relatively low overall incidence of PONV as compared with the results reported in the literature [19–21], because we defined an emetic episode as a single vomit. Nausea is a subjective parameter and is often difficult to quantify for preschool-aged children. Therefore, the incidence of PONV in this study may have been underestimated, and precludes the drawing of conclusions that are statistically significant.

Our study has several limitations. Firstly, similar to other studies of EA, our study was limited by the lack of a validated tool for measuring EA. We used a simple graded measurement that is very similar to those used by other investigators [1,3–5,8]. One blinded observer graded all scores to eliminate issues related to interrater variability. Moreover, we excluded children under 2 years of age because an objective evaluation of the psychological state of these young children during emergence is not feasible. Secondly, there may have been a difference in the depth of anesthesia between the sevoflurane and propofol groups. We used hemodynamic variables to indicate comparable depths of anesthesia, although these variables are not reliable for monitoring the depth of anesthesia. Nevertheless, recovery times were quite similar in all the study groups.

In conclusion, in preschool-aged children, as well as in school-aged children, propofol anesthesia resulted in a lower incidence of EA, despite recovery times being similar to those in children receiving sevoflurane anesthesia. This suggests that rapid awakening and young age does not fully explain the origin of EA.

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