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DIFFERENT DOSES OF INTRANASAL DEXMEDETOMIDINE ON EMERGENCY AGITATION PREVENTION IN CHILDREN UNDERGOING ADENOTONSILLECTOMY UNDER SEVOFLURANE ANESTHESIA

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Abstract

Emergence agitation (EA) is an aberrant mental condition arises during the transformation from unconsciousness to full awareness and can persist for up to two days in the early postoperative period. This study compared 2µg/kg versus 3µg/kg intranasal dexmedetomidine (DEX) in reducing EA in children undergoing adenotonsillectomy.

This randomized parallel double-blinded research involved 40 pediatric patients aged 2-10 years old of both sexes were classified by American Society of Anesthesiologists physical status of I, & II undergoing adenotonsillectomy with sevoflurane anesthesia. They were allocated into two groups, GI: received intranasal DEX (2µg/kg), and GII: received intranasal DEX (3µg/kg). General anesthesia was done by face mask with sevoflurane 6-8% inhalation and maintenance at 2-4%.

The results showed that GII had a significantly better Ramsay sedation score, parental separation anxiety scale, Watcha scale emergence delirium, and face mask acceptance scores compared to GI ($P<0.05$). GII had a significantly lower flacc score compared to GI ($P=0.017$), but without significant difference between both as to parents' satisfaction scores.

Keywords: Intranasal, Dexmedetomidine®, Emergence Agitation, Children, Adenotonsillectomy.

Introduction

Obstructive sleep apnea (OSA) is common in the Pediatric population, if untreated, the disease being associated with a wide range of cardiovascular and cognitive morbidities (Kaemingk *et al,* 2003). Adenotonsillectomy is one of the commonest surgical procedures performed on children in the United States, with over 500,000 procedures done annually (Cullen *et al,* 2009).

Emergence agitation (EA) is an aberrant mental condition arises during the transformation from unconsciousness to full awareness and may persist up to two days in early postoperative period. Perception, consciousness, cognition, hypersensitivity to external stimuli, and bodily agitation were disturbed in a child (Ramachandran *et al*, 2021).

Adenotonsillectomy is usually associated with EA in children (Vecchia *et al*, 2020). EA, which is characterized by purposeless restlessness, crying, disorientation, writhing and incoherence, frequently happens during extubation in pediatric surgical procedures. It may cause complications as an extended stay in post-anesthesia care unit (PACU), airway blockage, and bleeding. It can result in accidental removal of bandages and intravenous cannulas, self-injury, and damage to surgical repair and drains (Menser *et al*, 2020). Several characteristics involved adaptability, pain, and temperament are associated with EA. The incidence of EA was as high as 42% in younger children with otorhinolaryngology, mainly after inhaled anesthetic received (Xiao *et al*, 2022).

Sevoflurane (1,1,1,3,3,3-hexafluoro-2-(fluuoromethoxy)propane) is a colourless, volatile, & non-flammable liquid with a characteristic smell, stable at room temperature with 58.6°C boiling point and a vapour pressure of 157mmHg (Patel and Goa, 1996). It is frequently utilized in pediatric anesthesia due to quick induction and lack of substantial airway irritation (Lee and Sung, 2021). Despite being closely linked to EA due to low solubility and quick recovery (Karanth *et al*, 2018). Several pharmacological and non-pharmacological approaches assisted children with a more uniform recovery profile (Naveen *et al*, 2022). To lower EA occurrence, hydroxyzine, opioids, propofol, ketamine, benzodiazepines, clonidine, gabapentin, and magnesium have been utili-

zed (Rao *et al*, 2020).

Intranasal administration showed the safest approach to sedatives and anesthesia to children among the several drug administration routes for pediatric sedation by being relative simplicity, high bioavailability due to the airway mucosa of high vascularity and skipping the first-pass hepatic metabolism, and quick onset of action, as opposed to the IV route (Fantacci *et al*, 2018).

Dexmedetomidine (DEX) is a highly selective α2-agonist that offers anxiolytics, sympatholytic sedation similar to natural sleep, and an anesthetic-sparing action without any clinical significant respiratory depression (Wang *et al*, 2019). These effects were mediated via locus cerulean α2 adrenoceptors of the central nervous system (Sinnott *et al*, 2021). DEX analgesic and sedative effects were crucial in agitation prevention in children underwent the sevoflurane anesthesia, and was more effective than fentanyl, propofol, or midazolam in lowering EA incidence (Ramachandran *et al*, 2021).

The study aimed to evaluate 2μg/kg versus 3μg/kg the intranasal dexmedetomidine (DEX) in reducing EA in children subjected to adenotonsillectomy/tonsillectomy under sevoflurane® anesthesia.

Patients and Methods

This randomized parallel double-blinded study included 40 pediatric patients aged 2 to 7 years old, of both sexes, and American Society of Anesthesiologists (ASA) physical status classification of I, & II having adenotonsillectomy/tonsillectomy under general anesthesia (GA) with Sevoflurane® in Kobry El-Kobba Military Medical Campus from January 2022 to November 2022.

The study was done after approval by the Military Ethical Committee which agreed the Helsinki Declaration (2008). After simplifying the study procedure, informed written consent was obtained from the guardians of the pediatric patients.

Exclusion criteria were those with respiratory issues, circulatory or nervous system/ hepatic malfunction, developmental delay and mental retardation with known DEX adverse reactions.

Inclusion criteria: Randomly by a computer generated sequence, 40 children were allocated by sealed opaque envelopes into two equal categories. Before induction, GI: D2 intranasal DEX (2μg/kg) was given 30 minutes, & GII: D3 intranasal DEX (3μg/kg) was given 30 minutes. Solutions were critically prepared

Preoperatively: All patients were subjected to a comprehensive history taking, a thorough physical examination with focusing on the airway, and standard laboratory examintions. Before surgery, guardians were constructed to give patients nothing/mouth for 2hrs (clear liquids), 4hrs (breast milk), and 6hrs (fortified breast milk, formula, and /or solid foods). Children received intranasal DEX 30 minutes pre-operation. One parent was allowed to accompany the child into the preoperative room.

During parental separation a 4-point scale, parental separation anxiety scale (PSAS) was utilized for recording and grading the child's anxiety degree: 4 = crying need for restraint, 3 = moderate fear, crying not quite with reassurance, 2 = mild fear or crying quiet and 1 = operative, unafraid and asleep (Mostafa and Morsy, 2013).

Sedation was evaluated using the Ramsay sedation score (RSS), which was the simplest and allowed for a numeric value from 1-6 based on child response; where 6= no response to any stimuli, 5= responds slowly to a loud auditory stimulus or light glabella tap, 4 = responds rapidly to loud auditory or light glabella tap, 3= child responds only to directives, 2= cooperative, oriented stimulus and 1= worried and agitated or restless, or both (Rasheed *et al*, 2019).

Anesthetic management: Before operation, no more sedatives were supplied. Children was monitored by a temperature probe, electrocardiogram (ECG), capnogram, noninvasive blood pressure, and pulse oximeter. Induction response was evaluated by the mask acceptance scale and graded using the

four point scales; 4 = calm and cooperative, 3 = cooperative with reassurance, 2 = moderate dread of mask and difficulty to soothe, and 1 = combative, crying (Wang *et al*, 2020). Both groups induced GA with the Sevoflurane® 6-8% and IV induction with 2mg/kg Propofol® IV bolus. Maintenance was done with O_2 and sevoflurane 2-4 %. A suitable size endotracheal tube was inserted when proper anesthetic depth was obtained, and patient was allowed to breathe spontaneously. Anesthetic concentration was administered to reach a steady heart rate (HR), mean arterial blood pressure (MAP), and respiratory rate (RR of baseline ± 20%). HR, MAP, RR, and SpO_2 were recorded at baseline, 10, 20, and 30 minutes.

At operation end, anesthetic gases were turned off and replaced with 100 % $O_2 \geqslant$ 4 L/min. Atropine (0.01mg/kg) and Neostigmine (0.05mg/kg) were supplied to reverse the muscular relaxation. Patients were monitored following the reversal of GA in the PACU. After 10 minutes of extubation, EA was evaluated by using watcha scale featured a numeric scale ranged from 1 to 5, where 5 = thrashing behavior need restraint, 4= crying (for >3 minutes), 3= awake and responsive, 2 = sleepy but, receptive to movement or stimulation, and 1 = obtunded without stimuli response. Watcha scale proved to be a simpler tool used in the clinical practice and may have a higher overall sensitivity and specificity than PAED and Cravero scales (Menser and Smith, 2020).
The FLACC behavioral scale is an observation for pain evaluation that measure scores for 5 distinct pain behaviors: facial expression, leg movement, activity, crying, and consolation abilities. A value between 0 & 2 was assigned for each behavior, with total ratings ranged from 0=no pain to 10= extreme pain (Kochman *et al*, 2017).

The parents' satisfaction score was assessed by the numeric scale ranged from 1 to 5, where 5= very satisfied, 4= satisfied, 3= neutral, 2= unsatisfied, and 1= very unsatisfied (Neville *et al*, 2016).

The primary outcome was Watcha scale emergence delirium in the recovery room, and secondary outcomes were hemodynamics, sedation, parental separation, and parents' satisfaction.

Sample size calculation: Size was performed using G. power (Universität Kiel, Germany) 3.1.9.2. A pilot study (10 cases in each group), showed that the mean Watcha scale emergence delirium in the recovery room of primary outcome was 2.65±0.49 in the GI (D2) versus 2.20±0.41 in GII (D3). Sample size was based on a 0.99 effect size, 95% confidence limit, 80% power, and two additional cases were added to each group to compensate for dropouts. So, 20 patients were recruited for each group.

Statistical analysis: SPSS v27 (IBM, Armonk, NY, USA) was used for analysis. The histograms & Shapiro-Wilkes test were used to determine whether data had a normal distribution. Chi-square test was used for qualitative data analysis that provided as frequencies and percentages. Mann-Whitney test was used for non-parametric quantitative data analysis that was reported as the median and IQR. The unpaired student t-test was used for parametric quantitative data analysis that was reported as means and standard deviations. A two-tailed P value of < 0.05 was considered significant.

Results

Of 67 individuals evaluated, 18 didn't match inclusion criteria, and 9 ones declined to participate. Patient characters (age, sex, weight, and ASA physical status) were crosswatched one another.

HR measurements at baseline, 10min. & 20min. were insignificantly between groups but, significantly lower at 30min. in GII compared to GI ($P < 0.001$). MAP, RR, & SpO_2 were insignificantly between both at all-time measurements (baseline, 10, 20, & 30 min).

Median (IQR) of Watcha scale emergence delirium score was 2 (2-3) in GI and 2 (2-2) in GII with a significantly better Watch scale emergence delirium score and lower EA

than GI (P =0.013). GII had a significantly better Ramsay sedation score, parental separation anxiety scale, and face mask acceptance score (P <0.05). Also, GII had a significantly lower FlACC score compared to GI (P =0.017), but without significant difference between groups as to satisfaction scores.

Details were given in tables (1, 2 & 3).

Table 1: Patient characteristics of groups

Variations		GI (D2 n=20)	GII (D3 n=20)	P value
Age (years)		5.95 ± 2.49	6.3 ± 2.26	0.597
Sex	Male	10 (50%)	10 (50%)	1.0
	Female	10 (50%)	10 (50%)	
Weight (Kg)		21.8 ± 6.48	22.9 ± 6.27	0.578
ASA	I	17 (85%)	18 (90%)	1.0
	II	3 (15%)	2 (10%)	

*Significant P <0.05. ASA: American Society of Anesthesiologists

Table 2: Intraoperative vital signs of groups

Variations		GI (D2 n=20)	GII (D3 n=20)	P value
HR (beats/min)	Baseline	108.7 ± 14.97	101.7 ± 11.3	<0.106
	10 min	105.1 ± 14.57	97.5 ± 10.49	<0.068
	20 min	101.2 ± 14.11	95 ± 10.52	<0.126
	30 min	97.5 ± 13.71	82.6 ± 8.44	<0.001*
MAP (mmHg)	Baseline	71.1 ± 10.49	73.5 ± 9.19	<0.448
	10 min	67.1 ± 9.46	67.8 ± 7.7	<0.810
	20 min	65.4 ± 9.59	65 ± 7.57	<0.873
	30 min	64 ± 9.42	61.9 ± 6.76	<0.437
RR (breath/min)	Baseline	23.7 ± 3.62	22.5 ± 3.66	<0.324
	10 min	22.5 ± 3.69	21.2 ± 3.71	<0.274
	20 min	21.5 ± 3.52	20.4 ± 3.41	<0.321
	30 min	20.5 ± 3.36	19.6 ± 3.46	<0.384
SpO_2 (%)	Baseline	96.5 ± 1.1	95.9 ± 1.29	<0.156
	10 min	96.4 ± 1.27	95.7 ± 1.17	<0.101
	20 min	96.4 ± 1.27	95.8 ± 1.21	<0.106
	30 min	95.7 ± 0.88	95.8 ± 0.95	<0.607

HR: heart rate, MAP: mean arterial blood pressure, RR: respiratory rate, SpO_2: Peripheral oxygen saturation.

Table 3: Assessment scales of groups

Variations	GI (D2 n=20)	GII (D3 n=20)	P value
Ramsay sedation scores	3.5 (3-4)	5 (4-5)	<0.001*
Parental separation anxiety scale	2 (2-2.5)	1 (1-1)	<0.001*
Face Mask acceptance score	3 (2-3)	4 (4-4)	<0.001*
Watcha scale emergence delirium	2 (2-3)	2 (2-2)	<0.013*
FlACC score	6 (5-6)	5 (4-5)	<0.017*
Parents satisfaction score	5 (4-5)	5 (4-5)	<0.169

FLACC: Face, Legs, Activity, Cry, Consolability, *Significant P<0.05

Discussion

The American Society of Anaesthesiologists physical status classification system offered perioperative clinicians a simple categorization of a patient's physiological status to help predict operative risk (Howard *et al,* 2019). EA in children is one of the most frequent surgical complications in the recovery room, with an incidence of 80 % (Mason, 2017). Postoperative behavioral changes caused by hospitalization, anesthesia, and surgery can have a significant psychological effect. So, playing animated films on a smartphone and parental presence during induction and operating room where done (Yip *et al*, 2009). Although the frequency of sevoflurane-related EA ranged from 10- 80% was commonly used in paediatric children for GA (Lim *et al*, 2016). Optimal pre-aesthetic agent facilitated patient's face mask acceptance and smooth parents' separation during anaesthesia induction (Akin *et al*, 2012).

The present study was a unique in evaluating intranasal DEX on EA and parent separation. A higher dose of intranasal DEX (3µg/kg) provided a better Ramsay sedation score, face mask acceptance score, Watcha scale emergence delirium score, pain score, and parental separation anxiety scale versus intranasal DEX (2µg/ kg).

Guler *et al.* (2005) reported that EA and pain occurrence and intensity were prevented by administering a single dose of DEX 0.5µg /kg IV 5 minutes before the surgery completion. Begum *et al.* (2019) found that

infusion and bolus (0.4µg/kg/h) of DEX supplementations effectively prevented EA in children having ambulatory surgery. But, Ramachandran *et al*. (2021) compared intraoperative DEX infusions of 0.5 µg/kg/h & 0.3µg/kg/h found that a lower DEX dose was sufficient to offer effective relief from EA without any higher dose.

Yuen *et al.* (2007) reported that intranasal DEX dosages of 1 &1.5µg/kg might offer appropriate sedation, and the necessity of determining if these doses would offer clinical sedation in worried patients having surgery or other painful procedures was clarified. Yuen *et al.* (2008) added that intranasal administration of DEX to healthy adult volunteers and children having minor surgery had clinically significant sedative effects.

Peng *et al.* (2014) by meta-analysis, reported that more children had successful IV cannulation after receiving intranasal DEX (RD= -0.48, 95% CI: -0.92 to -0.04, P = 0.03) as compared to placebo. Kumar *et al. (*2017) reported that paediatric patients given 1µg/kg DEX intranasal showed superior sedative scores during separation and induction with normal behavioural scores versus oral midazolam. Kumar *et al.* (2020) concluded that 4% nebulized lidocaine gave adequate airway anaesthesia and optimal intubating conditions with stable hemodynamics for awake fiberoptic intubation as compared to 2% nebulized lidocaine.

Conclusions

Compared to intranasal DEX 2µg/kg, intranasal DEX 3µg/kg provided better results in reducing EA, higher sedation, lowering pain score, better parental separation, and face mask acceptance.

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