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

By
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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 dexametomidine (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, Dexametomidine®, 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, whirring 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-(fluoromethoxy)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-
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 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 Koby 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 examinations. 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, non-invasive 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 O₂ 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 SpO₂ were recorded at baseline, 10, 20, and 30 minutes.

At operation end, anesthetic gases were turned off and replaced with 100 % O₂ 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 Craver 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, & SpO₂ 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 Watcha 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

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

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

### Table 2: Intraoperative vital signs of groups

<table>
<thead>
<tr>
<th>Variations</th>
<th>GI (D2 n=20)</th>
<th>GII (D3 n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>108.7 ± 14.97</td>
<td>101.7 ± 11.3</td>
<td>&lt;0.106</td>
</tr>
<tr>
<td>10 min</td>
<td>105.1 ± 14.57</td>
<td>97.5 ± 10.49</td>
<td>&lt;0.068</td>
</tr>
<tr>
<td>20 min</td>
<td>101.2 ± 14.11</td>
<td>95 ± 10.52</td>
<td>&lt;0.126</td>
</tr>
<tr>
<td>30 min</td>
<td>97.5 ± 13.71</td>
<td>82.6 ± 8.44</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>71.1 ± 10.49</td>
<td>73.5 ± 9.19</td>
<td>&lt;0.448</td>
</tr>
<tr>
<td>10 min</td>
<td>67.1 ± 9.46</td>
<td>67.8 ± 7.7</td>
<td>&lt;0.810</td>
</tr>
<tr>
<td>20 min</td>
<td>65.4 ± 9.59</td>
<td>65 ± 7.57</td>
<td>&lt;0.873</td>
</tr>
<tr>
<td>30 min</td>
<td>64 ± 9.42</td>
<td>61.9 ± 6.76</td>
<td>&lt;0.437</td>
</tr>
<tr>
<td>RR (breath/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23.7 ± 3.62</td>
<td>22.5 ± 3.66</td>
<td>&lt;0.324</td>
</tr>
<tr>
<td>10 min</td>
<td>22.5 ± 3.69</td>
<td>21.2 ± 3.71</td>
<td>&lt;0.274</td>
</tr>
<tr>
<td>20 min</td>
<td>21.5 ± 3.52</td>
<td>20.4 ± 3.41</td>
<td>&lt;0.321</td>
</tr>
<tr>
<td>30 min</td>
<td>20.5 ± 3.36</td>
<td>19.6 ± 3.46</td>
<td>&lt;0.384</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>96.5 ± 1.1</td>
<td>95.9 ± 1.29</td>
<td>&lt;0.156</td>
</tr>
<tr>
<td>10 min</td>
<td>96.4 ± 1.27</td>
<td>95.7 ± 1.17</td>
<td>&lt;0.101</td>
</tr>
<tr>
<td>20 min</td>
<td>96.4 ± 1.27</td>
<td>95.8 ± 1.21</td>
<td>&lt;0.106</td>
</tr>
<tr>
<td>30 min</td>
<td>95.7 ± 0.88</td>
<td>95.8 ± 0.95</td>
<td>&lt;0.607</td>
</tr>
</tbody>
</table>

HR: heart rate, MAP: mean arterial blood pressure, RR: respiratory rate, SpO₂: Peripheral oxygen saturation.

### Table 3: Assessment scales of groups

<table>
<thead>
<tr>
<th>Variations</th>
<th>GI (D2 n=20)</th>
<th>GII (D3 n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramsay sedation scores</td>
<td>3.5 (3-4)</td>
<td>5 (4-5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Parental separation anxiety scale</td>
<td>2 (2-2.5)</td>
<td>1 (1-1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Face Mask acceptance score</td>
<td>3 (2-3)</td>
<td>4 (4-4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Watcha scale emergence delirium</td>
<td>2 (2-3)</td>
<td>2 (2-2)</td>
<td>&lt;0.013*</td>
</tr>
<tr>
<td>FLACC score</td>
<td>6 (5-6)</td>
<td>5 (4-5)</td>
<td>&lt;0.017*</td>
</tr>
<tr>
<td>Parents satisfaction score</td>
<td>5 (4-5)</td>
<td>5 (4-5)</td>
<td>&lt;0.169</td>
</tr>
</tbody>
</table>

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

### Discussion

The American Society of Anaesthetists 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 supplemenations 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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References


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