

Intranasal Dexmedetomidine versus Oral Paracetamol as a Pre-anesthetic Medication in Children Undergoing Adeno-tonsillectomy: A Randomized Clinical Trial

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Abstract:

Background and aim: Anesthetic premedication with dexmedetomidine helps to alleviate anxiety, reduces analgesic need, and prevents unfavorable postoperative psychological events. In addition, it helps in rapid inhalational induction and oro-tracheal intubation. This study aims to assess the premedication efficacy of oral paracetamol and intranasal dexmedetomidine regarding alleviating anxiety and tolerance to separation from the parents.

Methods: This prospective, randomized, double-blinded, comparative clinical trial was done on 86 children ASA I or II of either sex who were scheduled for adeno-tonsillectomy and received either oral paracetamol or intranasal dexmedetomidine. The primary goal of our trial was to evaluate anxiety level and assess tolerance to separation from the parents; this was assessed by the modified Yale scale. Our secondary goals were perioperative hemodynamic parameters and SPO₂, which were followed up in the preoperative period and after receiving the drug. Intraoperatively, the anesthesiologist recorded child's heart rate and MAP. Postoperatively, parents' satisfaction was assessed. **Results:** Preoperative anxiety score showed no significant difference between both groups. Also, baseline HR, MAP, and SpO₂ were comparable. No significant differences were noted at 10 and 20 minutes after drug administration in all vitals ($P > 0.05$). However, 30 minutes later, till the operation ended, the blood pressure and heart rate were significantly higher in group P than in group D. No significant difference was reported between both groups regarding SpO₂ ($P > 0.05$). **Conclusions:** Oral paracetamol is similar to intranasal dexmedetomidine in reducing preoperative anxiety. As a result, paracetamol is a good substitute for dexmedetomidine.

Keywords: Dexmedetomidine, paracetamol, preoperative anxiety, intranasal, general anesthesia.

Introduction:

Preoperative anxiety is a major concern in children because it produces unwanted results on induction and postoperative outcome as nightmares, eating problems, increased fear from physicians, and behavior changes.[1] Postoperative anxiety can activate the hypothalamus-hypophyseal-adrenal axis, which increases glucocorticoid level, immune system changes, infection, and affects blood glucose level due to restricted energy reserve and increased glucose requirements.[2]

Dexmedetomidine is a specific alpha two adrenergic receptor agonist. Trials suggest that dexmedetomidine administration is safe as it is less invasive with a short half-life. Its bioavailability is (72.6 – 92.1%) when given intra-nasally. However, dexmedetomidine is relatively expensive. [2]

Paracetamol is a powerful physical pain killer. It reduces psychological reactivity and alleviates physical and social pain by inhibiting activity in the brain areas associated with emotional awareness and motivation, such as the anterior insula and anterior cingulate cortex.[1,3,4]

The current study aimed to compare oral paracetamol, a safe drug in therapeutic doses,

and intranasal dexmedetomidine in reducing preoperative anxiety in children prepared for adenotonsillectomy.

Material and Methods

In Benha University Hospital, this prospective, double-blinded, comparative clinical trial was performed on 86 children who underwent elective adeno-tonsillectomy under general anesthesia between June 2021 and January 2022. The study was approved by the Benha Faculty of Medicine Ethical Committee (RC/8/5/2021). The trial was registered in clinicaltrials.gov (NCT04949477). In addition, informed consent was received from each patient's parent. Eligible children were allocated into two equal groups (P and D; 43 children for each).

In group (P), children were given oral paracetamol (20 mg/kg) 50 minutes before the procedure and 2 ml saline intranasally.

In group (D), children were given intranasal dexmedetomidine (1µg/kg) 50 minutes before the procedure and 2ml saline orally.

Children aged 2 to 8 years who were healthy or who had controlled medical conditions (ASA I or II) prepared for

adenotonsillectomy were included in the trial. We excluded patients with ASA III or IV who were older than eight years, children with obstructive sleep apnea, children with known hypersensitivity to any of the medications used, patients using any other sedatives, patients with nasal infection or pathology, and patients whose parents refused to participate in the trial.

The research aims were discussed with the parents, and prior to the study, signed informed consent was obtained. Then, before intravenous catheterization, each child was brought to the operating room. His or her degree of anxiety was measured using a modified Yale preoperative anxiety score (m-Yale PAS). Anxiety was measured by observing their activities (1-4), emotional expression (1-4), vocalization (1-6), arousal level (1-4), and contact with family members (1-4). The minimum score is 5, and the maximum is 22, indicating minimal and extreme anxiety, respectively.

A sevoflurane mask was applied to the patient, and an intravenous line was established and guarded. Induction of anesthesia was done with intravenous one $\mu\text{g}/\text{kg}$ fentanyl, 1-2 mg/kg propofol, and atracurium (0.5 mg/kg). The child's airway was then nasally intubated according to his or

her age, and he or she was mechanically ventilated using pressure mode. Pulse oximetry (SPO₂), electrocardiography (ECG), non-invasive blood pressure (NIBP), and capnography were used as standard monitors. Sevoflurane was then used to maintain anesthesia, and an atracurium bolus dose was given every 20 minutes at a dose of 0.1 mg/kg . Children were brought to the PACU following extubation, where Aldrete's score was evaluated at ten-minute intervals. By the time the Aldrete's scoring system got equal or more than 9, the patient discharged to the ward.

Data Collection and Outcomes:

The two drugs were organized by one of the investigators who was no longer directly concerned with the patient's care. The surgeon, anesthetist, and patients were all ignorant of the medication used. The anesthesiologist recorded heart rate, MAP, and oxygen saturation for each child in the preoperative period at 10 minutes (T1), 20 minutes (T2), 30 minutes (T3), and 50 minutes (T4) after receiving the drug. **Intra-operatively**, the anesthesiologist recorded each child's heart rate and MAP (at 10 minutes (T1), 20 minutes (T2), and 30 minutes (T3)). **Postoperatively**: heart rate, oxygen saturation (at 20 minutes (T1), 30

minutes (T2), 40 minutes (T3), 80 minutes (T4), 100 minutes (T5) , 120minutes (T6)) and parents' satisfaction were assessed. The primary outcome was the anxiety degree.

Statistical methods:

SPSS version 25 was used to analyze the data (IBM, Armonk, New York, United States). The unpaired student t-test was used to evaluate quantitative parametric data reported as mean ± standard deviations. Qualitative data were presented as numbers and percentages and compared using the Chi-square test. A P-value < 0.05 indicates statistical significance.

Sample size calculation

The calculation was done based on a study performed in Pakistan in 2009[1] which reported an effect size of 0.635 between groups regarding preoperative anxiety. Alpha and power were adjusted at 5% and 80%,

respectively. G*Power software (Universitat Keil, Germany) version 3.1.9.4 calculated 40 patients per group. To prevent dropouts, the sample size was increased to 43 children per group.

Results:

Ninety children were evaluated for inclusion. Four children were excluded (one patient was 16 years of age, two patients were suffering from a chest infection, and one patient's parent refused participation. Eighty-six patients were enrolled; 43 were allocated to the paracetamol group (**group P**), and 43 patients were assigned to the dexmedetomidine group (**group D**) (Fig 1).

Both groups were comparable regarding demographic and general characteristics, including age (P = 0.713), sex (P = 0.669), weight (P = 0.696), ASA (P = 0.645), and surgery duration (P = 0.504) (Table 1).

Table 1: Demographic data

		Group (D)	Group (P)	p-value
Age (yrs.)		5.12± 1.75	4.98± 1.75	0.713
sex	♂	23	25	0.669
	♀	20	18	
weight (kg)		16.14± 1.61	16±1.69	0.696
ASA	I	41	40	0.645
	II	2	3	
Duration of surgery (min.)		27.49±5.1	26.63± 6.68	0.504

Values are presented as mean ± SD and were compared withunpaired student t-test. No significant differences were seen among the two group.

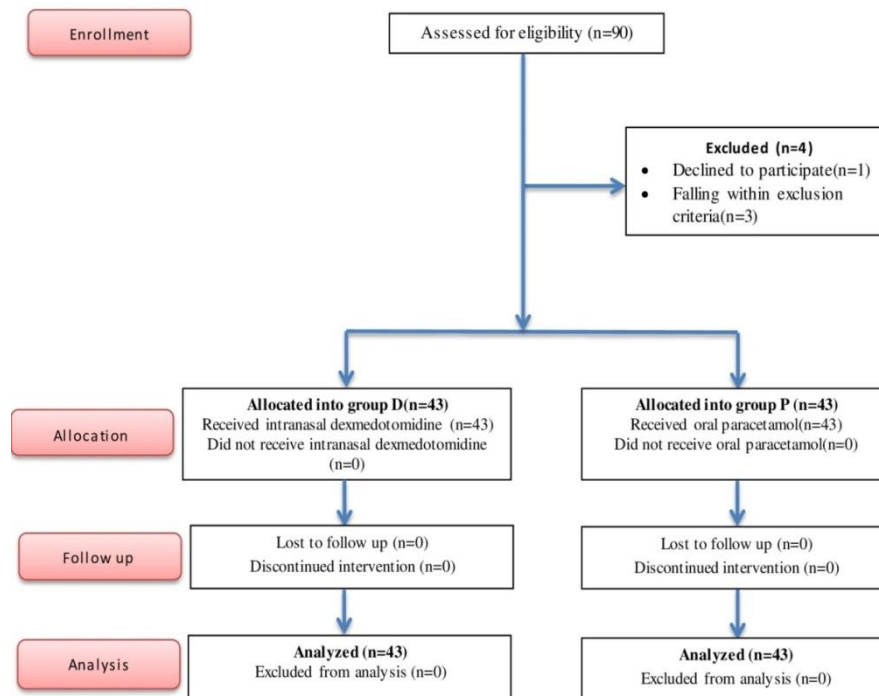


Fig (1):- Consort flow chart

No significant differences were noted between the studied groups regarding baseline HR, MAP, and oxygen saturation. Also, vital data showed no significant differences after 10 and 20 minutes of drug administration ($P > 0.05$). In contrast, the blood pressure and heart rate were significantly higher in group P than in group D after 30 minutes of drug administration ($P < 0.05$) (figure 2-3). In addition, no

significant difference in oxygen saturation was observed throughout the whole procedure ($P > 0.05$) (figure 4).

No significant differences between both groups were reported regarding anxiety score and parents' satisfaction ($P > 0.05$). The mean anxiety score in the dexmedetomidine group was 6.19 ± 0.73 , and in the paracetamol group was 6.35 ± 0.84 (figure 5) (table 2).

Table 2:

	Group D		Group P		p-value
	Mean	SD	Mean	SD	
Anxiety score	6.19	0.73	6.35	0.84	0.341
Parents' satisfaction	4.19	0.59	4.05	0.62	0.285

Values are presented as mean ± SD and were compared with unpaired student t-test. No significant differences were seen among the two groups.

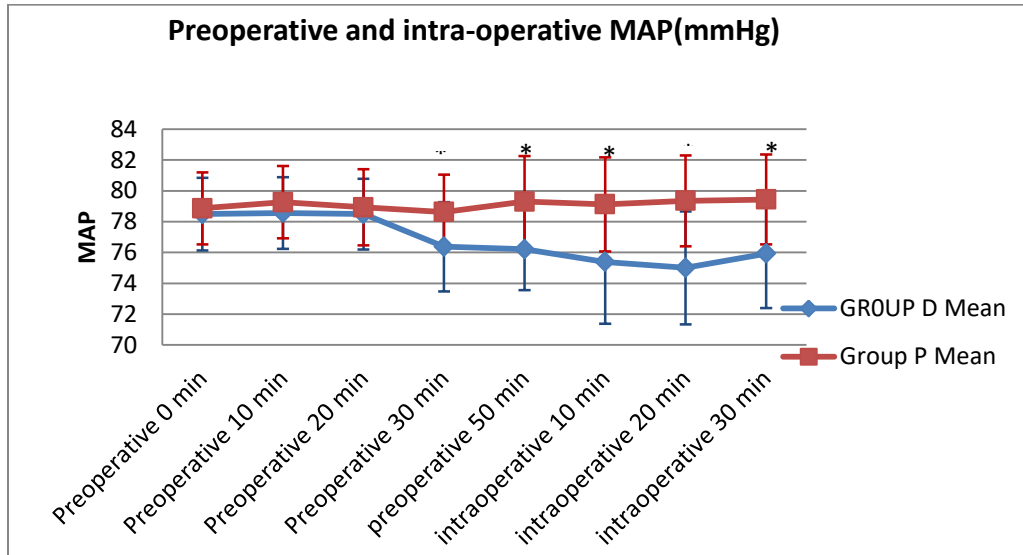


Figure 2: Preoperative and intraoperative MAP

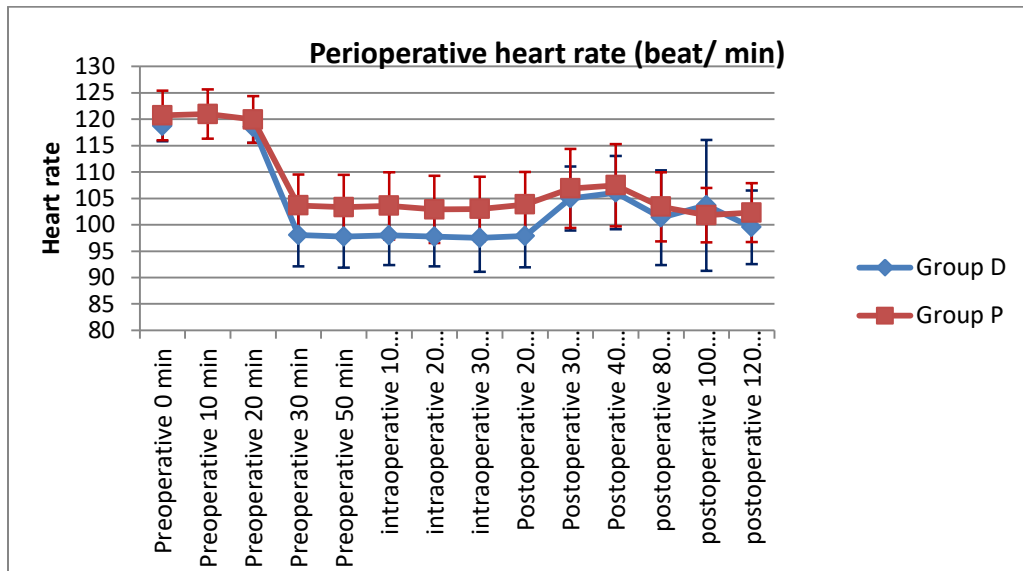


Figure 3: Perioperative heart rate

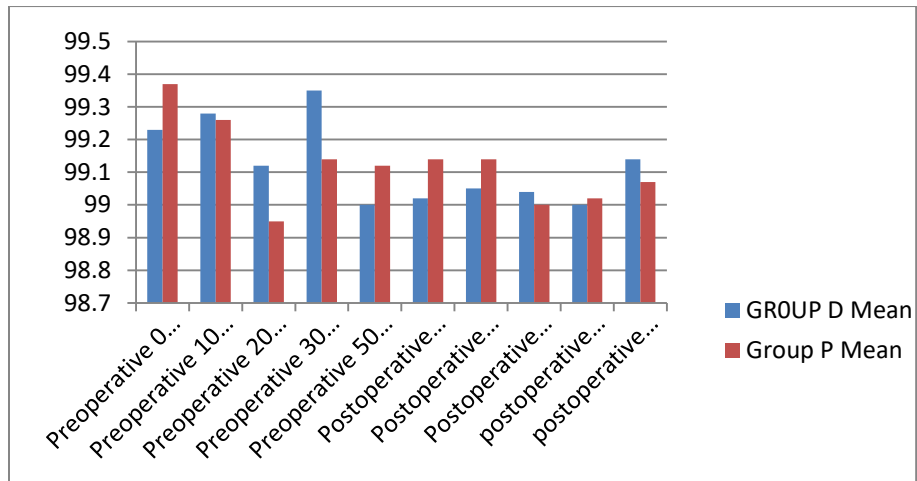


Figure 4: Preoperative and postoperative SPO2

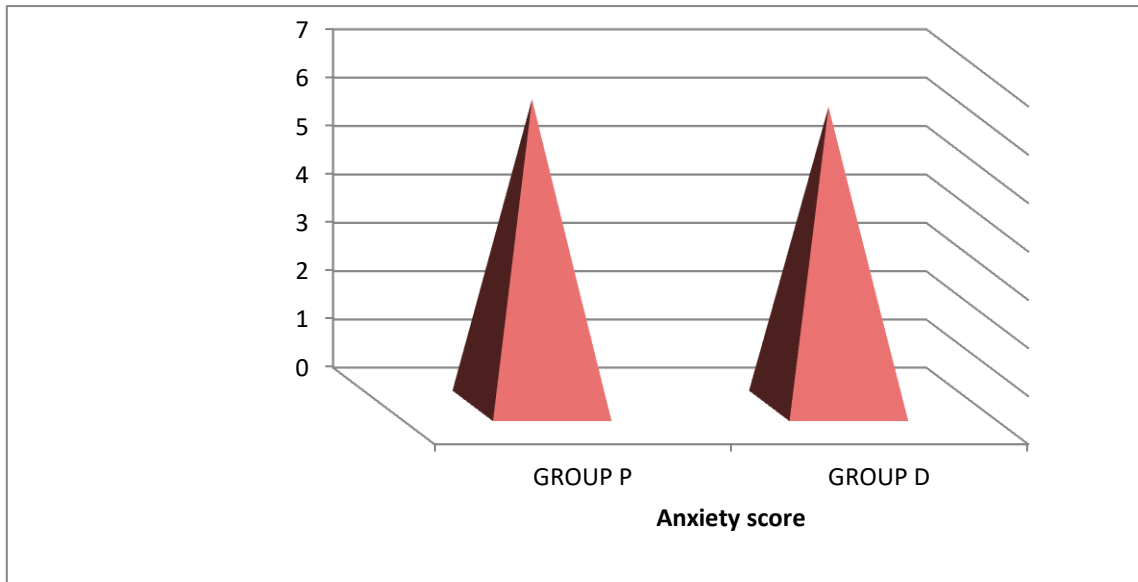


Figure5: Anxiety score

Discussion:

Anxiety is an essential factor that affects postoperative outcomes.[5] Children are more vulnerable to postoperative anxiety. It was found to affect 60% of children undergoing surgery.[1] Therefore, pediatric

anesthesiologists are deeply concerned about relieving pre-and postoperative anxiety in this age group.[6]

Dexmedetomidine is known for its anxiolytic, sedative, and analgesic effects

being a selective, short-acting α_2 -adrenoceptor agonist [7] without causing respiratory depression.[8] Paracetamol is a cyclo-oxygenase enzyme inhibitor. It is frequently used to relieve pain and fever.[9] Several recent studies suggested that paracetamol can also ease anxiety and minimize discomfort. [10] This anxiolytic activity occurs by acting on cannabinoid receptors in the central nervous system and mediated through N-arachidonylphenolamine.[11]

In the current trial, we evaluated the effect of oral paracetamol (20 mg/kg) and intranasal dexmedetomidine (1 μ g/kg) in reducing preoperative anxiety in children prepared for adenotonsillectomy. We found that both drugs effectively relieved preoperative anxiety with no statistically significant difference.

In a Pakistani study, researchers compared preoperative anxiety between clonidine and oral paracetamol in pediatric patients undergoing adenotonsillectomy. They reported that both drugs significantly reduced the anxiety score compared to placebo, but no significant difference was noted between clonidine and Paracetamol groups.[1]

Another study compared oral midazolam and intranasal dexmedetomidine in pediatric dental patients undergoing general anesthesia. It reported a high mask acceptance scale rate in both groups (93.33%), but no significant difference was reported ($P > 0.05$). The rates of successful separation from parents were 96.67% and 93.33% in DEX and MID groups, respectively, with no significant difference ($P > 0.05$). Agitations were significantly higher in the MID group (20%) than in the DEX group (0.0%) ($P < 0.05$). Both oral midazolam and intranasal dexmedetomidine provided adequate sedation, but no significant differences were reported in terms of mask acceptance and parental separation anxiety ($P > 0.05$).[12]

Furthermore, researchers compared oral midazolam and paracetamol versus nasal midazolam and ketamine for sedation in children scheduled for dental treatment. They found that combined nasal midazolam/ketamine provided easier separation from parents (88.9% vs. 8.9%) and higher face mask tolerance "scale 1" (73.3% vs. 22.2%). In addition, it helped earlier PACU discharge (88.9% vs 66.7%), hospital discharge (77.8% vs 46.7%), and a higher satisfaction (77.7% vs 22.2%). [13]

In the current trial, we studied both drugs' effects on heart rate and blood pressure. No significant differences were reported at 10- and 20-minutes following drug administration. However, significant differences in heart rate and blood pressure were observed in group D after 30 minutes of administration this was mostly due to central alpha 2 agonist effect, which was clinically irrelevant, and no clinical intervention was required.

A more recent study compared oral midazolam and intranasal dexmedetomidine in pediatric dental patients undergoing general anesthesia. It reported significantly lower heart rate in the dexmedetomidine group 30 minutes after administration. The heart rate change was within normal, with no significant difference compared to the midazolam group.[11]

Another study compared intranasal midazolam and intranasal dexmedetomidine for premedication in children undergoing adeno-tonsillectomy. It reported comparable baseline preoperative vital signs between the two groups. Also, no significant differences were reported after 10 and 20 minutes of intranasal drug administration ($P > 0.05$), but 30 minutes after premedication, the blood pressure and heart rate were

significantly higher in group M than in group D ($P < 0.05$). Oxygen saturation showed no significant difference between the studied groups ($P > 0.05$), and both drugs reported no desaturation throughout the procedure.[14] These hemodynamic changes were also observed in other studies and required no intervention.[15,16,17]

The current study sample was demographically homogeneous, which helped avoid potential bias in pre-anesthesia anxiety scores, but it has some limitations. For example, Dexmedetomidine intravenous form was used because the intranasal form is no longer available. Also, despite growing evidence that dexmedetomidine may be used safely in pediatric anesthesia, several nations, including the FDA, have suspended its usage. As a result, it remains an off-label drug. In addition, we did not assess the studied drug's sedative effect, so we recommend studying it in further studies. Furthermore, additional research with a larger sample is required to find the most accurate DEX dosages and to assess their safety and effectiveness in children.

Conclusion:

Paracetamol is as effective as dexmedetomidine in relieving preoperative anxiety in children undergoing

adenotonsillectomy. In addition, paracetamol harbors the advantage of being cheaper than dexmedetomidine.

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