The change of sevoflurane to desflurane after anesthesia induction induces rapid emergence without increased cardiovascular responses and emergence delirium in pediatric strabismus surgery patients

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INTRODUCTION

Sevoflurane and desflurane, both used in pediatric anesthesia, have stability and a low risk of life-threatening side effects [1]. Both inhalation agents have been shown to induce rapid induction and recovery due to their low blood/gas partition coefficient. The use of desflurane for the maintenance of anesthesia has been associated with a faster emergence and a higher incidence of coughing [2]. The inhalation of a high concentration of desflurane increases the heart rate (HR), blood pressure (BP), and cardiac index (CI) transiently in all age groups. In pediatric patients, HR and BP increase more rapidly than in young adults and elderly patients [3]. Because of these cardiac responses, desflurane is not usually used for inhalational induction as a solitary anesthetic, although there are some reports that desflurane does not increase the critical respiratory risk [4,5]. Rapid inhalation of desflurane does cause cardiovascular changes [6]. The pharmacokinetics and pleasant odor of sevoflurane make mask induction feasible, which is an obvious advantage in pediatric anesthesia [7].

Predisposing factors of emergence agitation are not fully known, but rapid emergence may lead to emergence agitation [8-10]. These adverse effects can cause sympathetic hyperactivity, prolonged hospital stay, and decreased patient satisfaction. Sethi et al. [11] reported that the occurrence of emergence agitation...
in pediatric patients was not significantly different between sevoflurane and desflurane. We hypothesized that desflurane may cause more emergence delirium if it is caused by rapid recovery, but desflurane maintenance after sevoflurane induction can provide gentle induction and rapid emergence while minimizing cardiovascular changes during induction. There have been no studies comparing the separate use of each inhalation agent and combined use of both anesthetics. We designed this study to discover ways to use inhalation agents more efficiently in accordance with their characteristics. We compared the effects of these inhalation agents using the Pediatric Anesthesia Emergence Delirium (PAED) scale, cardiovascular responses, respiratory complications, and the post-anesthesia care unit (PACU) length of stay following pediatric strabismus surgery.

### MATERIALS AND METHODS

#### Study design

The study protocol was approved by the Institutional Review Board, and the parents of patients provided informed consent before a surgery. In the pilot study, we included 10 pediatric patients who had undergone strabismus surgery. The largest difference of mean PAED scores between any two groups was 1.2. Therefore, the estimated sample size was 41 subjects in each group, which was calculated from a β-risk of 80% and an α-level of 0.05 for detecting the largest difference in mean PAED score (10 in S group vs. 11.2 in D group) of at least 1.2 at the time that PAED scale had the largest score after patients arrived at PACU, with a standard deviation of 2.0 for each group in the preliminary test. Ultimately, 135 patients were assessed for study after assuming a 10% exclusion rate. Data are expressed as mean ± SD.

#### Subjects

In all, 135 patients who were American Society of Anesthesiologists physical status classification class I or II and scheduled for elective strabismus surgery were enrolled in the study. Patients of both genders, aged 2 to 10 years old, were selected. Patients were randomized into three groups (S group, D group, and C group). Randomization was accomplished with computer-generated numbers, and patients were randomized by numbered envelopes before they entered the operating room. Children were excluded if they had a history of airway disease, neurological disorder, or psychological disorder.

### Treatment

The primary end point was to compare PAED and cardiovascular responses among the three groups. Secondary outcomes were the duration of PACU stay, and the incidence of side effects such as cough, laryngospasm, nausea, and vomiting.

Anesthesia was standardized in all groups. Glycopyrrolate (5 μg/kg) was intramuscularly injected in all patients 30 min before induction of anesthesia. One parent was allowed to come into the operating room to stabilize the child. After the patients arrived in the operating room, the patient’s baseline HR, mean arterial blood pressure (MBP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse oximetric oxygen saturation (SpO2) were obtained using a patient monitor. Pediatric BIS™ electroencephalographic sensor (Aspect TM Medical Systems [DSC-XP], Boston, MA, USA) monitoring was used to measure the depth of anesthesia during anesthesia. Thiopental (5 mg/kg), rocuronium (0.6 mg/kg), and remifentanil (0.5 μg/kg/min) were injected for the induction. Children were randomly divided into three groups: the S group (n = 45) received 5 vol% sevoflurane for induction and 3 ± 0.5 vol% sevoflurane for maintenance, the D group (n = 45) received 10 vol% desflurane for induction and 7 ± 0.5 vol% desflurane for maintenance, and the C group (n = 45) received 5 vol% sevoflurane for induction and 3 ± 0.5 vol% sevoflurane for maintenance for 5 min, and then the maintenance anesthetic was changed to 7 ± 2 vol% desflurane. After intubation, the infusion rate of remifentanil was decreased to 0.1–0.2 μg/kg/min.

Anesthesia was maintained to adjust the BIS scores within 40–60 during operation. If BIS scores decreased below 40, inhalation agents were also decreased. FiO2 was set to 0.5 and the respiratory rate and tidal volume were controlled to maintain end-tidal carbon dioxide partial pressure (PetCO2) within 32–38 mmHg. Noninvasive blood pressure measurements (NIBP), electrocardiogram (ECG), HR, SpO2, and PetCO2 were continuously monitored and recorded every minute until 5 min after intubation. We checked NIBP and HR at the time before the induction (Baseline), 1 min after thiopental injection (Induction), 2 min after thiopental injection (Pre-intubation), just after intubation (Post-intubation), and every minute after intubation for 5 minutes.

Ketorolac (0.75 mg/kg) and ondansetron (0.2 mg/kg) were injected in all patients 30 min before the end of the operation. When the surgeon finished the last suture, the inhalation agent was stopped, and the fresh gas flow was increased to 5 L/min.
Controlled mechanical ventilation was stopped when the patient regained the gag reflex and had a BIS score over 90. Then, assisted ventilation was started.

Exubation was performed after spontaneous breathing was attained, with a tidal volume over 5 ml/kg, sustained eye opening, and the return of gag and swallow reflexes. Residual neuromuscular relaxation was reversed with pyridostigmine (50 μg/kg) and glycopyrrolate (2 μg/kg). Patients were transferred to PACU, and stayed until their modified Aldrete score was greater than 8.

Time to extubation, time to first crying, and the incidence of cough and laryngospasm were obtained from the discontinuation of inhalation agents to discharge from the operating room. A blinded observer recorded the level of emergence delirium according to the PAED scale [12], PACU length of stay, and the incidence of postoperative complications in PACU. The PACU stay was considered to be the duration from admission to the PACU to the time that a modified Aldrete score was greater than 8. The PAED scale was used as a measure of emergence delirium, which was scored from 0 to 20, at each 5 min intervals until the patient was discharged from the PACU. The maximum PAED scale of each patient was used for evaluation.

### Statistical analysis

Continuous data such as age, weight, time to extubation, time to crying, and recovery are expressed as mean ± SD, and were compared using a one-way analysis of variance (ANOVA). Categorical data, such as the incidence of cough, emesis, and vomiting were compared using a chi-square test, and the incidence of bronchospasm was compared using Fisher’s exact t-test. The PAED was compared using a repeated measured ANOVA, and data were expressed as median (range). SBP and HR changes were analyzed using two-way repeated measures ANOVA and post-hoc analysis by Scheffe’s test. A probability of < 0.05 was considered to be significant. SPSS (21.0 IBM Statistics Data Editor SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

### RESULTS

In total, 135 patients were assessed, and there were no drop-outs for the study. P_{ETCO2} and BIS scores were maintained stably during the entire anesthetic period.

The age, sex, weight, operation time, anesthesia time, baseline HR, and baseline SBP were not different among the three groups (Table 1). The HR in all groups and SBP in the D group increased before intubation, and decreased after intubation. The trend of HR was not significantly different between the three groups, but the SBP trend was different in the D group as compared to the other groups. The SBP in the S and C groups decreased after the thiopental injection, showed a peak level at intubation time, and decreased after intubation. In contrast, the SBP in the D group increased after the desflurane inhalation, showed a peak level at intubation time, and decreased after intubation (Figs. 1 and 2). The time to extubation and time to crying were longer in the S group than in the other groups (Table 2, P < 0.05). There was no significant difference in the duration of the PACU stay and the maximal PAED scale score among groups. The incidence

| Table 1. Baseline Demographic Data and Vital Signs |
|-----------------|-----------------|-----------------|------------------|
| Number of patients | 45 | 45 | 45 |
| Age (yr) | 5.71 (2.3) | 5.62 (2.7) | 5.86 (1.9) |
| Sex (%) | | | 0.34 |
| Male | 19 (42.2) | 25 (56.6) | 25 (56.6) |
| Female | 26 (57.8) | 20 (44.4) | 20 (44.4) |
| Weight (kg) | 21.5 (7.2) | 24.9 (10.0) | 24.6 (10.3) |
| OP time (min) | 32.3 ± 14.1 | 36.2 ± 16.2 | 34.2 ± 14.4 |
| AN time (min) | 52.53 ± 17.7 | 56.1 ± 18.6 | 55.4 ± 17.0 |
| Pre-op HR (beats/min) | 106.9 ± 21.1 | 99.5 ± 21.7 | 107.2 ± 24.6 |
| Pre-op SBP (mmHg) | 111.8 ± 11.7 | 111.3 ± 11.8 | 112.7 ± 12.3 |

Data are expressed as mean ± SD or number (%). There is no difference in baseline demographic data, baseline vital signs, and anesthesia time between groups. OP time: operation time, AN time: anesthesia time, Pre-op HR: pre-operation heart rate, Pre-op SBP: pre-operation systolic blood pressure.
of nausea, vomiting, and laryngospasm were not different among groups, but that of cough was higher in the D group (Table 2, \(P = 0.014\)). All cough and laryngospasm subsided within two min.

### DISCUSSION

Sevoflurane and desflurane are frequently used in pediatric anesthesia, and they have been thought to be stable, safe, and economical. Desflurane can induce a more rapid induction and recovery due to its lower blood-gas coefficient, as compared to sevoflurane [2,4]. This study also showed that desflurane led to a shorter time to extubation and first crying time. This result suggests that the desflurane is economical because it shortens the anesthesia time. However, it has been thought to be unsuitable as an induction agent, due to concern that it provokes increased

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**Table 2. Recovery Profiles of Each Group**

|                  | S group       | D group       | C group       | P value |
|------------------|---------------|---------------|---------------|---------|
| Time to extubation (min) | 10.07 ± 2.5   | 5.79 ± 1.1    | 6.26 ± 1.9    | < 0.001 |
| Time to first crying (min) | 11.32 ± 2.5   | 6.85 ± 1.7    | 7.32 ± 1.9    | < 0.001 |
| PACU length of stay (min)  | 25.4 ± 7.1    | 21.56 ± 7.3   | 23.80 ± 8.4   | 0.059   |
| Maximal PAED score        | 12.1 ± 4.8    | 10.1 ± 4.5    | 11.3 ± 4.7    | 0.12    |
| Cough (number)            | 1 (2.2)       | 8 (17.8)      | 2 (4.4)       | 0.014   |
| Laryngospasm (number)     | 0             | 1             | 0             | 1.000   |
| Nausea/Vomiting (number)  | 0/0           | 4/0 (8.9)     | 2/0 (4.4)     | 0.123   |

Data are expressed as mean ± SD or number (%). Time to extubation and time to crying in the S group was significantly longer than those in the D and C groups (\(P < 0.001\)). However, there was no significant difference in the duration of stay in the post-anesthesia care unit (PACU length of stay) or maximal pediatric anesthesia emergence delirium (PAED) scale between the groups. The incidence of cough in the D group (17.8%) was significantly higher than the S (2.2%) and C groups (4.4%).
sympathetic activity and respiratory complications, such as laryngospasm and coughing, during induction. Therefore, we used thiopental and remifentanil before administering the inhalation agents for induction. In cases with desflurane, the concentration was increased slowly. In this study, desflurane caused a more frequent cough and increased blood pressure, even though we used thiopental and remifentanil. However, there was no increase in severe respiratory complications, such as laryngospasm or bronchospasm. Valley et al. [13] also reported that coughing occurs more frequently with desflurane, but also that it does not increase the risk of severe respiratory complications.

Desflurane increased blood pressure compared to the other groups in this study. Several studies have also shown that desflurane increased HR and MAP [3]. Desflurane is known to increase sympathetic activity and the prior administration of fentanyl, esmolol, or clonidine can blunt this response [14,15]. The HR in propofol-remifentanil anesthesia has been shown to be lower than desflurane-N₂O-based anesthesia in pediatric patients [16]. In the present study, the HR in all groups was not different, although we use desflurane for induction. The reason is unclear. We suggest that the remifentanil infusion before desflurane inhalation repressed the increase of heart rate.

Sevoflurane and desflurane are known to induce postoperative emergence delirium. Emergence delirium includes inconsolable crying, agitation, excitement, and restlessness, among other symptoms. Most emergence delirium disappeared within 1 hour, but it can be dangerous, as patients may fall out of the bed, pull out an IV line, and it makes parents anxious. It also results in a prolonged PACU stay [8-10]. Although emergence delirium has recently been investigated by several studies, the exact etiology remains unclear. It has been known to be related with pain, a side effect of the medicine, age, preoperative anxiety, and rapid emergence due to the low solubility of inhaled agents [8-10]. Volatile anesthetics such as sevoflurane and desflurane have been known to aggravate emergence delirium because of their rapid recovery. Dalens et al. [17] suggested that small doses of ketamine or nalbuphine administered just before discontinuing anesthesia could prevent emergence delirium. Oral clonidine 4 μg/kg prior to induction has been shown to decrease emergence delirium compared with midazolam 0.5 mg/kg [18]. We selected patients who underwent strabismus operations, and injected analgesics before emergence in order to minimize the effect of pain. In addition, one parent stayed with the patient in the PACU to decrease anxiety due to the unfamiliar surroundings. Patients of each group were placed in the same environments and conditions, except for the volatile anesthetics used in this study. In this study, desflurane did not aggravate emergence delirium in spite of its lower blood gas coefficient and having a more rapid recovery than sevoflurane. We suggest that the type of inhalation agent, whether it is sevoflurane or desflurane, is not the main cause of emergence delirium.

We have some limitations in the current study. First, the concentrations of sevoflurane and desflurane during induction were not determined by the minimal alveolar concentration (MAC) of each agent and were instead determined empirically. The MAC of sevoflurane in children is about 3 vol% and that of desflurane is about 8 vol%. The MAC of sevoflurane and desflurane in this study were 1.67 MAC (5 vol%) and 1.25 MAC (10 vol%), respectively. This difference in MAC between agents may influence the cardiovascular response during induction. Second, we used a glycopyrrolate intramuscular injection and intravenous catheterization 30 min before the operation. This protocol could induce an increase in preoperative anxiety and HR. If patients showed severe anxiety before the operation, they had to be excluded from the study. However, we tried to minimize the anxiety of patient by having a parent accompany him or her until anesthetic induction. Glycopyrrolate itself may affect emergence delirium, but there have been no such reports.

In conclusion, changing to desflurane following a sevoflurane induction in pediatric strabismus surgery provided a rapid emergence compared with continuous sevoflurane, and attenuated cardiovascular responses and showed lesser respiratory complications compared with desflurane alone. Emergence delirium was not influenced by the inhalational anesthetics, sevoflurane or desflurane.

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