ORIGINAL ARTICLE

Clonidine is Better than Diphenhydramine to Reduce Post-sevoflurane Emergence Agitation and Delirium in Pediatric Patients Undergoing Labioplasty

SATRIO ADI WICAKSONO[1], RIKEN MEDIANA EKA PUTRI[1], HERU DWI JATMIKO[1], SULISTIYATI BAYU UTAMI[2]
[1]Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
Correspondence to Satrio Adi Wicaksono, Email: drsaw11@yahoo.com., Fax . +62 (0) 24-76928010.

ABSTRACT

Background: One of anesthesia techniques in pediatrics undergoing labioplasty is inhalation of anesthetic sevoflurane. Emergence agitation and delirium (EAD) is a common effect of sevoflurane. Several drugs are used to prevent EAD, such as diphenhydramine and clonidine.
Aim: This study was To compare clonidine and diphenhydramine to reduce post-sevoflurane EAD in pediatric patients undergoing labioplasty.
Methods: This was a double blind randomized controlled trial. A total of 50 pediatric patients, age of 9 months – 2 years old, that underwent labioplasty in two hospitals in Semarang, with ASA I-II status, were enrolled in this study. The subjects underwent general anesthetic sevoflurane and randomized into two groups. Group I received diphenhydramine 0.5 mg/kg, while group II received clonidine 2 µg/kg, both at 15 minutes before turning off the sevoflurane. The EAD was examined with PAED scale at pre-anesthesia, 1 minute post-extubation, at recovery of consciousness, and at 15 minutes post-extubation.
Results: PAED scale in clonidine group was significantly lower than in diphenhydramine group at the time the patients started to recover the consciousness (8.2±0.61 vs 8.9±0.68, *p*=0.000) and at 15 minutes post-extubation (8.0±0.58 vs 8.5±0.58, *p*=0.000). There was a lower increase of PAED scale at the recovery of consciousness in clonidine group compared to diphenhydramine group (2.5% vs 11.2%, respectively, *p*=0.000).
Conclusion: Clonidine was better than diphenhydramine to prevent post-sevoflurane EAD in pediatric patients undergoing labioplasty procedure. These findings may have important implications for the early prevention management of EAD in pediatric patients.
Keywords: sevoflurane, emergence agitation and delirium, PAED scale, clonidine, diphenhydramine

INTRODUCTION

Inhalation anesthetics is considered as the pivot of general anesthesia and the ideal method in pediatric patients since it was firstly given to pediatric patients in the mid-19th century[1,2]. Newborns and toddlers can absorb inhalation anesthetics faster than adults because of higher alveolar ventilation levels and blood distribution coefficients to smaller gas for anesthetics agents. The distribution of anesthetic agents is influenced by the loose extracellular space and the differences in membrane permeability, which in pediatrics, the blood brain barrier is immature and allowing anesthesia to penetrate the barrier more readily. This causes induction with inhalation agents more convenient and faster in pediatric patients.[3,4] Anesthetic maintenance is also better provided through inhalation agents than intravenous agents since the metabolic rate in pediatrics is slower, especially in newborns. This may prevent incomplete hepatic metabolism, such as in intravenous agents which may bring residues[1,5].

Sevoflurane is one of several inhalation anesthetics agents used in pediatrics. It is an ideal choice for inhalation induction since it has a rapid induction and recovery, minimal respiratory irritation, and a pleasant smell[6,7]. The depth of anesthesia with sevoflurane is also easily controlled, making it as an ideal pediatric anesthesia. However, in pediatric patients, emergence agitation and delirium (EAD) events are higher with sevoflurane compared with halothane due to the rapid recovery of sevoflurane[7,8].

Emergence agitation and delirium (EAD) are significant problems at the recovery of conciousness after general anesthesia that are common in pediatrics who receive anesthesia with desflurane and sevoflurane. Post anesthetic EAD can be defined as a dissociated state of consciousness characterized by abnormal perception to the surroundings with symptoms of disorientation, irritable, uncompromise, uncooperative, incoherence, hypersensitivity to stimuli, and hyperactive motor behaviour such as fighting back, kicking, and thrashing as the patients wake up from general anesthesia[8,9].

The incidence and aetiology of EAD remains unclear. Pain seems to be a promoting factor since administration of analgesic agents reduce its incidence. Its occurrence during the recovering of consciousness in pediatrics is an acute phenomenon that can subside itself within 5–15 minutes. But it can deteriorate if it is not treated immediately[10,11]. Several risks of complications may include bleeding risk, falling risk, trauma risk, greater drug use and longer hospital stay at Post Anesthesia Care Unit (PACU). Other more severe complications may include removal of venous access, drain, catheter, and other monitoring devices[9].

Several instruments and therapies for post-sevoflurane EAD in pediatrics have been studied. The Pediatric Anesthesia Emergence Delirium (PAED) scale is recognized standard for the diagnosis of EAD. The PAED scale are using five criterias, including eye contact, purposeful action or movement, awareness of surroundings, restless, and inconsolability[12,13]. It is valid

and reliable in assessing the severity of post-anesthetic agitation and delirium. A score of ≥10 displays 64% sensitivity and 86% specificity and a score of >12 yields 100% sensitivity and 94.5% specificity for the diagnosis of EAD[13].

Prophylaxis with midazolam, fentanyl, clonidine, ketamine, propofol, nalbuphine, or dexmedetomidine have been shown to decrease the incidence of post-anesthetic agitation and delirium[8,9,11,14,15]. Diphenhydramine is a first-generation antihistamine used to treat several conditions including allergic symptoms, itching, colds, insomnia, motion sickness, and extrapyramidal symptoms. It can easily penetrate the blood brain barrier and work on the receptors on the central nervous system. As with other first-generation antihistamines, diphenhydramine is a non-selective H-1 agonist, which means that in addition to work on H-1 receptors, it can also interact with other receptors. Its effect on H-1 receptors in the central nervous system is drowsiness, but without respiratory depression. Diphenhydramine also interacts with opioid receptors, thereby having an analgesic potensiazing effect. The effect of diphenhydramine on ion-channel sodium voltage is also similar to that is produced by local anesthesia[16,17].

Clonidine, an imidazoline derivate, is an alpha-2 adrenergic agonist that works as an anti-hypertensive drug by decreasing the sympathetic response of the central nervous system (CNS)[18-20]. Its other effects include sedation effects, analgesia, anti-anxiety, decreased need for anesthetic drugs, maintaining perioperative hemodynamic stability and sympathetic stability[15,21,22].

Diphenhydramine and clonidine are currently an alternative medicine for the treatment of acute delirium and agitation in pediatrics in the intensive care unit.[21] However, there was a lack of study investigating the comparison between these drugs in the prevention of delirium and agitation at the recovery of consciousness state post-anesthesia.

MATERIAL AND METHOD

Study Design and Population: This study was a randomized double blind controlled trial conducted to compare clonidine and diphenhydramine administered prior to extubation to the incidence of agitation at the recovery of consciousness state after general anesthesia in pediatric patients who underwent surgical procedures under general anesthesia with sevoflurane inhalation gas.

The study subjects comprised 50 pediatric patients who underwent labioplasty in two hospitals in Semarang, Indonesia. Subjects were determined by consecutive sampling method that met the inclusion criteria. The inclusion criterias included pediatric patients undergoing elective labioplasty with physical ASA I-II status, no other major congenital abnormality, no cardiovascular disorders, age of 9 months – 2 years old, and no contraindications to the use of sevoflurane, diphenhydramine, clonidine, ketamine and bupivacaine. The exclusion criterias were other congenital abnormalities known during postoperative, bleeding more than 15% estimated blood volume (EBV), shock or major anesthetic or surgical complications during surgery (hypoxia, atelectasis, revoked endotracheal tube (ETT) or infusion line, etc.). Yet in this study, no research subjects were excluded.

Subjects were randomly divided into two groups. Group I received slow bolus intravenous injection of diphenhydramine 0.5 mg/kg body weight (n=25), and group II received clonidine 2 µg/kg body weight (n=25). Both drugs were administered 15 minutes prior to the end of anaesthesia or before the inhalation agent was switched off.

Clinical and Laboratory Measurements: Study data included medical history, physical and anthropometric examination to elaborate the physical status and other congenital abnormalities, laboratory measurements, and information provided by a self-administered questionnaire from patients' parents or relatives. The medical and drug prescription histories were assessed by the examining physicians.

Participants who have been fulfilled the inclusion criteria underwent a routine blood sampling as a pre-surgical protocol from an antecubital vein. The serum glucose was measured using the hexokinase method. Serum creatinine were determined using the Jaffe reaction method (Advia 1650 kit, Bayer Corp, PA, USA).

Perioperative and Anesthetic Procedure: The systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were simultaneously recorded by automated non-invasive hemodynamic and blood pressure monitoring (IntelliVue MX500, Philips, Germany). Electrocardiography (ECG) electrodes and pulse oxymeter probes were applied in monitoring the ECG and peripheral oxygen saturation of the patients during the study, respectively. At baseline (B), at 1 minute post extubation (T1), at the time of conciousness recovery (T2), and at 15 minutes post extubation (T3), all hemodynamic data were recorded. To prevent hypothermia in pediatric patients, the room temperature was set at more than 25^{o}C. The electrical heater and thick blankets were used if it was not adequate to maintain the room temperature.

Induction of anesthesia was performed by sevoflurane inhalation with one breath technique. After the patient relaxed, ETT was intubated without muscle paralytic agents. Inhaled sevoflurane of 2% concentration and oxygen were used to maintain the anesthesia. Oxygen saturation was maintained between 95%–100%. Infraorbita block with 0.125% bupivacaine was performed immediately after intubation.

By the time the surgery was complete, diphenhydramine or clonidine injection was given according to the subject group. Sevoflurane was turned off 15 minutes later, and extubation was made. Extubation was performed after the patient was conscious, adequate respiratory protective reflex, and adequate spontaneous breathing. Immediately after extubation, the patient was positioned in a steady oblique position and given a 6–8 L/minute oxygen mask.

Measurements : At baseline (B), at 1 minute post extubation (T1), at the time to regain conciousness (T2), and at 15 minutes post extubation (T3), the patient was assessed for the PAED scale. The PAED scale consisted of five listed behaviours, including eye contact, purposeful action or movement, awareness of surroundings, restless, and inconsolability. Each of item was scored 0–4 point. The maximum score of all five items was 20. [13] If the PAED

scale was ≤10, the patient would be transferred to the post-anaesthesia care unit (PACU) or recovery room (RR). However, if PAED scale was >10, the patient received slow bolus intravenous injection of ketamine 0.1 mg/kg body weight as a rescue. In the PACU, all patients received 6 L/minute or 3 L/minute oxygen depend on their clinical status. The PAED scale was examined again at 15 minutes post extubation and at the time when the patient achieved Steward score of >5 without a score of 0.

Steward score was measured to assess the feasibility of post-general anesthesia for pediatric patients to return to the ward. It consisted of 3 items, including consciousness (awake, responding to stimuli, not responding), respiration or airway (coughing or crying, maintaining good airway, airway requires maintenance), and motoric or movement (moving limbs purposefully, non-purposeful movements, not moving). Each item was scored 0–2. The maximum score of all three items was 6[23]. Steward score was measured at the time entering the PACU and repeated every 5 – 10 minutes. All measurements of PAED scale and Steward score were done by trained anesthesiologist due to protocol and blinded to the patients' status and drugs administered.

Statistical Analysis: The demographic data, PAED scales, the duration to achieve Steward score of >8 without value 0, and the amount of tranquilizers rescue were recorded. The duration of surgery and the duration of anesthesia were also recorded. Data were presented as mean±standard deviation (mean±SD); median (minimum-maximum) for continuous variables and as proportions (n, %) for categorical variables. Categorical variables were presented as frequency distribution tables. The chi-square test was used to determine the differences in proportions for categorical variables. The continuous independent variables were compared using independent *t*-test, if normally distributed, or non-parametric Mann-Whitney test, if not normally distributed. Statistically significance was considered as $p<0.05$. All statistical analyses were performed using statistical computing program.

Ethical consideration

Ethics approval for the study protocol and analysis of the data was obtained from the Ethics Committee of Health and Medical Research (KEPK) Faculty of Medicine, Diponegoro University / Dr. Kariadi General Hospital Semarang, Indonesia. All parents or family of subjects had been given explanation of the purpose, benefits, research protocols, possible side effects, and a written informed consent.

RESULTS

Characteristics of the Study Population: Clinical and demographic characteristics of the study population are presented in Table 1. A total of 50 labioplasty patients consisted of 24 (48.0%) male and 26 (52.0%) female, and it was no difference in gender distributions between diphenhydramine group and clonidine group ($p=0.571$). Overall, the mean age was 13.3±3.74 months old. There was no difference in the mean age between diphenhydramine group and clonidine group (13.3±4.09 months vs 13.3±3.40 months old, respectively, $p=0.970$). The mean body weight in overal population was 9968±2389 grams, and there was no difference in mean body weight between diphenhydramine group and clonidine group (

9952±2431 grams vs 9984±2348 grams, $p=0.962$). The overall mean body mass index (BMI) was 17.4±0.73 kg/m2, and there was no difference in mean BMI between diphenhydramine group and clonidine group (17.4±0.54 vs 17.5±0.88, respectively, $p=0.066$) (Table 1).

The mean score of PAED scale at baseline (pre-anesthesia) was 8.9±0.68. At baseline (pre-anesthesia), there were no differences in PAED scale between diphendyramine group and clonidine group (9.0±0.76 vs 8.96±0.61, respectively, $p=0.847$) (Table 1). Meanwhile, the mean duration of surgery and the mean duration of anesthesia were 19.7±4.13 minutes and 26.4±2.96 minutes, respectively. There was no difference between diphendyramine group and clonidine group, on the duration of surgery (19.8±3.95 minutes vs 19.6±4.31 minutes, respectively, $p=0.810$) and the duration of anesthesia (26.5±2.91 minutes vs 26.4±3.01 minutes respectively, $p=0.851$).

Pediatric Agitation and Emergency Delirium (PAED) Scale

The mean PAED scale between the two groups at baseline (pre-anesthesia), at 1 minute post-extubation, at recovery of consciousness, and at 15 minutes post-extubation are presented on table 2 and figure 1. In all study subjects, the PAED scale at baseline and at 1 minute post-extubation were 8.9±0.68 and 8.0±0.64, respectively. There were no statistically differences in mean PAED scale between diphenhydramine group and clonidine group at baseline (pre-anesthesia) (9.0±0.76 versus 8.9±0.61, respectively, $p=0.847$) and at 1 minute post-extubation (8.0±0.70 versus 8.0±0.58, respectively, $p=0.642$). No subjects experienced agitation up to 1 minute post-extubation (Table 2, Figure 1).

In all study subjects, the PAED scale at the time of recovering consciousness and at 15 minutes post-extubation were 8.5±0.64 and 8.2±0.69. The mean PAED scale in diphenhydramine group was significantly higher than in clonidine group at the time the patients started to recover the consciousness (8.9±0.68 vs 8.2±0.61, $p=0.000$, respectively) and at 15 minutes post-extubation (8.5±0.58 vs 8.0±0.58, $p=0.002$, respectively). The study showed that there was a lower increase of PAED scale at the recovery of consciousness (ΔT2-T1) in clonidine group compared to in diphenhydramine group (2.5% vs 11.2%, respectively, $p=0.004$). There was also a decreased PAED scale at 15 minute post-extubation compared to at the recovery of consciousness (ΔT3-T2) both in diphenhydramine and clonidine group (4.5% vs 2.5% decrease, respectively, $p=0.049$) (Table 2, Figure 1).

The diphenhydramine group was significantly longer than clonidine group in the duration needed to recover consciousness (14.2±3.12 vs11.72±2.21, $p=0.007$, respectively) (Table 3). There were no significant differences between diphenhydramine group and clonidine group in the intial Steward score measured in PACU (5.2±0.50 vs 5.1±0.33, $p=0.459$) and in the last Steward score measured in PACU before returning to the ward (5.3±0.48 vs 5.2±0.44, $p=0.533$), respectively (Table 3).

All study subjects who showed a PAED scale of >10 at the time they started to recover their consciousness, were administered with rescue tranquilizer. In overal, there were four subjects who experienced agitation and needed rescue tranquilizer, i.e. three subjects (12%) from diphenhydramine group and one subject (4%) from clonidin group (p = 0.609). There was no difference in the average amount of rescue tranquilizer required between diphenhydramine group and clonidine group (0.16±0.47 µg/kg body weight and 0.04±0.2 µg/kg body weight, p=0.293). The effective dose of rescue tranquillizer ketamin ranged from 0.1 to 0.2 mg/kg body weight. Although it might calm the agitation, but it required prolonged supervision in the PACU due to delayed of the fully awake state in pediatric patients.

There was no significant difference in the duration in acheiving the Steward score >5 (without score 0) and with the PAED scale <10 between diphenhydramine group and clonidine group (15.0 ± 2.89 vs 13.6±3.07, p=0.098). No side-effects of the drugs used in this study were observed during the study

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Table 1. Characteristics of Study Subjects

Parameter	Group		Total (n=50)	*P*
	Diphenhydramine(n=25)	Clonidine (n=25)		
Gender (Male : Female)	11 : 14	13 : 12	24 : 26	0.571*
Age (months)	13.3 ± 4.09	13.3 ± 3.40	13.3 ± 3.74	0.970**
Body Weight (g)	9952 ± 2431	9984 ± 2348	9968 ± 2389	0.962**
Height (cm)	75.3 ± 0.70; 75 (74 – 76)	75.4±0.71; 76 (74 – 76)	75.4 ± 0.69; 75.5 (74 – 76)	0.814***
Body Mass Index (BMI) (kg/m^2)	17.4±0.54; 17.4(15.7–18.2)	17.5±0.88; 17.7 (15.1 – 18.9)	17.4±0.73; 17.6 (15.1– 8.9)	0.066***
Systolic BP (mmHg)	87.1±3.27; 86(85–100)	88.3±3.16; 88.0 (85.0 – 100.0)	87.7 ± 3.24; 87.0 (85 –100)	0.050***
Diastolic BP (mmHg)	60.0 ± 3.59; 60(50 – 65.0)	61.3 ± 3.80; 60.0 (50.0 – 69.0)	60.6 ± 3.73; 60 (50– 69)	0.194***
Mean Arterial Pressure (mmHg)	68.7 ± 2.58; 69(62 –73.0)	70.1 ± 3.15; 70.0 (63.0 – 79.0)	69.4 ± 2.93; 69 (62– 79.0)	0.096***
Heart Rate (beats/min)	75.0 ± 8.11; 75 (60–85.0)	77.5 ± 6.88; 80.0 (60.0 – 86.0)	76.2 ± 7.55; 79 (60 – 86.0)	0.276***
Hemoglobin (g/dL)	12.6±1.29; 12.7 (11–14.6)	12.9 ± 1.21; 13.0 (11.0 – 14.9)	12.7 ± 1.24; 2.9 (11 – 14.9)	0.435***
Leukocyte (10^3/µL)	7.5 ± 1.03; 7.1(6.0 – 9.8)	7.4 ± 0.82; 7.2 (6.0 – 9.0)	7.4 ± 0.92; 7.1 (6.0 – 9.8)	0.808***
Platelet (10^3/µL)	268.5±48.64; 267(202–425)	273.8 ± 58.59; 263.0 (213– 435)	271.2±53.36; 265(202–435)	0.892***
Random blood glucose (mg/dL)	129.3±17.29; 126(101–173)	127.8 ± 16.29; 129(104– 79)	128.5±16.64; 129(101–179)	0.930***
Ureum (mg/dL)	25.4 ± 8.32; 24.0 (11 –39)	26.8 ± 7.40; 26.0 (12.0 – 39.0)	26.1±7.83; 24.5 (11.0 – 39)	0.424***
Creatinine (mg/dL)	0.5 ± 0.13; 0.5 (0.4 – 0.8)	0.6 ± 0.11; 0.6 (0.4–0.9)	0.5 ± 0.12; 0.6 (0.4–0.9)	0.083***
Pre-anesthesia PAED scale	9 ± 0.76	8.9 ± 0.61	8.9 ± 0.68	0.847***
Surgery Duration (min)	19.8 ± 3.95	19.6 ± 4.31	19.7 ± 4.13	0.810***
Anesthesia Duration(min)	26.5 ± 2.91	26.4 ± 3.01	26.4 ± 2.96	0.851***

Significant if p< 0.05. Presented as mean ± SD; median (min – max).
*Chi-square test; **Independent *t*-test; ***Mann-Whitney test.

Table 2: Pediatric Agitation and Emergency Delirium (PAED) Scale

PAED Scale	Group		Total (n=50)	*P*
	Diphenhydramine (n=25)	Clonidine (n=25)		
Baseline (Pre-anesthesia) (B)	9.0 ± 0.76	8.9 ± 0.61	8.9 ± 0.68	0.847*
At 1 minute Post-extubation (T1)	8.0 ± 0.70	8.0 ± 0.58	8.0 ± 0.64	0.642*
At Recovery of Conciesness (T2)	8.9 ± 0.68	8.2 ± 0.61	8.5 ± 0.64	0.000*
At 15 minutes Post-extubation (T3)	8.5 ± 0.58	8.0 ± 0.58	8.2 ± 0.69	0.002*
ΔT2 – T1	0.9 ± 0.02 (11.2%)	0.2 ± 0.03 (2.5%)		0.004*
ΔT3 – T2	0.4 ± 0.10 (4.5%)	0.2 ± 0.03 (2.5%)		0.049*

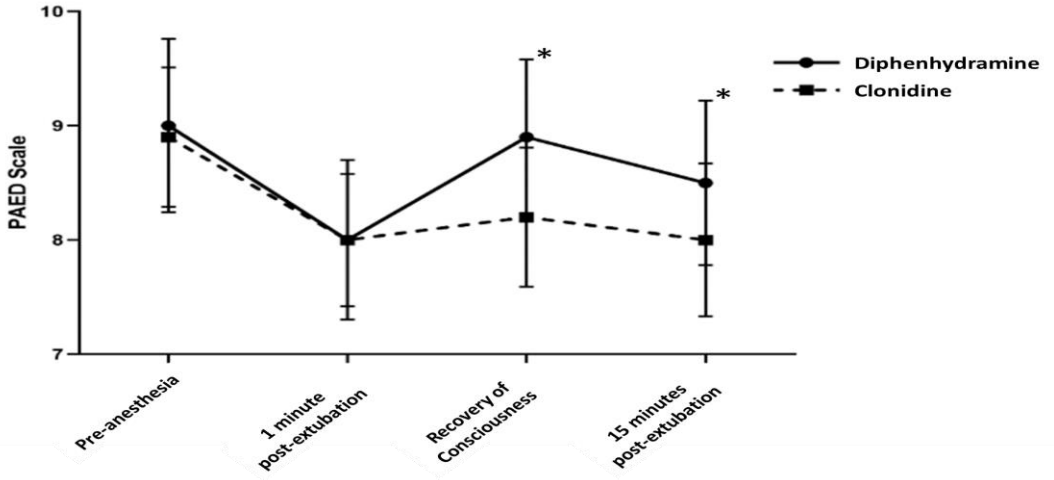
Significant if p< 0.05 between diphenhydramine group and clonidine group. Presented as mean ± SD; median (min – max). *Non-parametric Mann-Whitney test.

Table 3. Comparison between Diphenhydramine and Clonidine on the Recovery of Consciousness and Emergence Agitation and Delirium (EAD) events in pediatric patients

Parameter	Group		*P*
	Diphenhydramine (n=25)	Clonidine(n=25)	
Initial Steward Score	5.2 ± 0.50	5.1 ± 0.33	0.459**
Steward score when returning to the ward	5.3 ± 0.48	5.2 ± 0.44	0.533**
Duration for recovering consciousness (minutes)	14.2 ± 3.12	11.7 ± 2.21	0.007**
Agitation events after recovering of consciousness	3 (12%)	1 (4%)	0.609*
Amount of rescue tranquilizer given (µg/kg body weight)	0.16 ± 0.47	0.04 ± 0.2	0.293**
Duration to achieve Steward Score >5 without 0 and PAED scale <10 (minute)	15.0 ± 2.89	13.6 ± 3.07	0.098**

Significant if p< 0.05 between diphenhydramine group and clonidine group.
*Chi-square test; **Non-parametric Mann-Whitney test.

Figure 1. Pediatric Agitation and Emergency Delirium (PAED) Scale between diphenhydramine groups and clonidine group. *significant if $p < 0.05$ at each timeline.



DISCUSSION

Labioplasty is one of the most common surgical procedure performed on pediatric patients. As other labioplasty, the study surgical procedures were also performed within short duration and required general anesthesia. The mean duration of surgery was less than 20 minutes, i.e. 19.7±4.13 minutes, while the mean duration of anesthesia was less than 30 minutes, i.e. 26.4±2.96 minutes. Anesthetic procedure in labioplasty is generally performed with inhalation induction, ETT intubation, and maintenance with inhaled anesthetic agents with or without N_2O. One of the most common inhaled anesthetic agents used in labioplasty surgery is sevoflurane, as we used in this study. This inhaled anesthetic is safe in the induction and in the maintenance since this drug is rapid onset and not causing airway irritation.

Our study showed increased PAED scale both in diphenhydramine group (11.2% increase) and in clonidine group (2.5% increase) at the recovery of consciousness compared to at 1 minute post-extubation. It represented that even though adequate management of analgesia have been administered, there were still some increase in PAED scale in post-sevoflurane pediatric patients, although not all of them were catagorized as EAD yet. In line to our study, several studies showed incidence of post-sevoflurane EAD in patients who did not receive any premedication before or during anesthesia, although adequate analgesia has been given to them.[14,24] Meta-analysis revealed that sevoflurane might lead to agitation in pediatrics[24,25].

Study from Dalens *et al*[14] showed that the incidence of post-anesthetic agitation with sevoflurane on painless anesthetic procedure was around 23%. This study also revealed that the amount of agitation events at the recovery of consciousness were 3(12%) patients in diphenhydramine group and 1(4%) patient in clonidine group. However, this study showed lower incidence of EAD in both diphenhydramine and clonidine groups compared to the study from Dalens *et al*[14]. This might represent that both diphenhydramine and clonidine were effective in reducing the incidence of EAD after general anesthesia in pediatric patients.

Although both diphenhydramine and clonidine were effective in reducing the incidence of EAD in our study, clonidine seemed to give better result in preventing EAD in post-sevoflurane pediatric patients. The result showed that there was a lower increase of PAED scale at the recovery of consciousness in clonidine group compared to in diphenhydramine group (2.5% increase vs 11.2% increase, respectively). Both at the recovery of conscioussness and at 15 minutes post-extubation, the mean PAED scale observed in the clonidine group was lower than in the diphenhydramine group.

The mechanism and the prevention method of post-sevoflurane anesthetic agitation remain unclear. The mechanism of post-sevoflurane anesthetic agitation has been thought to be similar to the agitation in stage 2 anesthesia in ether anesthetic, and could be overcome by increasing inhibitory neurotransmitter activity, especially from GABA receptors. It was hypothesized that after the cessation of sevoflurane in pediatric patients, the concentration of sevoflurane in blood decreased rapidly, but it was not accompanied by its clearance from the airway and alveoli and so caused the low concentration residue of sevoflurane agents that decreased the receptor-mediated inhibition by GABA-A. It then led to agitation and delirium although the patients were not painful. Not all drugs that could prevent or overcome post-sevoflurane anesthetic agitation would work on GABA receptors, but they could work by increasing the neuroinhibitory activity. Propofol, midazolam, fentanyl, α2-agonists such as clonidine and dexmedetomidine, diphenhydramine, and ketamine have been shown to be effective in reducing the incidence of agitation[26].

The results showed several advantages of clonidine compared to diphenhydramine, such as clonidine gave a significantly faster duration needed to recover the consciousness than diphenhydramine, clonidine had lower amount of rescue tranquilizer used compared than diphenhydramine, and clonidine had a faster duration to achieve Stewart score of more than 5 (without value of 0) in which the PAEDS score was less than 10 compared to diphenhydramine.

Children who experienced agitation should not be transferred to the ward and should be reassessed immediately, as it might cause harm to the children and those surround them. In the study, if subjects experienced EAD during the recovery of consciousness, they will be administered with tranquilizer rescue of ketamine 0.1mg/kg. Those given tranquilizer rescue would show a decrease in Steward score, so they were not yet allowed to be transferred to the ward. They should be re-monitored in the PACU until the Steward score was greater than 5 without a score of 0 and the PAED scale was less than 10.

Diphenhydramine is a potent antihistamine but can penetrate the blood brain barrier and has mild sedative side effects. Sedative effects caused by diphenhydramine at usual dose do not cause respiratory depression or decrease respiratory protective reflexes. Diphenhydramine is often used in premedication to prevent allergies to drugs used during general anesthesia. The ability of these drugs to decrease the incidence of agitation is suspected due to the sedation and anxiolytic effects[16,17,27].

Clonidine is an alpha-2 adrenergic agonist that can penetrate central nervous system and provide analgesia effects through local neuroaxial and supraspinal. The sedation effect produced by clonidine will decrease sympathetic nervous activity and the degree of consciousness, so patients are more cooperative and easier to be awakened. This is an inhibitory reflex of the pontine nucleus locus ceruleus. This nuclues is associated with regulation between sleep and awake. This nucleus is inhibited by alpha-2 adrenergic agonists through a mechanism mediated by G-proteins that would inhibit adenylate cyclase. While drugs that work on GABA receptor inhibitors will create a misty awareness and paradoxical agitation[11,15,20].

Clonidine acts on the α_2 adrenergic receptor. There are 3 subtypes of the adrenergic α_2 receptor in humans; α_2A, α_2B and α_2C, each scatters everywhere with different functions. The α_2A receptors spread mainly in the periphery, mediate sedation, analgesia and sympathy. While α_2B receptors mediate vasoconstriction and anti-shivering and α_2C in the brain and spinal cord. The α_2 postsinaps receptor in peripheral blood vessels causes vasoconstriction, whereas in the presinaps it inhibits the release of norepinephrine which is the agent that causes vasoconstriction. The stimulation of α_2 receptors in the central nervous system will lead to sympatholytics, sedation, and anti-nociception[11,20,28,29].

Nonetheless, several limitations should be considered. First, this research only studied pediatric patients with stable non-complicated surgical condition, we were not able to generalize this results to patients in more severe clinical condition. Second, the real mechanism of how clonidine could prevent EAD could not be fully explained yet from our study.

CONCLUSION

In conclusion, our study was the first study that provided evidence for a positive effect of clonidine administration over diphenhydramine in preventing EAD events and preventing the increased PAED scale after general anesthetic sevoflurane in pediatric patients undergoing labioplasty surgery that may partly work on central nervous system that lead to sympatholytics, sedation, and anti-nociception. These findings may have important implications for the early prevention management of EAD in pediatric patients. The underlying mechanisms of clonidine decrease EAD events, not yet fully understood, remain to be clarified.

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