



## Original Research Article

## Comparative effectiveness of intranasal dexmedetomidine dosing as premedication in paediatric surgery: Randomized controlled trial

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## ABSTRACT

**Background:** The use of alpha 2 agonists are now becoming the standard of care pre-medication drug in paediatric patients to induce induction and reduce separation anxiety. A prospective, randomized, double-blind, controlled study was designed to assess and compare the effectiveness and safety of two different strengths of intranasal dexmedetomidine in children between the ages of 2 and 8.

**Materials and Methods:** Sixty children between ages 2-8 years and of ASA physical status I or II scheduled for elective surgery were randomly assigned to one of two groups. Group A received 1 µg/kg of intranasal dexmedetomidine while Group B received 2 µg/kg as pre-medication. Patients sedation status, behaviour (mask acceptance) and parental separation scores were assessed over 30 min as primary endpoints along with its effect on haemodynamic and respiratory parameters over the same duration as secondary endpoints.

**Results:** 7.4% of children in group A while 96.5% of children in group B achieved a satisfactory sedation score, 11.1% of children in group A while 100% of children in group B achieved a satisfactory mask acceptance score and 7.4% of children in group A while 100% of children in group B achieved a satisfactory parent child separation score (p<0.001). We did not observe any clinically significant effects of dexmedetomidine on RR, SpO<sub>2</sub>, HR or MAP and no child required atropine or supplemental oxygen.

**Conclusions:** We conclude that 2µg/kg dose as compared to 1µg/kg offers multiple advantages of being good sedative, analgesic and anxiolytic in this age group when used as pre-medication.

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## 1. Introduction

Psychological trauma and anxiety caused by maternal deprivation are the major challenges in paediatric anaesthesia.<sup>1,2</sup> Preoperative anxiety often can lead to negative responses postoperatively which is displayed several ways including difficulty accepting anaesthesia masks or difficulty separating from parents.

Anxiety associated with operative procedures is reported to be as high as 60% and often is stressful for children & families.<sup>3,4</sup> Pre-anaesthetic medications should aim at

relieving this psychological trauma and anxiety in children in addition to facilitating anaesthesia induction without prolonging recovery along with having the properties of being acceptable and having a non-traumatic route of administration in order to reduce stress to the child which has led several drugs to be evaluated along with its route of administration to find the best sedative agent.

Children can still benefit from the intranasal route of premedication and sedation compared to IV administration because it is painless, non-invasive, and relatively easy. In addition, due to the presence of a rich blood supply of the airway mucosa and bypassing the first pass hepatic metabolism, the drug has a rapid onset of action with high

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bioavailability.<sup>1,5–9</sup>

Currently the most commonly used drugs are midazolam, ketamine and fentanyl. Various routes of clonidine, an alpha 2-adrenergic agonist, have been demonstrated to have superior sedative effects during induction, reduce agitation during emergency situations, and enhance early post-operative analgesia.

Dexmedetomidine, a relatively new highly selective alpha 2a adrenoreceptor agonist with anaesthetic and sedative properties thought to be due to G-proteins activation by the presence of alpha 2a receptors in the brainstem resulting in inhibition of norepinephrine release, with a short half-life and having a bioavailability of around (72.6–92.1%) when administered via the intranasal route.<sup>1,10,11</sup> One  $\mu\text{g}/\text{kg}$  dose of intranasal Dexmedetomidine produces satisfactory sedation in clinical trials.<sup>12</sup> There have been reports using higher doses of intranasal Dexmedetomidine.<sup>12,13</sup> It has been administered preoperatively to provide sedation without respiratory depression, reduce emergence delirium and postop negative behaviour such as aggression.

Aim of this analysis is to compare safety, efficacy, feasibility and sedation levels of intranasal Dexmedetomidine in two different doses of  $1\mu\text{g}/\text{kg}$  and  $2\mu\text{g}/\text{kg}$  as premedication in paediatric patients of age group between 2–8 yrs.

## 2. Materials and Methods

### 2.1. Design

The anaesthesiology department at a tertiary health care center conducted a prospective randomized double-blind controlled study between 2018 and 2020. The institutional ethics committee approved the study (2018/SC/1/26) and it complied with the Declaration of Helsinki and the international conference on harmonization and best clinical practice guidelines. Upon admission to the hospital and before surgery, all participants (parents/guardians) gave their informed consent.

### 2.2. Study population

A total of 60 children aged 2–8 years posted for minor elective surgical procedures like tonsillectomy, inguinal hernia, circumcision was selected for this randomized clinical trial in accordance with American Society of Anaesthesiologists (ASA) physical status I & II. A few of the exclusion criteria were absence of consent, known adverse reactions to dexmedetomidine (like hypotension/bradycardia/diaphoresis/fever), mental retardation, cerebral palsy, autism, recurrent epistaxis/nasal mass, uncorrected congenital heart disease, and use of analgesics or anticonvulsants during the perioperative period.

### 2.3. Intervention

The children were transported half an hour prior to sedation to the pre-medication room near the operating theatre with parental presence maintained throughout the process. The children were randomly assigned to one of two groups by a computer-generated algorithm. After placing the child in the recumbent position, Group A (n = 30) received  $1\mu\text{g}/\text{kg}$  dexmedetomidine intranasally (dripped into both nostrils), Group B (n = 30) received  $2\mu\text{g}/\text{kg}$  dexmedetomidine intranasally (dripped into both nostrils). About 30 minutes before induction of anaesthesia, all children received the study drug. A 1-ml tuberculin syringe was used to administer dexmedetomidine as a pure undiluted drug. An independent investigator prepared the study drugs without being involved in the child's observation or anaesthesia administration. Trained nursing staff who were not involved in the study's data collection administered the study drugs. There was no information provided regarding the dose of the drug administered to the child by the researcher/observer who attended clinical observations.

### 2.4. Methods of assessment

The response of the child to drug administration were recorded as follows (Table 1)

1. Level of sedation was assessed by using a five-point university of Michigan scale (0: Awake and alert, 1: Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound; 2: Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command, 3: Deeply sedated: deep sleep, arousable only with significant physical stimulation, 4: Unarousable. A sedation score of 3 and above was considered satisfactory.
2. Mask acceptance was evaluated by a 4-point scale: 1 = Poor (combative, crying), 2 = Fear (moderate fear of the mask), 3 = Good (cooperative with reassurance), 4 = Excellent (calm, cooperative, or sleeping). Mask acceptance scores of 3 and above was considered satisfactory.
3. Parent child Separation was evaluated by a 4-point scale: 1 = Calm and Cooperative, 2 = Anxious but reassuring, 3 = Anxious and not reassuring, 4 = Crying, or resisting. Parental separation scores of 2 or less was considered satisfactory.
4. Routine monitoring was performed before and after premedication which included respiratory rate (RR), oxygen saturation - peripheral (SpO<sub>2</sub>) and heart rate (HR) which were recorded at 5 min intervals for the next 30 min and plotted on a graph.
5. Sedation status, Behaviour status (mask acceptance and parent child separation) were assessed by a blinded observer every 5 min for the next 30 min

with a 4-point sedation scale (Table 1). Parents were allowed to accompany their children during induction if they refused to be separated from them. The study concluded when patient was transferred to the operation theatre.

### 2.5. Endpoints

Sedation scores at parental separation, anxiety at parental separation and quality of mask induction were the primary endpoints of this study, while secondary endpoints were changes in Respiratory rate (RR), Oxygen Saturation (SpO<sub>2</sub>), Heart rate (HR) and Mean arterial Pressure (MAP) during the sedation period. A note of adverse effects which included respiratory depression (RR < 12/min), desaturation (SpO<sub>2</sub> < 90% for 15 sec), and bradycardia (HR < 70 beats/min), were also made. A facemask of oxygen and/or intravenous atropine would be administered if RR, SpO<sub>2</sub>, or HR fell below expected levels.

### 2.6. Sample size

In prior studies, the administration of intranasal dexmedetomidine at a dosage of 1 µg/kg resulted in satisfactory sedation scores for 57% of subjects. To detect a 20% difference in satisfactory sedation scores at parent separation with an 80% power level and a significance level of 0.05 between the two groups, 29 children in each group would be needed to achieve a 20% increase after premedication with 2 µg/kg. To account for potential dropouts, we enrolled a total of 60 children.

The choice of a 30-minute study duration was informed by a study conducted by Yeun et al., in which they demonstrated that the median time (95% CI) for the onset of satisfactory sedation in children following the administration of 1 µg/kg of intranasal dexmedetomidine was 25 minutes.<sup>11</sup>

### 2.7. Statistical analysis

In addition to mean values, data are presented as medians with ranges or with a 95% confidence interval (CI) for proportions. The sedation, mask acceptance, and parental separation scores were compared using the nonparametric Mann–Whitney U-test, and the student's t-test was used to compare normally distributed continuous variables between the two groups. A chi-square test or Fisher's exact test was used to analyze categorical data. Statistical significance was determined by a p-value of 0.05.

## 3. Results

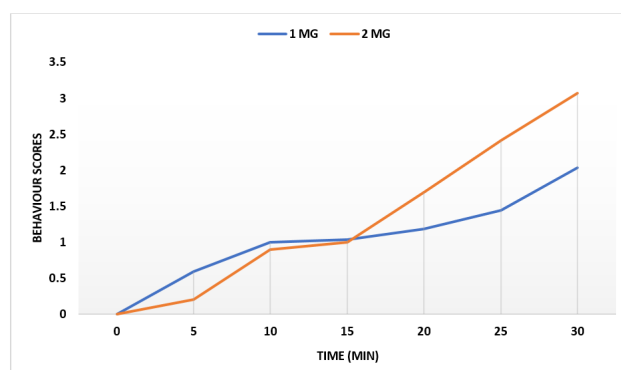
### 3.1. Patient characteristics in both groups (Table 2)

A total of 60 children were randomized and included in the trial. Demographic characteristics for all the children have been summarized in Table 2. Four of 60 (6.6%) children

resisted intranasal drug administration following which the parents withdrew consent, these included three children in group A (ASA Grade 2) and 1 in group B (ASA Grade 1). An analysis was not conducted on the children who refused to take the medication. None complained of pain or discomfort with Intranasal drug administration. In this study the mean age of patients in group A and group B were 5.70 years and 4.52 years respectively, the mean weight in group A and group B were 16.85 kgs and 13.86 kgs respectively, the mean height in group A and group B were 109.26 cms and 100.62 cms respectively and the mean duration of surgery in the groups were 82.78 min and 84.31 mins respectively.

### 3.2. Assessment of sedation, mask acceptance and behaviour at separation

The mean sedation scores of group A and group B were 2.04 ± 0.34 and 3.07 ± 0.37 respectively. The mean sedation scores at 5 min, 20 min, 25 min and 30 min were significantly different between the two groups (p = < 0.003, <0.001, <0.001 and <0.001 respectively). Moreover, 7.4% of children in group A and 96.5% of children in group B achieved a satisfactory sedation score (Figure 1).



**Figure 1:** Behaviour scores during pre-medication period

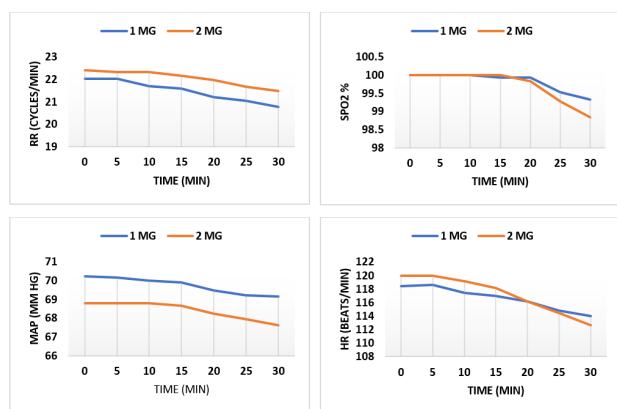
The mean mask acceptance scores of group A and group B were 1.78 ± 0.64 and 3.28 ± 0.45 respectively, the difference was statistically significant p < 0.001. Moreover, only 11.1% of children in group A while 100% of children in group B achieved a satisfactory mask acceptance score.

The mean parent child separation scores of group A and group B were 3.19 ± 0.56 and 1.72 ± 0.45 respectively, the difference was statistically significant p < 0.001. Moreover, only 7.4% of children in group A while 100% of children in group B achieved a satisfactory parent child separation score.

### 3.3. Haemodynamic and respiratory effects (Figure 2)

Overall, no clinically significant effects of dexmedetomidine was observed on RR, SpO<sub>2</sub>, HR or

MAP and none of the children required atropine or supplemental oxygen.



**Figure 2:** Hemodynamic and respiratory effects during pre-medication period (Top left) – Mean respiratory rate ± SD; (Top right) – Mean Oxygen saturation ± SD; (Bottom left) – Mean arterial pressure (Mean) ± SD; (Bottom right) – Mean Heart rate ± SD

There was a significant time effect i.e. time vs RR (x and y-axis) interaction on RR ( $p < 0.05$ ) after administration of dexmedetomidine in both the groups as RR reduced after administration of the drug i.e. in group A the RR reduced from 22/min to 20/min at 30 min while in group B the RR reduced from 22/min to 21/min at 30min but no significant difference between the groups were observed ( $p = 0.297$ ).

There was significant time effect i.e. time vs SpO2 (x and y-axis) interaction on SpO2 ( $p < 0.05$ ) after administration of dexmedetomidine in both the groups as there was a fall in SpO2 i.e. in group A the SPO2 changed from 100% to 99% at 30 min while in group B the SPO2 changed from 100% to 98% at 30min, but there was no significant different groups except only at 30<sup>th</sup> min in Group B after drug administration as compared to Group A ( $p = 0.038$ ).

There was significant time effect i.e. time vs HR (x and y-axis) interaction on HR ( $p < 0.05$ ) after administration of dexmedetomidine in both the groups as HR reduced after administration of the drug i.e. in group A the HR reduced from 118 beats/min to 113 beats/min at 30 min while in group B the HR reduced from 120 beats/min to 112 beats/min at 30min but no significant difference between the groups were observed ( $p = 0.604$ ).

There was a significant time effect i.e. time vs MAP (x and y-axis) interaction on MAP ( $p < 0.05$ ) after administration of dexmedetomidine in both the groups as MAP reduced after administration of the drug i.e. in group A, the MAP reduced from 70 mm Hg to 69 mm Hg at 30 min while in group B the MAP reduced from 68.79 mm Hg to 67.62 mm Hg at 30min but there was no significant different groups except only at 5<sup>th</sup> min in Group B after drug administration as compared to Group A ( $p = 0.048$ ).

**Table 1:** Evaluation scale

Sedation scores	
0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable
Mask acceptance scores	
1	Poor (combative, crying)
2	Fear (moderate fear of the mask)
3	Good (cooperative with reassurance)
4	Excellent (calm, cooperative, or sleeping)
Parent child separation scores	
1	Calm and Cooperative
2	Anxious but reassuring
3	Anxious and not reassuring
4	Crying, or resisting

**Table 2:** Characteristics of patients in both the groups

Category	Group A	Group B	p-value
Age (years)	5.7 ± 1.88	4.52 ± 1.82	0.083
Weight (kg)	16.85 ± 5.14	13.86 ± 3.54	0.140
Height (cm)	109.26 ± 13.41	100.62 ± 12.95	0.072
Duration of surgery (min)	82.78 ± 20.11	84.31 ± 32.67	0.201
Sex (M,F)	18, 9	24, 5	0.165
ASA	Grade 1 – 27	Grade 1 – 25	0.205
Grading	Grade 2 – 0	Grade 2 - 4	

Data shown as mean ± SD, unless otherwise specified.

#### 4. Discussion

Premedication in paediatric patients is intended to ease the stress and fear associated with surgery, promote a smooth induction of anaesthesia and ease parent child separation, the result is a reduction in postoperative behavioural disturbances caused by a bad preoperative experience. To avoid emotional trauma associated with parent-child separation and facemask application during anaesthesia induction, premedication needs must be tailored according to the child’s underlying medical condition, surgery length, and length of anaesthesia induction. It is possible to deliver drugs orally, rectally, intravenously, or intramuscularly, but well tolerated routes are intranasal and per-oral. Intranasal administration has numerous advantages, including ease of use, painlessness, non-first pass metabolism, and direct delivery of the drug to the CSF. With minimal respiratory depression, dexmedetomidine is both sedative and analgesic and highly selective alpha 2 agonist.

Among the 60 patients recruited for the study, 56 received the study drug, and the patients in both groups had comparable age, gender, weight, height, ASA grading of surgery (I and II), duration of surgery, and type of induction. Several studies have found that dexmedetomidine is dose-dependently sedating when given intravenously, so we expected that doubling the dose of intranasal dexmedetomidine would increase the proportion of patients with satisfactory sedation.<sup>14–16</sup> Petroz et al.<sup>17</sup> reported no difference in sedation levels in children between different intravenous dexmedetomidine doses of 0.33, 0.66 and 1  $\mu\text{g}/\text{kg}$  over 10 min. Despite the authors' assertions of the number of patients being small to detect any significant differences, it may actually be that insufficient plasma concentrations were achieved at the doses administered. When administered as a concentrated veterinary formulation (84  $\mu\text{g}$  in 0.2 ml) in adults the bioavailability of intranasal dexmedetomidine has been estimated at around 65%.<sup>18</sup> Young children have a smaller intranasal surface area than adults, which may result in less systemic drug absorption. Dexmedetomidine was demonstrated to sedate 75% and 92% of healthy adults after intranasal administration of 1 and 1.5  $\mu\text{g}/\text{kg}$ , respectively.<sup>11</sup> In this study, we found that 96.5% of children achieved satisfactory levels of sedation following intranasal dexmedetomidine treatment at 2  $\mu\text{g}/\text{kg}$ , compared to 7.4% after 1  $\mu\text{g}/\text{kg}$ . Multiple reports have also shown higher doses of intranasal dexmedetomidine to have a better sedation score even though some of them were not statistically significant.<sup>19,20</sup>

To determine the lowest effective dose, 1 and 2  $\mu\text{g}/\text{kg}$  intranasal dexmedetomidine were chosen in this preliminary study. Despite 1  $\mu\text{g}/\text{kg}$  intranasal dexmedetomidine's effectiveness as a sedative, it didn't work in the operating theatre when the children were transferred to the Operation theatre. This investigation showed that children who received 2  $\mu\text{g}/\text{kg}$  intranasal dexmedetomidine showed better behaviour at separation from parents and mask acceptance based on our behaviour and mask acceptance scale which is in accordance with other studies using higher doses of intranasal dexmedetomidine.<sup>19</sup>

It has been shown that 2-agonists - dexmedetomidine produce modest reductions in BP in a dose dependent fashion ranging from 14 to 27% and also on HR when infused as an IV bolus over 2 minutes of 0.25 to 2  $\mu\text{g}/\text{kg}$  in healthy volunteers.<sup>15</sup> Significant reductions of SBP (<25% compared with baseline) and HR (<15% compared with baseline) were observed in children receiving 1 and 0.66  $\mu\text{g}/\text{kg}$  IV dexmedetomidine respectively given over 10 min in a pharmacokinetic study.<sup>17</sup> When children were sedated with an initial dose of 1  $\mu\text{g}/\text{kg}$  IV dexmedetomidine followed by a maintenance infusion, Munro et al. reported a reduction of blood pressure and

heart rate by <20% of baseline.<sup>20</sup> But when used as an intranasal formulation/administration neither Pavithra et al. nor Wang et al. could find any statistical difference in hemodynamic parameters between the two groups.<sup>21,22</sup> We also found no significant differences in RR, SpO<sub>2</sub>, HR, and MAP between preoperative 1 and 2  $\mu\text{g}/\text{kg}$  intranasal dexmedetomidine in healthy children during the first 30 min after drug administration which could probably also be due to the short follow-up time.

## 5. Limitations

1. It is difficult to draw a conclusion on impact of dexmedetomidine on different age groups as this study did not investigate the sedative effects of intranasal dexmedetomidine on the same.
2. Some children did not achieve a satisfactory sedation score, which may be attributed to the short 30-minute premedication period.
3. The study did not assess the onset time, peak effect, or blood concentrations of intranasal dexmedetomidine.
4. Various other variables that could influence behaviour scores, such as the child's age, prior medical experiences, and parental anxiety, were not evaluated.

## 6. Conclusion

In this study dexmedetomidine was administered at a dose of 2  $\mu\text{g}/\text{kg}$  as intranasal pre-medication to children aged 2-8 years. The results indicated that this dosage provided satisfactory sedation, mask acceptance, and favourable behaviour scores (parent separation). Importantly, it did so without causing adverse hemodynamic or respiratory effects when compared to the 1  $\mu\text{g}/\text{kg}$  dose. These findings suggest that a 2  $\mu\text{g}/\text{kg}$  dose offers the advantage of serving as an effective sedative, analgesic, and anxiolytic agent in this specific age group when used as pre-medication.

Based on these results, we recommend the use of 2  $\mu\text{g}/\text{kg}$  dexmedetomidine for pre-medication in children aged 2-8 years. This dosage effectively mitigates the increase in mean arterial pressure (MAP), attenuates the rise in heart rate (HR) resulting from intubation, and enhances sedation.

## 7. Future Research

There is potential for future studies to examine the sedative effects of intranasal dexmedetomidine on children of different ages.

## 8. Source of Funding

None.

## 9. Conflict of Interest

None.

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