# Efficacy of 0.5 mg/kg of propofol at the end of anesthesia to reduce the incidence of emergence agitation in children undergoing general anesthesia with sevoflurane

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## Abstract

**Background and Aims:** Emergence agitation (EA) is a common transient behavioral disturbance after inhalational anesthesia and may cause harm to the patient. This study evaluated the efficacy of 0.5 mg/kg of propofol administered at the end of anesthesia to reduce the incidence of EA in children undergoing general inhalational anesthesia.

**Material and Methods:** This double-blind randomized clinical trial was done in children aged 1–5 years undergoing general anesthesia with sevoflurane. One hundred and eight subjects were included using consecutive sampling method and randomized into two equal groups. Propofol in the dose of 0.5 mg/kg was administered at the end of anesthesia to children in the propofol group, while those in the control group did not receive any intervention at the end of anesthesia. Incidence of EA, transfer time, postoperative hypotension, desaturation, and nausea-vomiting were observed. Aono and *Pediatric Anesthesia Emergence Delirium* scale were used to assess EA.

**Results:** Incidence of EA was 25.9% in the propofol group compared to 51.9% in the control group (RR = 0.500; 95% CI 0.298–0.840; $P$ = 0.006). Mean transfer time in propofol group was longer (9.5 ± 3.9 min) than control group (7.8 ± 3.6 min) (mean difference 1.71 min; 95% CI 0.28–3.14; $P$ = 0.020). Hypotension was found in one patient (1.9%) in propofol group, while in control group there was none. Nausea-vomiting was found in five patients (9.3%) in propofol group and eight patients (14.8%) in control. There was no desaturation in both the groups.

**Conclusion:** Administration of 0.5 mg/kg of propofol at the end of anesthesia effectively reduces the incidence of EA in children undergoing general inhalational anesthesia with sevoflurane.

**Keywords:** Agitation, children, delirium, emergence, propofol, sevoflurane

## Introduction

Sevoflurane is an inhalation anesthetic agent commonly used for pediatric patients; however, it is associated with a high incidence of emergence agitation (EA) in the postoperative period.[1] EA is a postoperative behavior disorder marked by a temporary excitation period during the recovery phase of anesthesia. The incidence of EA varies around 10% to 80%, with the highest incidence found in patients aged 2 to 5 years.[2,3] A previous study by Aktara showed that the incidence of EA in our population was 39.7%.[4] Although it is a temporary and self-limiting condition, EA potentially endangers patients and threatens patient safety. Many studies have been performed to reveal possible causes, prevention, and treatment of EA, but no definite guidelines have been established.

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Propofol is a hypnotic amnestic agent with a short duration of action, commonly used for sedation, induction, and maintaining anesthesia. Studies show that administration of intravenous (IV) propofol 1–3 mg/kg at the end of inhalation anesthesia may reduce the incidence of EA. However, it is also associated with a prolonged time for extubation, time to transport to the Postanesthesia Care Unit (PACU), and return to consciousness, hence hindering the readiness of patient turnover in the operating room.[5-7] There is a paucity of the literature on the effectiveness of doses less than 1 mg/kg of propofol given at the end of inhalation anesthesia to decrease the incidence of EA. We expected that a smaller dose of propofol would not prolong the patient's tracheal extubation time. This study aimed to determine the efficacy of 0.5 mg/kg of propofol given at the end of inhalation anesthesia in reducing-the incidence of postoperative EA after general anesthesia with sevoflurane.

## Material and Methods

This randomized double-blinded clinical trial was conducted after approval from the Ethics Committee of the Institution on 108 physical status ASA 1 or 2 children aged 1 to 5 years, undergoing surgical procedure under general anesthesia using sevoflurane. The sample size was calculated using unpaired categorical comparative analytic tests, with an expected clinical difference of 20%, power of 84%, baseline incidence of EA of 40%, and an alpha error of 5%.[4] Hence, the calculated sample size was 108. Accessible population during the study period included 266 children. Twenty-four subjects did not fulfill inclusion criteria, while 134 subjects were excluded. The parents or caregiver of the patients gave written consent. Exclusion criteria were as follows: emergency surgery, ophthalmologic procedures, adenotonsillectomy, ICU admission with mechanical ventilation, psychology or neurologic deficits, delayed growth and development, sedative drugs therapy, history of allergy to propofol, susceptible for malignant hyperthermia, predicted difficult airway, cardiovascular disorders that affects physical status, and hemodynamic instability. A drop out criterion was the occurrence of perioperative emergency and the unplanned need for postoperative care in the ICU with mechanical ventilation.

Randomization was performed in the preparation room with the help of www.randomizer.org. The results of the randomization were put in a sealed numbered envelope to a third-party responsible for the anesthesia without involvement of the research team. After premedication with 0.5 mg/kg of ketamine intravenously, patients were taken into the operating room, standard monitoring devices such as pulse oximetry, electrocardiogram, and non-invasive blood pressure (NIBP) were placed. Pediatric anesthesia behavior score was recorded for each patient during the induction of anesthesia.[8] Anesthesia was induced with sevoflurane, and atracurium was used to facilitate endotracheal intubation or laryngeal mask airway (LMA) insertion. Sevoflurane 1-2 MAC was given for maintenance of anesthesia. Mechanical ventilation was adjusted to maintain an end-tidal $CO_2$ ($ETCO_2$) between 35 and 40 mmHg. Toward the end of the procedure, neuromuscular blockade was reversed, followed by IV infusion of 15 mg/kg of paracetamol for postoperative pain relief. Sevoflurane was stopped upon spontaneous breathing with a regular pattern. Duration of surgery was measured from the skin incision until the last wound dressing had finished. Duration of anesthesia was measured from the time of induction until sevoflurane was stopped. Children in the propofol group received a bolus propofol in a dose of 0.5 mg/kg IV, while the control group did not receive any medication. The administration of propofol was performed by the OR team depending on the randomization.

Removal of the supraglottic airway device was done after the child was able to open eyes spontaneously and had regular spontaneous breathing. The child was then transported to the recovery room for observation. The transport time was measured from the cessation of sevoflurane until the child fulfills the transfer criteria to the recovery room. The transfer criteria included clear and patent airway without any maneuver, adequate ventilation and oxygenation, and hemodynamic stability. The child was monitored using a pulse oximeter during the transport to the recovery room.

Upon arrival and up to 30 min of care in the recovery room, the research team blinded to the allocation of the patients, conducted assessment of EA. EA was first screened using the Aono scale.[9] Patients with Aono scale of ≥3 was then reassessed using the Pediatric Anesthesia Emergence Delirium (PAED) scale, while patients with a score of <3 in the Aono scale was not reassessed with the PAED scale and recorded as non-EA. A diagnosis of EA was determined when a score of ≥3 in the Aono scale and ≥10 on the PAED scale was obtained. Children with a PAED score of ≥16 were considered to have severe EA and were administered a propofol bolus of 1 mg/kg for treatment of severe EA. Any hypotension in the PACU was treated with 20 mL/kg of intravenous crystalloid solution. In accordance with the Pediatric Advanced Life Support guidelines, hypotension was defined as systolic blood

**Table 1: Study characteristics**

| Characteristic | Propofol (*n*=54) | Control (*n*=54) | *P* |
|---|---|---|---|
| Age (years) | 2.9±1.6 | 2.8±1.5 | 0.95 |
| Gender | | | 1.0 |
|   Male | 37 (68.5) | 37 (68.5) | |
|   Female | 17 (31.5) | 17 (31.5) | |
| Body height (cm) | 94.9±14.9 | 91.3±13.4 | 0.20 |
| Body weight (kg) | 13.8±4.9 | 13.1±5.0 | 0.46 |
| Type of surgery | | | 0.94 |
|   Lower abdominal | 35 (64.8) | 35 (64.8) | |
|   Craniomaxillofacial | 15 (27.8) | 14 (25.9) | |
|   Orthopedic surgery | 3 (5.6) | 4 (7.4) | |
|   Dental | 1 (1.9) | 1 (1.9) | |
| Physical Status | | | 0.61 |
|   ASA 1 | 8 (14.8) | 10 (18.5) | |
|   ASA 2 | 46 (85.2) | 44 (81.5) | |
| Fentanyl (mcg/h) | 19.7±13.6 | 20.9±13.1 | 0.64 |
| Time of last fentanyl administration (min) | 77.5 (15-330) | 67.5 (30-285) | 0.51 |
| Preanesthesia behavior (PAB) score | 2 (1-3) | 2 (1-3) | 0.62 |
| Length of surgery (min) | 147.3±101.5 | 123.1±75.3 | 0.16 |
| Length of anesthesia (min) | 187.3±105.3 | 158.4±79.8 | 0.11 |

*The data is presented as mean±S.D, n (%), or median (IQR)*

pressure <70+ (2 × age in years) mmHg. Ephedrine 0.1 mg/kg was given in cases where fluid resuscitation was not sufficient. In cases of desaturation, airway maneuver of chin lift or jaw thrust was performed and bag-mask-valve ventilation given with oxygen. Desaturation was defined as oxygen saturation less than 92% using standard equipment. Cases of hypotension, desaturation, and postoperative nausea-vomiting were recorded. Patients were monitored in the recovery room for 60 min and discharged to the ward once they obtained an Aldrete score ≥9 and did not have any agitation or vomiting. In the recovery room, all children were accompanied by their guardians. Cases of perioperative emergencies were handled in accordance to set guidelines and algorithms and were dropped out of the study.

Data acquired was then analyzed using the Statistical Package for Social Scientist (SPSS). Analysis of the proportion of EA was done using Chi-square, while the difference of transport time was analyzed using the unpaired *t*-test for normally distributed data and Mann–Whitney for not normally distributed data. Statistical analysis was determined to be significant when $P < 0.05$.

## Results

A total of 108 children were included in this study, with 54 children in each group. The demographic data, duration of surgery and anesthesia, fentanyl use, and preanesthesia behavior score are shown in Table 1.

The incidence of EA was observed to be significantly lower in the propofol group compared to that in the control group (25.9% vs. 51.9%). RR = 0.5, CI 95% = 0.298–0.840, $P = 0.006$.

The average transport time was significantly longer in the propofol group compared to the control group (9.5 ± 3.9 vs. 7.8 ± 3.5 min, mean difference 1.7 min [0.3–3.1]).

Hypotension was found in one case (1.9%) in the propofol group, while none was observed in the control group. Nausea-vomiting was observed more in the control group (14.8%) in comparison to the propofol group (9.3%). There were no observed cases of desaturation in either group. Additional propofol was not administered to any subjects.

## Discussion

Incidence of EA varies greatly between 10% and 80%.[2,3] An earlier study in our institution observed the incidence of EA in children undergoing inhalational anesthesia as 39.7%.[4] We found the incidence of EA of 42 (38.9%) in the control group, which was similar to the previous study. We also observed that the incidence of EA in the propofol group was significantly less in comparison to the control group.

Administration of propofol in the dose of 1 mg/kg at the end of sevoflurane anesthesia to reduce incidence of EA was first reported by Aouad *et al.* in children undergoing strabismus procedure. Children who received propofol had an incidence

of EA of 19.5% compared to 47.2% in the control group.[10] Costi *et al.* reported similar results for children undergoing MRI.[5] Two meta-analyses have shown that administration of propofol in the dose range of 1–3 mg/kg was effective in reducing the incidence and severity of EA in children without affecting recovery time and time of care in the PACU.[2,3] Results from the present study indicate that a lower dose of 0.5 mg/kg of propofol exhibits a similar response in reducing the incidence of EA.

The mechanism of propofol in prevention of EA is still unclear. Sevoflurane is known to have a biphasic effect, which contributes to the clinical appearance of EA. The biphasic effect of sevoflurane potentiates postsynaptic inhibition by $GABA_A$ at high concentrations and blocks the inhibition at lower concentrations.[11] Low concentrations of sevoflurane block inhibition of $GABA_A$, hence causing a dominance in excitation synapses, presenting with agitation during emergence. Propofol given at the end of inhalational anesthesia acts as a sedative during the clearing process of sevoflurane to suppress the excitation synapses to prevent agitation during emergence. Propofol also reduces the hangover effect and provides an antiemetic effect that may be linked to the lower incidence of EA.[5,6,12]

Pain may elicit agitation that presents as EA; however, EA also occurs in painless procedures. Hence, it is thought that pain is not the main cause of EA and administration of opioids for operative analgesic does not guarantee a lower incidence of EA.[13-15] In this study, the incidence of pain varies due to the variety of procedures. Ideally, to reduce bias from pain and type of procedure toward the incidence of EA, the procedure type should have been uniform. However, to translate study results to a wider population and simplify the recruitment process, the authors decided to include a variety of procedure types. In order to reduce possible bias, randomization was done and the use of the PAED scale was performed to objectively differentiate pain from EA.

The difference in surgery and anesthesia time between the two groups is thought to be a source of bias toward the difference in EA incidence. However, studies by Singh *et al.* and Voepel-Lewis *et al.* observed that surgery and anesthesia time does not affect incidence of EA.[16,17] Hence, it is assumed that the difference between surgery and anesthesia time did not affect the incidence of EA between the two groups.

Physiological conditions such as hypoxemia, hypercapnia, sepsis, hypoglycemia, hypotension, elevated intracranial pressure, and electrolyte imbalance are thought to be confounding factors. Through an extensive inclusion and exclusion criteria, the study population is thought to be physiologically normal preoperatively. Significant physiologic changes during anesthesia is an emergency condition and a dropout criterion.

The mean transport time in the propofol group was significantly higher in comparison to the control group. Several studies have shown that although propofol is effective in reducing the incidence of EA, it was related to an increase in time to extubation, time to transport to PACU, and return to consciousness.[2,5-7,10] A study by Makkar *et al.* in children undergoing infraumbilical surgery observed similar results to the ones found in this study.[7] The administration of propofol after inhalational anesthesia is thought to reduce EA through its sedative effect; however, it also prolongs the time needed for emergence.[18,19]

Time to emergence is known to be positively correlated with the duration of anesthesia.[20] In the propofol group, the duration of surgery and anesthesia was observed to be longer than the control group. This prolonged duration may, in fact, contribute to the long transport time observed in the propofol group. There is a lack of the literature in regards to the minimum difference in surgery or anesthesia time that significantly affects time to emergence. A time of emergence above 30 min or known as delayed emergence is known to significantly affect morbidity.[21] Hence, although statistically significant, the 1.7 min time difference observed in this study is thought to be not clinically significant.

There was only one case of hypotension and none of desaturation in the propofol group. This shows that propofol 0.5 mg/kg at the end of inhalation anesthesia does not pose a significant risk factor for postoperative hypotension and desaturation. The results seen in this study are in accordance to a meta-analysis conducted by Van Hoff *et al.* in where there was no significant difference between propofol and control group for cases of desaturation and hypotension.[2] Hypotension and desaturation due to propofol are attributed more to induction dose or patients with hypovolemia and cardiovascular or respiratory compromised.

The incidence of nausea-vomiting was found to be lower in the propofol group in comparison to the control group. Sub-hypnotic propofol doses are known to have an antiemetic event, possibly attributed to propofol's mechanism of action as a dopamine receptor antagonist and serotonin antagonist.[22]

In this study, the efficacy of propofol was based on the incidence of EA and transport time. Propofol 0.5 mg/kg was determined to be effective if it was able to lower the incidence of EA without significantly increasing transport time. This study showed a lower incidence of EA, but a longer transport time.

However, the difference in transport time between the groups was only 1.7 min, providing little to no clinical significance. Hence, propofol 0.5 mg/kg was found clinically effective in reducing the incidence of EA in children undergoing inhalational anesthesia.

One of the limitations faced in this study was the variety of procedure types. A variety of procedure types was a source of bias, affecting the surgery and anesthesia durations, possibly affecting the transport time. As a result of the variety of procedure types, the level of pain was also not fully controlled. Pain is known to be a risk factor for EA. In order to reduce the possible bias from pain, the PAED scale was used to differentiate pain with EA.[13]

## Conclusion

In conclusion, the use of propofol 0.5 mg/kg at the end of general anesthesia reduces the incidence of EA in children after inhalation anesthesia with sevoflurane.

### Acknowledgements

### Financial support and sponsorship

### Conflicts of interest

There are no conflicts of interest.

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