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ORIGINAL ARTICLE

Subanesthetic-dose propofol infusion for preventing emergence agitation in children: a retrospective observational study

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Abstract

Purpose Anesthesia maintenance using propofol and a propofol bolus dose at the end of surgery have been shown to prevent emergence agitation (EA). However, the preventive effect of subanesthetic propofol infusion during sevoflurane anesthesia on EA remains unknown. We aimed to evaluate the effect of subanesthetic propofol infusion on EA in children.

Methods We retrospectively compared the incidences of severe EA requiring pharmacological intervention in children who underwent adenoidectomy, tonsillectomy with or without adenoidectomy, or strabismus surgery between maintenance with sevoflurane alone (sevoflurane group) and maintenance with subanesthetic propofol with sevoflurane (combination group). A multivariable logistic regression model adjusted for confounders was used to assess the association between anesthesia methods and the occurrence of EA. Additionally, we estimated the direct effect of anesthesia methods by a mediation analysis, excluding the indirect effects of intraoperative fentanyl and droperidol administration.

Results Among 244 eligible patients, 132 and 112 were in the sevoflurane and combination groups, respectively. The crude incidence of EA was significantly lower in the combination group (17.0% [$n=19$]) than in the sevoflurane group (33.3% [$n=44$]) ($P=0.005$). After adjusting for confounders, the incidence of EA was still significantly lower in the combination group (adjusted odds ratio [aOR]: 0.48, 95% confidence interval [CI] 0.25–0.91). The mediation analysis revealed a direct association of anesthesia methods with a lower EA incidence in the combination group (aOR: 0.48, 95% CI 0.24–0.93) than in the sevoflurane group.

Conclusion Subanesthetic propofol infusion may effectively prevent severe EA requiring the administration of opioids or sedatives.

Keywords Emergence delirium · Subanaesthetic-dose propofol · Child · Mediation analysis

Introduction

Postoperative behavioral disturbance, known as emergence agitation (EA), is a common complication of emergence from sevoflurane anesthesia in children [1]. The reported incidence of EA after sevoflurane anesthesia has ranged from 10 to 80% [2, 3]. EA can cause the accidental removal of intravenous catheters or drains, wound dehiscence, rebleeding, bruising, and increased nursing care requirements. Although EA usually subsides within tens of minutes [4], severe EA sometimes requires pharmacological intervention and is among the most important problems in pediatric anesthesia.

Anesthesia maintenance with propofol has been shown to prevent EA effectively compared with the maintenance with inhalational anesthetics [5, 6]. Additionally, administration of a propofol bolus dose at the end of surgery has

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been shown to prevent EA [6, 7]. A recent meta-analysis found that administering a bolus propofol dose at the end of surgery reduced the incidence of EA after inhalational anesthesia in children [8]. In another study on adults, compared with sevoflurane alone, the coadministration of propofol and sevoflurane reduced the incidence of EA [9]. However, the preventive effects of subanesthetic propofol infusion with sevoflurane on EA have not been investigated in children.

We hypothesized that subanesthetic propofol infusion during sevoflurane anesthesia would reduce the incidence of EA in children. This retrospective observational study aimed to determine the effectiveness of subanesthetic propofol infusion during sevoflurane anesthesia for preventing EA in children undergoing surgical procedures. Additionally, we also explored the association between subanesthetic propofol infusion and the incidence of postoperative vomiting (POV).

Methods

Study preparation

The institutional review board of Kanagawa Children's Medical Center approved this study (approval number: 2006–12) on August 31, 2020 and waived the requirement for informed consent due to the retrospective observational study design. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology Statement [10].

Patients inclusion and exclusion criteria

We screened 485 consecutive children aged 0–16 years who underwent adenoidectomy, tonsillectomy with or without adenoidectomy, or strabismus surgery under general anesthesia between April 2018 and September 2020 in our tertiary care children's hospital. We excluded children with developmental delays due to chromosomal abnormalities or other causes. We also excluded patients who were maintained with propofol alone or with sevoflurane combined with propofol infusion above 6 mg/kg/h or were given a propofol bolus dose within five minutes before extubation. We included only the first anesthesia event if a patient had undergone more than one operation during the study period.

Data collection

Two authors (TM and YM) mutually checked the extracted data throughout the data collection process and validated the included data.

Exposure variable and patients' characteristics

The main exposure was the anesthesia maintenance methods: sevoflurane alone (sevoflurane group) or subanesthetic propofol infusion with sevoflurane (combination group). We defined a subanesthetic propofol infusion as an infusion of 6 mg/kg/h or less [11]. The following patient data were collected from the medical records: age, sex, body weight, American Society of Anesthesiologists physical status, comorbidities, history of motion sickness or POV, surgical procedures, premedication, anesthesia induction, perioperatively administered drugs and their dosages, anesthesia and surgical times, duration of recovery room stay, and attending anesthesiologists.

Outcome measures

This study's a priori primary outcome was the incidence of severe EA. We defined severe EA as pharmacological intervention by fentanyl or sedatives after extubation. Children were presumed to have been affected by severe EA if they received fentanyl or sedatives (propofol, midazolam, or droperidol) either within 30 min after extubation or between extubation and exit from the recovery room if they left the recovery room earlier than 30 min after extubation. We did not consider the occurrence of EA if the anesthetic chart or recovery room documentation suggested that fentanyl or propofol was administered due to pain or laryngospasm.

The secondary outcome was POV incidence. POV was defined as vomiting or retching within 24 h after surgery. In our institution, patients undergoing adenoidectomy or strabismus surgery are usually discharged on the first postoperative day, while those undergoing tonsillectomies are discharged on the fourth postoperative day. Therefore, we evaluated POV based on the discharge time for patients discharged earlier than 24 h after surgery. Additionally, we assessed the association between POV and the anesthetic method, stratified by the timing of occurrence, namely, early (occurring within 6 h after surgery) and late (occurring between 6 and 24 h after surgery).

Statistical analysis

Continuous and categorical variables are reported as the median (interquartile range) and the proportion (number of individuals), respectively. Between-group comparisons of continuous and categorical variables were performed using the Mann–Whitney *U* test and Fisher's exact test, respectively. Statistical significance was set at a two-sided

P value < 0.05. Statistical analyses were conducted using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 14 (Stata Corp., College Station, TX, USA).

Logistic regression analysis

We conducted a multivariable logistic regression analysis to estimate the association between the anesthesia maintenance method and the incidence of severe EA requiring pharmacological intervention, with adjustment for priori-determined potential confounders, including age, sex, premedication, and surgical procedures. Based on our previous study [12], we included these confounders, except for data regarding behavior during induction, because they were not systematically collected in our daily practice. Additionally, we conducted a multivariable logistic regression analysis to evaluate the association between the anesthesia maintenance method and POV, adjusting for age, age squared, sex, premedication, surgical procedures, and history of motion sickness or POV. We added the term "age squared" in the model because the incidence of POV increases with age > 3, followed by a subsequent decrease with puberty [13]. Hence, we thought a quadratic function could more accurately describe the relationship between POV and age. There were missing data regarding the history of motion sickness in 9 patients, excluded from the POV analysis. There was no multicollinearity among the independent variables as determined using the variance inflation factor. We checked the goodness of fit for logistic regression analyses using the Hosmer–Lemeshow test.

Mediation analysis

We conducted a mediation analysis [14] to estimate the direct effect of anesthesia methods on the incidence of severe EA because intraoperative doses of fentanyl and droperidol could have affected the incidence of EA. In the primary logistic regression analysis, we estimated the "total" effect, including the impact of intraoperative drugs such as fentanyl and droperidol on the outcome by only adjusting for confounding variables. Intraoperative administration of fentanyl and droperidol is performed after an anesthesia method is chosen; therefore, it can be affected by the anesthesia method. Moreover, intraoperative fentanyl and droperidol can also affect the incidence of EA (Fig. 1). Consequently, we considered the administration of fentanyl and droperidol as mediators rather than confounders. We conducted the mediation analysis using an imputation-based approach, where counterfactual values were imputed for the outcome mean and fitted a natural effect model [15] with robust standard errors to estimate natural direct and indirect effects with the R package "medflex" [16]. Here, the natural direct effect represents the expected effect of an anesthesia method on the outcome, with the mediators (doses of intraoperative fentanyl and droperidol) set to values that would have naturally been observed if anesthesia had been maintained with sevoflurane alone. The natural indirect effect represents the expected effect of mediators on the outcome if anesthesia had been maintained with subanesthetic propofol and sevoflurane in all patients. Each effect is assessed with an odds ratio scale, and the product of natural direct and indirect effect odds ratios equals the total effect odds ratio. We included age, sex, premedication, and surgical

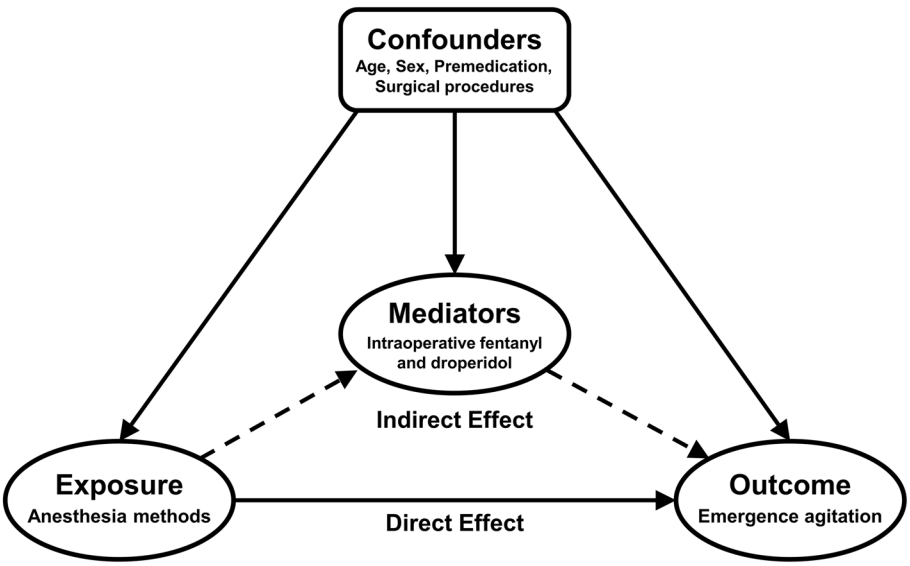

Fig. 1 Diagram of the presumed causal relationships. Intraoperative administration of fentanyl and droperidol is carried out after selecting an anesthesia method (maintenance with sevoflurane or a combination of subanesthetic propofol and sevoflurane). Consequently, the chosen anesthesia method may influence the administration of these agents. Additionally, their use during surgery may impact the incidence of emergence agitation. Thus, we considered these agents as mediators that convey indirect effects, rather than confounders

procedures as exposure-outcome, exposure-mediator, and mediator-outcome confounders. We also included an exposure-mediator interaction term in the model.

Sensitivity analyses

We performed a mixed-effects logistic regression analysis with random intercepts, incorporating attending anesthesiologists as a random effect, considering clustering by attending anesthesiologists. This was done to account for the potential influence of individual preferences of attending anesthesiologists on the decision-making process regarding pharmacological interventions for severe EA.

In addition, we calculated *E*-values [17] representing the strength of association on the risk ratio scale to assess the potential impact of unmeasured confounders. If the strengths of the association of an unmeasured confounder with both the exposure (anesthesia method) and the outcome (incidence of EA) are weaker than indicated by the *E*-value, it is implausible for the confounder to fully negate the observed exposure-outcome association.

Sample size

The sample size was determined based on the number of cases during the study period. There was a 90% power of detecting a 20% absolute reduction in the incidence of EA in 132 and 112 patients in the sevoflurane and combination groups, respectively, with a presumed incidence of EA requiring pharmacological interventions being 50% in the sevoflurane group based on our previous findings [18]. Moreover, there was a 90% power of detecting an absolute reduction of 19% or 17%, with the presumed incidence of EA being 40% or 30% in the sevoflurane group, respectively.

Results

We screened 485 cases of adenoidectomy, tonsillectomy with or without adenoidectomy, or strabismus surgery conducted between April 2018 and September 2020. We excluded 51 patients with developmental delay, 184 in whom anesthesia was maintained with propofol alone, one in whom > 6 mg/kg/h propofol infusion was used with sevoflurane, four who

Table 1 Baseline characteristics and surgery-related data of the study groups: maintenance with sevoflurane alone (sevoflurane group) and subanesthetic propofol with sevoflurane (combination group)

	Sevoflurane group ($n=132$)	Combination group ($n=112$)	*P* value
Male, *n* (%)	79 (59.8)	62 (55.4)	0.517
Age (month)	57 (39–72)	72 (52–89)	< 0.001
Weight (kg)	16 (13–20)	18 (15–24)	0.001
ASA-PS, *n* (%)			0.442
I	62 (47.0)	47 (42.0)	
II	70 (53.0)	65 (58.0)	
POV risk[a], *n* (%)	10 (7.8)	15 (14.0)	0.141
Surgery, *n* (%)			0.253
Adenoidectomy	29 (22.0)	19 (17.0)	
Tonsillectomy ± adenoidectomy	71 (53.8)	54 (48.2)	
Strabismus surgery (unilateral)	21 (15.9)	22 (19.6)	
Strabismus surgery (bilateral)	11 (8.3)	17 (15.2)	
Premedication, *n* (%)	5 (3.8)	0 (0)	0.064
Duration of surgery (min)	37 (25–51)	41 (27–56)	0.242
Duration of anesthesia (min)	80 (63–94)	85 (68–100)	0.070
Time from extubation to discharge from the recovery room (min)	32 (24–40)	38 (29–45)	0.001

Values are presented as the median (25th–75th percentile) or number of patients (%)

P values are from Mann–Whitney *U* tests for continuous variables and Fisher's exact tests for categorical variables

ASA-PS American Society of Anesthesiologists physical status, *POV* postoperative vomiting

[a]POV risk represents a history of motion sickness or postoperative vomiting. Data regarding the POV risk were missing in 9 patients. Proportions were calculated solely among those with available data

received a propofol bolus dose within five minutes before extubation, and one who underwent surgery twice during the study period. Regarding the last excluded patient, only the first operation data were included in the analysis. Accordingly, 244 patients were included in the analysis (132 and 112 in the sevoflurane and combination groups, respectively). Table 1 summarizes the baseline characteristics and surgery-related data of the two study groups. The age distribution was significantly different between groups; age in months was higher in the combination group (72 [52–89] vs. 57 [39–72], $P<0.001$). Premedication with ramelteon was administered to five children in the sevoflurane group, who all participated in another trial conducted in our institution [18], while the remaining children received no premedication. Surgical procedures were not significantly different between the two groups ($P=0.253$).

Table 2 summarizes the anesthesia-related characteristics of the patients. Inhalational induction was the most common anesthesia induction method in both groups. The sevoflurane concentration for anesthesia maintenance was significantly higher in the sevoflurane group than in the combination group (3.0% [3.0–3.0] vs. 2.0% [2.0–2.5], $P<0.001$). The median maintenance dose of subanesthetic propofol in the combination group was 3 (3–3) mg/kg/h, which was usually initiated during the induction of anesthesia. There was no significant difference in the intraoperatively administered fentanyl dose between the sevoflurane and combination groups (3.8 μg/kg [3.1–4.4] vs. 4.0 μg/kg [3.2–4.8], $P=0.076$). Remifentanil was administered to only one patient each in both groups. Intraoperative administration of droperidol was more frequent in the combination group than in the sevoflurane group (28.6% [$n=32$] vs. 15.2% [$n=20$], $P=0.012$). No children received other drugs intraoperatively, which can affect the incidence of EA, including midazolam, ketamine, or dexmedetomidine.

Comparison of the EA incidences among anesthesia methods

The crude incidence proportions of severe EA in the sevoflurane and combination groups were 33.3% ($n=44$) and 17.0% ($n=19$), respectively ($P=0.005$). The multivariable logistic regression analysis showed that the incidence of EA was significantly lower in the combination group compared with the sevoflurane group (adjusted odds ratio [aOR]: 0.48, 95% confidence interval [CI] 0.25–0.91, $P=0.024$) (Table 3) . The mediation analysis indicated a direct preventive effect on the incidence of severe EA in the combination group (aOR: 0.48, 95% CI 0.24–0.93, $P=0.030$) and no significant indirect effect through intraoperative fentanyl and droperidol (aOR: 0.99, 95% CI 0.84–1.19, $P=0.995$) (Table 4) .

Table 2 Anesthesia-related characteristics of the study groups: maintenance with sevoflurane alone (sevoflurane group) and subanesthetic propofol with sevoflurane (combination group)

	Sevoflurane group ($n=132$)	Combination group ($n=112$)	*P* value
Inhalational induction, *n* (%)	128 (97.0)	108 (96.4)	1.000
Sevoflurane, maintenance dose (%)	3.0 (3.0–3.0)	2.0 (2.0–2.5)	< 0.001
Propofol, maintenance dose (mg/kg/ h)	–	3.0 (3.0–3.0)	
Intraoperative[a] fentanyl (μg/kg)	3.8 (3.1–4.4)	4.0 (3.2–4.8)	0.076
Perioperative[b] fentanyl (μg/kg)	4.0 (3.4–4.9)	4.1 (3.2–4.9)	0.781
Intraoperative remifentanil, *n* (%)	1 (0.8)	1 (0.9)	1.000
Remifentanil dose[c] (μg/kg/min)	0.4 (0.4–0.4)	0.1 (0.1–0.1)	
Intraoperative[a] droperidol, *n* (%)	20 (15.2)	32 (28.6)	0.012
Droperidol dose[c] (μg/kg)	28 (23–37)	21 (19–23)	
Perioperative[b] droperidol, *n* (%)	23 (17.4)	34 (30.4)	0.022
Droperidol dose[c] (μg/kg)	30 (25–48)	21 (20–23)	
Dexamethasone, *n* (%)	0 (0.0)	9 (8.0)	< 0.001
Extubated under anesthesia, *n* (%)[d]	61 (58.1)	46 (48.4)	0.202

Values are presented as the median (25th–75th percentile) or number of patients (%)

P values are from Mann–Whitney *U* tests for continuous variables and Fisher's exact tests for categorical variables

[a]"Intraoperative" represents the period between induction and extubation

[b]"Perioperative" represents the period between induction and exit from the recovery room

[c]"Dose" means the doses among patients given the concerned drug

[d]Data regarding anesthetic depth at extubation were missing in 44 patients. Proportions were calculated solely among those with available data

Table 3 Association between anesthesia methods and emergence agitation

	Multivariable logistic regression analysis			Mixed-effects logistic regression analysis		
	aOR	95% CI	*P* value	aOR	95% CI	*P* value
Anesthesia methods[a]						
Sevoflurane	Reference			Reference		
Combination	0.48	0.25–0.91	0.024	0.47	0.24–0.93	0.030
Sex						
Female	Reference			Reference		
Male	0.80	0.44–1.47	0.481	0.80	0.43–1.48	0.479
Age, month	0.99	0.98–1.00	0.066	0.99	0.98–1.00	0.062
Premedication	1.53	0.24–9.90	0.655	1.36	0.18–9.99	0.765
Surgery						
Adenoidectomy	Reference			Reference		
Tonsillectomy ± adenoidectomy	0.99	0.46–2.17	0.988	1.01	0.46–2.24	0.974
Strabismus surgery (unilateral)	1.40	0.51–3.87	0.513	1.34	0.47–3.85	0.588
Strabismus surgery (bilateral)	0.62	0.19–2.01	0.421	0.60	0.18–1.98	0.401

Between-group comparisons of the incidence of emergence agitation requiring pharmacological intervention were performed using a multivariable logistic regression model and a mixed-effects logistic regression model with random intercepts adjusted for age, sex, premedication, and surgical procedures

aOR adjusted odds ratio, *CI* confidence interval

[a]Anesthesia methods: sevoflurane, maintenance with sevoflurane alone; combination, maintenance with subanesthetic propofol with sevoflurane

Table 4 Decomposition of the total effect of subanesthetic propofol with sevoflurane into the natural direct and indirect effects

	aOR	95% CI	*P* value
Natural direct effect	0.48	0.24–0.93	0.030
Natural indirect effect	0.99	0.84–1.19	0.995
Total effect	0.48	0.25–0.91	0.024

Natural direct and indirect effects of subanesthetic propofol with sevoflurane were estimated by a mediation analysis using a natural effect model adjusted for age, sex, premedication, and surgical procedures. Conceptually, the direct effect refers to the effect of the exposure on the outcome that is not mediated by any intermediate variable, while the indirect effect represents the effect of the exposure on the outcome transmitted through intermediate variables. Specifically, the natural direct effect represents the expected effect of the anesthesia method (maintenance with sevoflurane alone or maintenance with a combination of subanesthetic propofol and sevoflurane) on the incidence of emergence agitation requiring pharmacological intervention, with the mediators (intraoperative fentanyl and droperidol doses) set to values that would have naturally been observed if maintained with sevoflurane alone. On the other hand, the natural indirect effect represents how much the outcome would have changed, on average, if anesthesia had been maintained with the combination of subanesthetic propofol and sevoflurane but the mediators' values had changed to the values they would have taken if maintained with sevoflurane alone. The product of natural direct and indirect effect odds ratios equals the total effect odds ratio

aOR adjusted odds ratio, *CI* confidence interval

Sensitivity analyses

The mixed-effects logistic regression analysis showed a significantly decreased incidence of severe EA in the combination group compared with the sevoflurane group (aOR: 0.47, 95% CI 0.24–0.93, $P = 0.030$) (Table 3).

The *E*-values for the point estimate and upper confidence bound for the incidence of severe EA were 2.25 and 1.28, respectively.

Comparison of the POV incidences between anesthesia methods

The incidence proportions of POV in the sevoflurane and combination groups were 27.3% ($n = 36$) and 27.7% ($n = 31$), respectively ($P = 1.000$). Also, the incidence proportions of early and late POV did not display a statistically significant difference between the two groups. The early POV incidence proportion was 15.9% ($n = 21$) vs. 12.5% ($n = 14$) ($P = 0.470$), while the late POV incidence proportion was 17.4% ($n = 23$) vs. 21.4% ($n = 24$) ($P = 0.515$) for the sevoflurane and the combination group, respectively. The multivariable logistic regression analyses indicated that the POV incidence in the combination group did not significantly differ from that in the sevoflurane group, regardless of the timing of POV (Table 5).

Table 5 Association between anesthesia methods and postoperative vomiting

	Overall POV (0–24 h)			Early POV (0–6 h)			Late POV (6–24 h)		
	aOR	95% CI	*P* value	aOR	95% CI	*P* value	aOR	95% CI	*P* value
Anesthesia methods[a]									
Sevoflurane	Reference			Reference			Reference		
Combination	0.97	0.51–1.83	0.923	0.61	0.28–1.34	0.216	1.29	0.62–2.67	0.491

POV Postoperative vomiting, *aOR* adjusted odds ratio, *CI* confidence interval

[a]Anesthesia methods: sevoflurane, maintenance with sevoflurane alone; combination, maintenance with subanesthetic propofol with sevoflurane

Discussion

Our findings demonstrated that the combination of subanesthetic propofol and sevoflurane was associated with a lower incidence of EA requiring pharmacological intervention in children. This suggests a preventive effect of subanesthetic propofol infusion against EA, which is consistent with previous reports on the effectiveness of propofol as a maintenance agent [5, 6], bolus dose at the end of surgery [6–8], and coadministration with sevoflurane [9]. Furthermore, the mediation analysis showed a significant direct effect in the combination group, implying an intrinsic influence of subanesthetic propofol on severe EA incidence rather than through intraoperative fentanyl and droperidol.

We did not define EA based on the Pediatric Anesthesia Emergence Delirium (PAED) scale [19] but rather as a postoperative event requiring fentanyl or sedative administration. The PAED scale is the standard for diagnosing emergence delirium in children. Strictly speaking, EA and emergence delirium are different clinical entities. The broader term "emergence agitation" includes emergence delirium, pain, and other conditions [20]. It is difficult to distinguish between EA caused by postoperative pain and emergence delirium [21]. Although we excluded patients who presumably received fentanyl for pain relief, the outcome cases might still include patients affected by emergence delirium and pain. Moreover, emergence delirium diagnosed based on a cut-off PAED score ≥ 10 ranges in severity from only requiring close observation to requiring intervention. We focused on cases requiring rescue drugs because severe EA was considered clinically relevant.

The abovementioned definition of EA could have led to overestimating the EA incidence because it might include patients who received rescue drugs for other reasons. Nonetheless, the incidence of severe EA in the sevoflurane group was 33.3%, which was comparable to the reported 45.8% (95% CI 25.6–67.2, $n = 11$) incidence of EA requiring rescue drugs after sevoflurane anesthesia in our previous study, where EA was assessed using the PAED scale [18]. Therefore, overestimation of the incidence of severe EA appears to be implausible. Furthermore, the threshold of administering rescue drugs could vary among anesthesiologists and affect the incidence of severe EA as defined in this study. However, our results were robust, as indicated by the mixed-effects analysis considering clustering by the attending anesthesiologists.

The sevoflurane concentration for anesthesia maintenance was lower in the combination group. This decrease in sevoflurane concentration may be ascribed to the following reasons. First, a theoretical standpoint posits that subanesthetic propofol infusion can reduce the required sevoflurane dosage. Second, sevoflurane concentration was titrated based on bispectral index (BIS) monitoring. In our institution, the BIS monitor is occasionally employed during anesthesia with the combination method, whereas it is not utilized during anesthesia with sevoflurane alone. Concerning anesthetic depth monitoring, although the monitoring approach for the combined sevoflurane-propofol anesthesia has not yet been established, we deduce that BIS monitoring can be a useful approach, given its utility in sevoflurane anesthesia in children [22] and the additive anesthetic effect of sevoflurane and propofol [23].

There are several possible advantages of subanesthetic propofol infusion with sevoflurane anesthesia. First, it can be easily implemented in facilities not accustomed to propofol anesthesia in children. Second, it obviates the need for remifentanil infusion, as indicated by the finding that only one patient in each group received remifentanil, as shown in Table 2. This contrasts with propofol-based total intravenous anesthesia, which often entails concomitant use of remifentanil infusion [24]. It, therefore, can preserve the patient's spontaneous breathing, which is crucial, especially for those with sleep apnea syndrome who can be highly sensitive to opioids [25]. Third, it can allow prompt coping with severe EA or laryngospasm because propofol is readily available. Fourth, it may shorten the time to emergence and extubation compared with anesthesia maintenance with sevoflurane alone [9]. Conversely, a prophylactic propofol dose of 1 mg/kg at the end of surgery was found to lengthen the time to awakening [8]. These findings collectively imply that the combination of subanesthetic propofol infusion and sevoflurane may lead to a shorter time to awakening compared to a propofol bolus at the end of the surgery, albeit these observations are not a direct comparison. Finally, it can reduce

propofol consumption in general anesthesia compared with total intravenous anesthesia using propofol. This could be beneficial considering the supply of propofol, which can be threatened by the likely increase in demand for sedatives in critically ill patients due to the coronavirus disease 2019 pandemic.

Although we expected that subanesthetic propofol could also prevent POV, there was no significant difference in the incidence of POV between the combination and sevoflurane groups. Several studies reported an association of subanesthetic propofol infusion in children with a lower incidence of POV, particularly early POV [11, 26]. Our study also suggested a potential preventive effect of subanesthetic propofol infusion with the point estimate of the OR for early POV being less than one; however, this association lacked statistical significance. This inconsistency between our findings and those of previous studies may be partly due to insufficient statistical power. Moreover, the use of antiemetic prophylaxis may have contributed to this discrepancy. Prior studies routinely administered either ondansetron or dexamethasone, while in our combination group, only 30.4% and 8.0% of patients received droperidol and dexamethasone, respectively, and no other antiemetics were administered. Therefore, subanesthetic propofol infusion alone may be ineffective in preventing POV.

Our study has several limitations. First, there could have been several unmeasured confounders, given the observational design. For example, preoperative anxiety or behavior during induction, which was not assessed in this study, can affect the incidence of EA [27, 28]. However, there are conflicting results regarding their impact on EA incidence [29, 30]. Moreover, we do not select an anesthesia method according to preoperative anxiety or behavior during induction in our practice. Therefore, they were unlikely to affect the selection of the anesthesia method and confound the results. Additionally, we estimated the influence of unmeasured confounders by *E*-values [17]. *E*-values for point estimates of aOR were over two, indicating that an unmeasured confounder should be at least two-fold prevalent in the sevoflurane group and should increase the severe EA risk by at least two-fold to negate the estimated association. Such a strong confounder is considered unlikely. However, regarding upper confidence bounds, *E*-values were relatively low, implying that a weaker confounder can make the observed association nonsignificant. Hence, our findings should be interpreted with caution. Second, we did not standardize the subanesthetic propofol dose and propofol bolus administration. Thus, the optimal dose and method of administering subanesthetic propofol necessary for preventing EA remain unclear. Third, approximately 40% of the patients left the recovery room within 30 min after extubation. Therefore, we might have missed EA cases after patients were transferred to the inpatient ward. However, according to our daily practice, this is unlikely because patients were discharged from the recovery room after confirmation of arousal signs, including eye-opening and purposeful movement. Even if this had been the case, this misclassification could have biased the association toward the null because the length of stay in the recovery room was longer in the combination group than in the sevoflurane group, leading to fewer missed EA cases in the combination group. Finally, our analyses did not incorporate the anesthetic depth at extubation. Information on the anesthetic depth at extubation was not available for approximately 20% of the children, which prevented us from investigating its effect on the incidence of EA. However, among the remaining 80%, the sevoflurane group had a higher frequency of tracheal extubation during anesthesia than the combination group, signifying a potential advantage in reducing the occurrence of EA in the former. Furthermore, while the anesthetic depth at extubation might influence the occurrence of EA, there are inconsistent reports concerning the association between the anesthetic depth during extubation and EA [31, 32]. Therefore, we do not deem it plausible that variations in the timing of extubation could have affected our findings.

In summary, subanesthetic propofol infusion combined with sevoflurane may reduce the incidence of severe EA requiring pharmacological intervention. Further studies are warranted to confirm the optimal dosage as well as the preventive effect of subanesthetic propofol against EA. Also, further investigation is needed to compare the effectiveness of preventing EA between maintenance with propofol alone and maintenance with the combination of sevoflurane and subanesthetic propofol.

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Data availability The data that support the findings of this study are available from the corresponding author, YM, upon reasonable request.

Declarations

Conflict of interest None for all authors.

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