

**Study Protocol and Statistical Analysis Plan for Research Project:**

“Emergence Agitation in Pediatrics after Dexmedetomidine vs.  
Sevoflurane Anesthesia: a randomized controlled trial”

Clinicaltrials.gov # NCT06482125

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## **1. ABSTRACT**

### **BACKGROUND**

Emergence Agitation (EA) is a common occurrence in pediatric anesthesia. (1) The incidence has been reported to vary from 10% to as high as 80% after being exposed to inhalation anesthesia, particularly Sevoflurane. Maladaptive behaviors such as kicking, screaming, and thrashing are seen during agitation and contributes to postoperative complications such as tongue edema, re-bleeding of surgical wounds, falling out of bed, accidental removal of the intravenous line, bronchospasm and wound dehiscence. Anesthesia using Sevoflurane remain the main choice for cleft lip and cleft palate (CP) surgeries in children at the current moment. (1-3) As a result, majority of these children experience intense agitation after recovering from anesthesia.

### **OBJECTIVES**

We propose a randomized controlled trial comparing emergence agitation in patients receiving Sevoflurane inhalation versus intravenous Dexmedetomidine infusion.

#### **Primary Hypotheses:**

The use of intravenous Dexmedetomidine reduces emergence agitation to children after anesthesia.

### **METHODS**

All children enrolled to undergo an elective cleft lip or palate surgery at Pelita Harapan University and Siloam Hospital Lippo Village who fulfill the inclusion criteria will be selected.

## **2. SPECIFIC AIMS**

Aim #1. To measure and compare emergence agitation between Sevoflurane and Dexmedetomidine group.

Aim #2. To measure and compare time to extubation between Sevoflurane and Dexmedetomidine group.

Aim #3: To measure and compare time to full recovery between Sevoflurane and Dexmedetomidine group.

Aim #4: Report any adverse events or side effects in both groups.

## **3. STUDY DESIGN**

- A randomized controlled trial, single-blinded.
- Allocation: Simple Randomized (1:1) Patients are selected randomly using a computer-generated device to become a control arm (Sevoflurane) or treatment arm (Dexmedetomidine)

- Number of Arms: 2 (Sevoflurane vs. Dexmedetomidine)
- Masking: Single (Participant)

#### **4. STUDY POPULATION**

Children ages 3 months to 120 months (10 years) scheduled for an elective cleft lip or palate surgery in Pelita Harapan University and Siloam Hospital Village, Tangerang, Indonesia.

#### **5. ELIGIBILITY TO PARTICIPATE ON THE STUDY**

Minimum Age: 3 months

Maximum Age: 10 years

Sex: All

Gender Based: No

Accepts Healthy Volunteers: Yes

Criteria:

Inclusion Criteria:

- Patients with weight ranging 5 kg - 25 kg
- Patients with American Society of Anesthesiologist (ASA) Physical Status Classification 1 and 2

Exclusion Criteria:

- Patients with any acquired congenital syndrome
- Patients who are actively taking anti-seizure medications and/or has been diagnosed with epilepsy
- Patients with functional and structural abnormalities of the heart, including arrhythmias
- Patients with liver disease

#### **6. RECRUITMENT**

All children admitted to undergo an elective cleft lip or palate surgery between July 31, 2024 up to December 1, 2024.

#### **7. DATA COLLECTION AND MEASURES**

Data will be measured and collected starting July 31, 2024 up to December 1, 2024.

#### **8. QUALITY ASSURANCE AND QUALITY CONTROL**

Preoperative assessment and randomization of group type was performed one day before the operation.

#### **9. RANDOMIZATION AND MASKING**

A computer-generated random array sealed and envelope

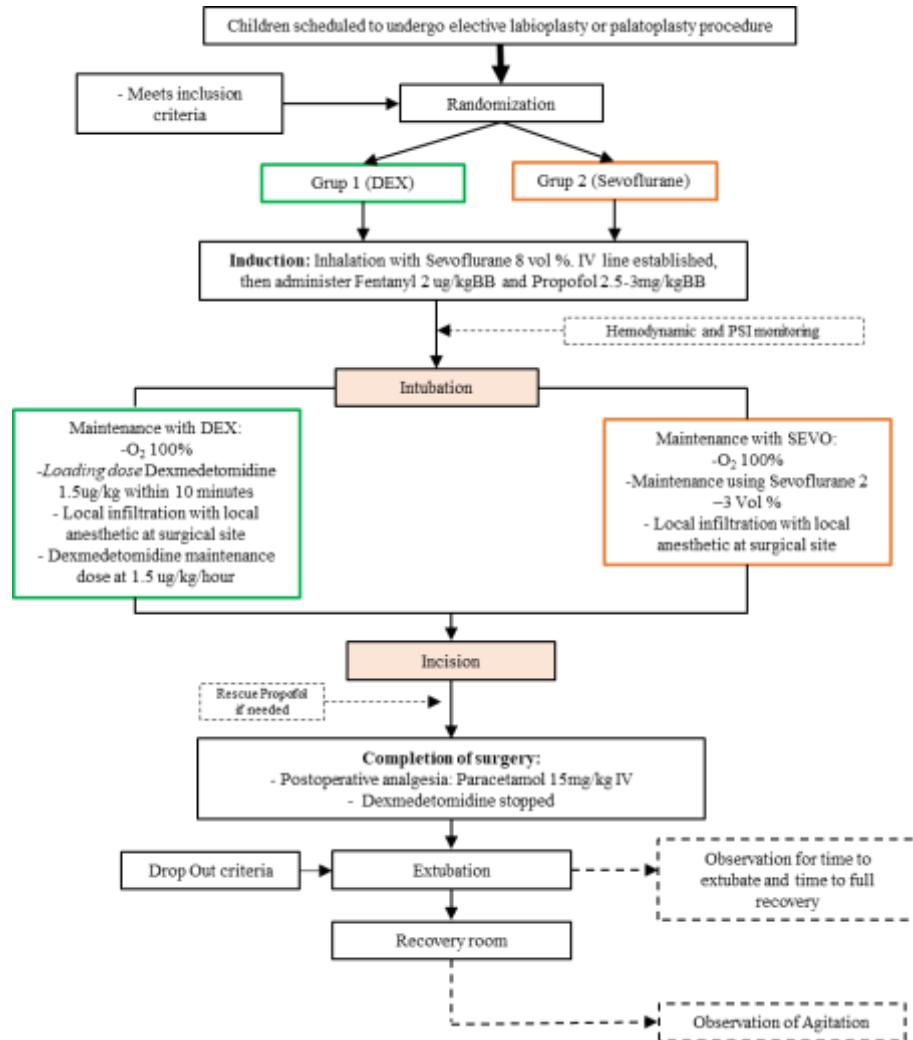
method was employed to divide enrolled pediatric patients into two groups by simple randomization (1:1 ratio allocation). Experimental medication was prepared and provided by research staff who were not directly involved in patient care, while the surgeon, anesthesiologist and participating families were blinded to the medication distribution and group allocation.

On the day of surgery, the anesthesiologist responsible of the case was informed on each child's allocation and gave medications according to their designated groups. Agitation scale upon awakening and extubation time were recorded by a nurse anesthetist inside the operating room; while agitation monitoring every fifteen minutes were carried out by a different nurse in the recovery room without prior knowledge of the child's group allocation.

## **10. INTERVENTIONS**

Anesthesia was administered using inhalation of 8% Sevoflurane in 100% oxygen until an intravenous line was secured. All patients were given Fentanyl 2 micrograms/kg, Propofol 3mg/kg and an oral endotracheal intubation of appropriate size was secured. After intubation, patients in Group DEX stopped receiving Sevoflurane. Dexmedetomidine infusion using an intravenous line was started at a loading dose of 1.5ug/kg for 10 minutes, followed by a maintenance dose of 1.5ug/kg/hour via a syringe pump while patients in Group SEVO continued receiving Sevoflurane at a concentration of 2-3 vol%.

All patients maintained spontaneous ventilation throughout the intraoperative period. Analgesia was supplemented with local anesthetic infiltration at the surgical site and intravenous Paracetamol 15mg/kg given 10 minutes before the end of surgical procedure. At the end of surgery, Dexmedetomidine infusion was stopped in group DEX and Sevoflurane inhalation was stopped in group SEVO: every one of them was extubated and moved to the post-anesthesia care unit for postoperative monitoring.



**Fig 1.** Flowchart of patient selection and grouping

## 11. SAFETY MONITORING

- Potential risks : bradycardia, hypotension, hypertension
- Alert values: Patients are continually monitored using standard monitoring which includes an electrocardiograph (ECG), non-invasive blood pressure and peripheral oxygen saturation (SpO2) which were recorded starting from induction and every 5 min, thereafter. Monitoring of anesthetic depth was ensured using SEDLine™ monitor, Masimo Corporation, Irvine, CA, USA to measure processed electroencephalograph or Patient State Index (PSI). Throughout the procedure, all patients retained their spontaneous respiration while maintaining their PSI value between 25-50.
- Reporting Procedures: written on a paper during research.

Preoperative anxiety status will be assessed by an anesthesiologist, the day before surgery. Time to extubation and agitation scale upon awakening will be recorded by the nurse anesthetist assisting the anesthesiologist on the day of operation. After transferring the child to the recovery room, another nurse will assess their agitation scale every 15 minutes using Cravero agitation scale. All these values are inputted on a computer after completion of anesthesia procedure, at the end of the day by a research staff who is not involved in patient care.

## **12. STATISTICAL POWER AND SAMPLE SIZE ESTIMATION**

This study compares the incidence of agitation between the Sevoflurane group and the Dexmedetomidine group. This study is a categorical data, so the sample formula uses the formula:

$$n_1 = n_2 = \left( \frac{Z\alpha\sqrt{2PQ} + Z\beta\sqrt{P_1Q_1 + P_2Q_2}}{P_1 - P_2} \right)^2$$

Dexmedetomidine (p1) versus Sevoflurane (p2) anesthesia were analyzed with p1 being 10% and p2 being 40% with a power of 0.8 and alpha of 0.05. The power analysis study yielded sample size of 35 patients in each group. Considering 20% dropout case, we needed 42 cases per group and a total of 84 cases. Results were expressed as range (median), mean  $\pm$  standard deviation, or number (%).

## **13. ANALYSIS PLAN**

Missing and Incomplete data will be reported, if there are any.

## **14. DATA MANAGEMENT**

Data confidentiality is ensured as all data are secured and locked in our institution. Access is only granted to the researchers involved.

## **15. TRIAL ADMINISTRATION - HOW INVESTIGATORS/STAFF WILL BE ORGANIZED**

- The surgeon, anesthesiologist and participating families were blinded to the medication distribution and group allocation.
- After preoperative assessment and patient met the inclusion criteria, patients or the patient's family chose an envelope with a number inside it. The selected number later specified whether the patient was a control group or a treatment group, as randomized by the computer with 1:1 ratio allocation.

- Experimental medication was prepared and provided by research staff who were not directly involved in patient care for use the following day that surgery took place. On the day of operation, the anaesthesiologist responsible in anesthetizing the child will be informed of the child's group allocation in order to provide the appropriate medication according to their designated groups. The surgeon and recovery room nurse were not informed of the child's group allocation.

#### **16. TIMELINE**

- Research data gathering will be performed starting July 31, 2024 up to December 31, 2024.
- Data processing will start from January 1, 2025 to February 28, 2025.
- Research writing is expected to be completed at July 1, 2025.

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**Appendix 1. Modified Yale Preoperative Anxiety Scale (mYPAS) <sup>1</sup>**

Behavior	SCORE					
	1	2	3	4	5	6
<b>Activity</b>	Looking around, curious, playing with toys, reading (or other age-appropriate behavior); moves around holding area/treatment room to get toys or go to parent; may move toward OR equipment.	Not exploring or playing, may look down, may fidget with hands or suck thumb (blanket); may sit close to parent while waiting, or play has a definite manic quality.	Moving from toy to parent in unfocused manner, nonactivity-derived movements; frenetic/frenzied movement or play; squirming, moving on table, may push mask away, or clinging to parent.	Actively trying to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or will not separate from parent, desperate clinging.		
<b>Vocalization</b>	Reading (nonvocalizing appropriate to activity), asking questions, making comments, babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond.	Responding to adults but whispers, "baby talk," only head nodding.	Quiet, no sounds or responses to adults.	Whimpering, moaning, groaning, silently crying.	Crying or may be screaming "no."	Crying, screaming loudly, sustained (audible through mask)
<b>Emotional Expressivity</b>	Manifestly happy, smiling, or concentrating on play.	Neutral, no visible expression on face.	Worried (sad) to frightened, sad, worried, or tearful eyes.	Distressed, crying, extremely upset, may have wide eyes.		
<b>State of apparent arousal</b>	Alert, looks around occasionally, notices or watches what anesthesiologist does with him/her (could be relaxed).	Withdrawn, child sitting still and quiet, may be sucking on thumb or face turned into adult.	Vigilant, looking quickly all around, may startle to sounds, eyes wide, body tensed.	Panicked whimpering, may be crying or pushing others away, turns away		

Scoring produce 4 mYPAS scores (1 for each behaviour). Each score is calculated by dividing each item rating by the highest possible rating (i.e., 6 for the “vocalizations” item and 4 for all other items), adding all the produced values, dividing by 4 and multiplying by 100. This calculation produces a score ranging from 23.33 to 100, with higher values indicating higher anxiety. In this study, the cutoff value of anxiety is taken from study by Eko et al<sup>2</sup> which reported a score of 29 to be non-anxious children; while a mYPAS score of  $\geq 29$  is considered as children who are anxious.

**Example 1:**

Activity =  $1/4 = 0.25$

Vocalization =  $1/6 = 0.16$

Emotional Expressivity =  $1/4 = 0.25$

State of apparent arousal =  $1/4 = 0.25$

Total points =  $(0.25 + 0.16 + 0.25 + 0.25) / 4 = 0.2275$

Multiply by 100 =  $0.2275 \times 100 = 22.75\%$

**Example 2:**

Activity =  $3/4 = 0.75$

Vocalization =  $3/6 = 0.5$

Emotional Expressivity =  $2/4 = 0.5$

State of apparent arousal =  $2/4 = 0.5$

Total points =  $(0.75 + 0.5 + 0.5 + 0.5) / 4 = 0.56$

Multiply by 100 =  $0.56 \times 100 = 56\%$

## Appendix 2. CRAVERO SCALE <sup>3</sup>

Scale	Behaviour
1	Obtunded with no response to stimulation
2	Asleep, but responsive to movement and/or stimulation
3	Awake and responsive
4	Uncosolable crying more than 3 minutes, without any combative behaviour
5	Unconsolable with thrashing and combative behavior such as kicking, pushing, arching back and/or pulling intravenous lines
A scale of 1.0-3.0 = not agitated; Scale > 3.1-5.0 = agitated	

Measurements are taken starting from extubation and repeated every 15 minutes until patient regain full consciousness or completely awakened.

### For example:

Cravero Scale at extubation = 3 (at the operating theatre)

At the recovery room area:

Cravero Scale at 15 min = 4

Cravero Scale at 30 min = 4

Cravero Scale at 45 min = 4

Cravero Scale at 60 min = patient awakened

Hence, the average Cravero scale is  $(3+4+4+4)/4 = 3.75$  (Classified as agitated)

Time to complete awakening is 60 minutes.

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