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INTRANASAL DEXMEDETOMIDINE 2µG/KG VERSUS 3µG/KG ON PARENT SEPARATION IN DENTAL SURGERY: A RANDOMIZED CLINICAL TRIAL

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Abstract

Children may become excessively uncooperative during venipuncture, mask installation, or parental separation. Harder induction, higher postoperative pain, emerging agitation, and possibly postoperative behavioral and psychological problems can result from untreated anxiety. This study aimed to compare intranasal dexmedetomidine (DEX) 2 µg/kg vs. 3µg/kg for children undergoing dental surgery. This randomized double-blinded study involved 80 children aged 2 to 10 years old of both sexes, planned for dental surgery. They were allocated into two groups according to DEX intranasal dose given 30 minutes before general anesthesia (GA) induction, GI: 2µg/kg and GII: 3µg/kg. IV cannulation was done before the GA induction.

The results showed that GII had a significantly better parental separation anxiety scale, Ramsay sedation score, and IV cannula acceptance score than GI (P <0.001), without significant difference as to parents' satisfaction score.

Keywords: Pediatrics, Intranasal, Dexmedetomidine, Premedication, Parent Separation.

Introduction

Children may become excessively uncooperative during venipuncture, mask installation, or parental separation (Liu *et al*, 2022). Harder induction, higher postoperative pain, emerging agitation, and possibly postoperative behavioral and psychological problems can result from untreated anxiety (Reddy and Deutsch, 2020).

Pediatric sedation is one of many difficulties encountered in anesthetic practice (Artunduaga *et al*, 2021). For any child underwent a procedure, the preoperative period was the most distressing, especially upon anesthesia induction (Agbayani *et al*, 2020).

Anxiolysis is the major objective of premedication in children, making parental separation and anesthesia induction easier (Heikal and Stuart, 2020). Premedication may also have the following effects: physiologic stress prevention, amnesia, reduction of total anesthetic requi-rements, vagolysis, lower likelihood of aspiration, reduced salivation, secretions, analgesia, and anti-emesis (Da ve, 2019). Common strategies for reducing preoperative worry and anxiety in children being accompanied by parents during anesthetic induction, appropriate preoperative communication, pharmacological interventions, and others (Getahun *et al*, 2020).

Practitioners continue depending on sedative premedications despite numerous breakthroughs in nonpharmacologic therapies. In clinical practice, the use of pharmaceutical therapies is prevalent. Ideal premedication characteristics involve a simple administration route readily accepted by children rapid onset of action, short duration, minimum adverse effects, dependable pain reduction, and autonomic modulation (Euteneuer *et al*, 2022).

Children routinely get sedative premedication orally, sublingually, rectally, and intranasally with varied acceptability degrees. Transmucosal administration, involving intranasal, buccal, and sublingual administration, was more successful for premedication due to its high mucosal vascularity and capacity to circumvent first-pass metabolism (Sengupta *et al*, 2022). In young pediatrics, sedation with intranasal route may be easier than oral route (Cai *et al*, 2021).

Dexmedetomidine (DEX) is a selective α-2 adrenoceptor agonist that causes anxiolysis, analgesia, and sedation without causing respiratory depression. For children, intranasal administration of DEX provides a non-invasive, convenient, and well-tolerated administration route (Lee, 2019). In children, intranasal DEX (1-2µg/kg) induces sedation

efficiently, reduced separation anxiety (Miller *et al*, 2018), and improved compliance during invasive approaches such as intravenous (IV) cannulation (Liu *et al*, 2021).

This study aimed to compare the different doses of intranasal DEX for better induction conditions under general anesthesia introduction in children undergoing dental surgery.

Patients and Methods

This randomized, double-blinded study involved 80 pediatric patients aged 2 to 10 years old of both sexes, American Society of Anesthesiologists (ASA) physical status I arranged for dental surgery at Kobri El Koba Medical Campus from January to December 2022. The study was done after the Ethical Committee Approval Also, the informed written consent was obtained from the guardians of the pediatric patients.

Exclusion criteria involved a history of clinically significant neurologic, renal, cardiovascular, or pulmonary disease, allergy to anesthetic drugs or DEX, mental retardation and utilization of psychotropic agents, and any nasal condition that could hinder the nasal delivery of medications.

Randomization and blindness: Unrelated to patient care, a statistician employed computer-generated software to randomly dividing the patients into two equal groups. GI: intranasal DEX (2μg/kg), GII: intranasal DEX (3μg/kg). Both patients and investigators were blinded. All cases were submitted to a comprehensive history taking, a thorough physical examination, and usual laboratory tests.

Before induction, they were permitted clear fluids for up to two hours. On the operation day morning, one parent was permitted to accompany their child into the preoperative room. Children were administered DEX intranasally 30 minutes before operation. They were monitored using a temperature probe, electrocardiogram, noninvasive blood pressure, capnogram, and pulse oximeter. After entering the operating room, IV access was acquired. Anesthesia was induced by 2-3mg/kg propofol IV bolus and 1μg/kg fentanyl, and 0.3mg/kg cis-atracurium to facilitate intubation using a suitable-sized endotracheal tube. Sevoflurane (0.5-1.5 MAC) was used to maintain anesthesia, and incremental cis-atracurium (0.07mg/kg) was used for muscle relaxation. They were mechanically ventilated (pressure-controlled mode) with the parameters adjusted to maintain an end-tidal CO_2 of 36-40mmHg.

Parental Separation Anxiety Scale (PSAS) was used to document and grade the child's anxiety level during parental separation, 4= Crying need for restraint, 3= Moderate fear, crying not quite with reassurance, 2= mild fear or crying quite when reassurance and 1= unafraid, cooperative and asleep (Mostafa and Morsy, 2013).

Sedation was evaluated using the Ramsay sedation score (RSS) based on the patient's response, where 6= no response to any stimulations, 5= a slow response to a loud auditory stimulus or light glabellar tap, 4= brisk response to a loud auditory stimulus or light glabellar tap, 3= responds to commands only, 2= cooperative, oriented and tranquil and 1= anxious and agitated or restless, or both (Rasheed *et al*, 2019).

Groningen distress rating scale (GDRS) was used to evaluate the IV cannulation response, where 5= panic, 4= severe distress, out of control, crying, uncooperative, unable to start IV line, 3= serious distress, in control, Withdrawal for painful stimuli, 2= mild distress, Calmno withdrawal for IV cannulation and 1= calm, asleep (Chau *et al*, 2019).

Heart rate (HR) and mean arterial blood pressure (MAP) were kept within 20% of their baseline by adjusting sevoflurane concentration. Sevoflurane concentration was decreased, and rescue drugs (ephedrine 0.5 mg/kg and atropine 20μg/kg) were supplied if HR and BP dropped to 20% of baseline. Intraoperative HR, MAP, respiratory rate, and SpO_2 were monitored at baseline and every 10 minutes till 30 minutes.

Sevoflurane was withdrawn after the procedure completion. Children were immediately transported to the PACU after surgery. Neostigmine (0.05mg/kg) and atropine (0.01 mg/kg) were administered to reverse muscular relaxation. The children were observed in accordance with PACU protocol after the

reversal of GA in the PACU. Vital signs and adverse effects were observed and monitored for each child in the PACU. The primary outcome was the assessment of Ramsay sedation scores. The secondary outcomes were measurements of intraoperative HR, MAP, RR, SpO_2, and assessment of parental separation anxiety and parents satisfaction.

Sample size calculation: G. power (Universität Kiel, Germany) 3.1.9.2 was used for sample size calculation. A pilot study was performed (20 cases in each group), and the mean (± SD) of Ramsay sedation scores (the primary outcome) was 3.50±0.67 in GI and 4.15±0.49 in GII. Sample size was based on the following considerations: 0.99 effect size, 95% confidence limit, 80% power of the study, and to combat dropout, 5 cases were added to each group. Consequently, 40 patients for each group were recruited.

Statistical analysis: SPSS v27 (IBM Corp., Armonk, NY, USA) was used for data analysis. Histograms and the Shapiro-Wilks test were employed to determine whether or not the data had a normal distribution. Chi-square tests were used to analyze qualitative variables shown as frequencies and percentages. Median and IQR described and analyzed quantitative non-parametric data using the Mann-Whitney test. All quantitative parametric data were summarized as means and standard deviations (SDs) and analyzed using the unpaired student t-test. If the two tails P value< 0.05, result was significant.

Results

Of the 113 eligible patients, 19 didn't match the criteria, 14 declined to participate and 80 patients were assigned randomly to two equalcross-matched groups.

MAP was insignificantly different between groups at baseline and 10 min, but was signific-antly lower in GII compared to GI at 20min & 30min (P =0.007, 0.005 respectively). HR, RR, & SpO_2 were insignifi-cantly different between both groups at all time measurements. GII had a significantly better parental separation anxiety scale, the Ramsay sedation score, and IV can-nula acceptance score than GI (P <0.001), without significant difference between both groups as to parents' satisfaction score.

Details were given in tables (1 & 2) and figures (1 & 2).

Table 1: Patient characteristics among groups

Variations		GI (n=40)	GII (n=40)	P value
Age (years)		6.4±2.4	5.8±2.32	0.421
Male		12 (48%)	9 (36%)	
Female		8 (32%)	11 (44%)	0.527
Weight (Kg)		23.7±6.55	21.4±6.68	0.279
ASA physical status	I	16 (64%)	18 (72%)	0.661
	II	4 (16%)	2 (8%)	

P value<0.05. ASA: American Society of Anesthesiologists

Table 2: Assessment scales among groups

Variations	G I (n=40)	GII (n=40)	P value
Ramsay sedation score	3 (3-4)	4 (4-4)	<0.001*
Parental separation anxiety scale	2 (2-2.5)	1 (1-1)	<0.001*
Intravenous cannula acceptance score	3 (2-3)	1 (1-2)	<0.001*
Parents satisfaction score	5 (4-5)	5 (5-5)	0.096

* P value<0.05.

Discussion

Appropriate and conventional pre-induction sedation for children continues to be challenging. During the perioperative phase, a worried and belligerent child causes stress for anesthesiologists, caregivers, and parents alike. Different children may vocally, behaviorally or explicitly communicate their preoperative fear, making induction of anesthesia problematic (Bhat *et al*, 2016).

The present study showed that better parental separation anxiety scale, sedation score, and IV cannula acceptance score were achieved by 3 μg/kg DEX compared to 2μg/kg DEX.

Intranasal DEX premedication is effective, safe, and has few side effects in children (Jun *et al*, 2017). The potential role of intranasal DEX as premedication before anesthesia induction was assessed (Wu *et al*, 2016)

crossover trials demonstrating that considerable sedation was achieved 45-60 minutes after intranasal DEX (1 to 1.5μg/kg), with the maximal effect happening 90-105 minutes later.

Olutoye *et al*. (2007), on healthy volunteers showed that DEX has a strong analgesic effect, making it particularly appropriate for intraoperative use. However, clinical evidence confirming the analgesic benefit of the DEX in children was lacking (Guo *et al*, 2022)

In the same context, Bonagua *et al.* (2020) demonstrated that nebulized DEX (2μg/kg) scored higher on IV cannulation acceptance and parental separation than those who were not premedicated. Gyanesh *et al*. (2014) obtained similar results in a randomized study for magnetic resonance imaging. They evaluated intranasal ketamine (5mg/kg), DEX (1μg/kg), and a placebo (saline) in 150 children aged 1-10 years received IV implantation to administer propofol administration. However, Lin *et al.* (2022) performed a meta-analysis on pediatric patients. They found intranasal atomized DEX administration as a premedication didn't demonstrate any advantage in achieving acceptable sedation or parental separation compared to other premedication regimes, such as the midazolam (Lang *et al*, 2020).

Using intranasal DEX at 2μg/kg as a premedication was more effective than oral midazolam at sleep induction preoperatively in Talon *et al.* (2009) study on burn children undergoing reconstructive surgery. A previous meta-analysis found that pediatric patients premedicated with DEX experienced a more satisfactory separation from their parents and required less postoperative rescue analgesia than those premedicated with midazolam. DEX-premedicated children had decreased HRs before induction (Peng *et al*, 2014). Two trials found that DEX intranasal administration to healthy adult volunteers & children had clinically significant sedative effects (Yuen *et al*, 2007; 2008). So, it was sought to compare the intranasal administration of both agents.

Intranasal DEX dosages of 1 &1.5μg/kg have comparable effects, in a study involved volunteers (Yuen *et al*, 2007). Yuen *et al.* (2008) reported that intranasal DEX doses of 1 & 1.5μg/kg gave sufficient sedation and determined whether such doses offered clinical sedation for worried patients awaiting surgery or other unpleasant approaches. Talon *et al.* (2009) advocatedthat large intranasal DEX dose (2μg/kg) for preoperative premedication in burn patients. They chose higher doses since the patient population experienced burn-related pain and anxiety. If investigation had waited longer, it might have caused more sedative effects from intra-nasal DEX.

In the present study, the effective sedation was achieved by 3μg/kg of intranasal DEX during parental separation, but insufficient mask induction. In a study of 96 children aged 2-12, 53.1%, 40.6%, & 18.8% of those who received 1μg/kg of intranasal DEX, 0.5μg/kg of intranasal DEX, and 0.5mg/kg of oral midazolam respectively, were satisfactorily sedated at anesthesia induction (Yuen *et al*, 2008). So, the present administered a greater intranasal DEX dose compared to Talon *et al*. (2009), who may have contributed to the strong efficacy of this treatment in promoting mask induction.

Conclusions

Compared to intranasal DEX (2μg/kg), intranasal DEX (3μg/kg) showed a better parental separation, higher sedation level, and intravenous cannula acceptance score.

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Explanation of figures

Fig. 1: CONSORT flow chart of enrolled patients

Fig/ 2: Intraoperative vital signs among groups