

## A Double Blinded Comparative Study of Intranasal Dexmedetomidine as a Premedicant in Children

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### Abstract

**Background:** The pre-anesthetic management in children can be challenging. The centrally acting alpha2 agonist, Dexmedetomidine provides unique sedation, with quick arousal and minimal respiratory depression. These properties render the sedative and hemodynamic effects of intranasal dexmedetomidine in children.

**Methods:** This is a prospective double-blinded comparative study in 90 children aged 2 to 9 years of age allotted to one of 3 groups, 30 children in each group- Group NS, SD and DD receiving intranasal normal saline, 1mcg/kg of intranasal dexmedetomidine and 2mcg/kg of intranasal dexmedetomidine respectively. The premedication time was 60 mins after drug administration. Baseline measurements of HR, spo2 were noted and every 10 mins after the drug was administered. Sedation at the time of parenteral separation and at the time of induction and Behaviour scores were noted for mask/IV cannula acceptance.

**Results:** Intranasal dexmedetomidine was well tolerated in both the groups with no side effects of nasal irritation, or bradycardia or respiratory depression. Both drug groups produced significant and satisfactory sedation when compared to the control group. 1mcg/kg and 2mcg/kg provided similar rates of sedation with no statistically significant difference between them.

**Conclusion:** The intranasal route is safe, effective and convenient to use for administration of dexmedetomidine in children. Further studies are needed to evaluate the dosing regimen and routine use of dexmedetomidine as a premedication in pediatric anesthesia.

### I. Introduction

The pre-anesthetic management of children can be a challenge to the anesthesiologist because children are usually uncooperative and anxious. Inadequate handling of an uncooperative child pre-operatively and children who are extremely anxious during induction of anesthesia are extremely at risk of developing post operative behaviour problems compared to children who appear calm during induction. Various methods available to decrease anxiety are: sedative premedication, parenteral presence during induction and pre operative preparation programs. In children pre anesthetic medications are administered as pharmacological adjuncts to

-alleviate stress and fear of surgery

-ease child parenteral separation

-smoothen induction

Various methods of drug delivery are oral, rectal, IV, IM but intranasal and oral routes are well tolerated. The intranasal route is advantageous in that it is easy to use, painless, avoids first pass metabolism and the drug is directly delivered to CSF through nose-brain pathways. It has its own limitations eg. fewer drugs availability and mucosal health may also impact absorption. Dexmedetomidine is a potent, highly selective, and specific alpha2 agonist that has both sedative and analgesic effects with minimal respiratory depression. Unlike traditional gabaminergic sedative drugs, such as midazolam, the primary site of action of Dexmedetomidine is the locus ceruleus rather than the cerebral cortex. Therefore its induced sedation is characterized by an easy and quick arousal from sedation resembling natural sleep. Other undesirable effects of midazolam including restlessness, paradoxical reaction, and negative postoperative behavioral changes have made it a less than ideal premedication. Several case reports<sup>1</sup> are available on use of iv Dexmedetomidine for sedation in radiographic investigations and recent studies show use of Intranasal Dexmedetomidine for pre-procedural sedation in children undergoing general anesthesia.

### II. Aims & Objectives:

This prospective study was designed to assess the sedative effects of IN Dexmedetomidine using 2

different doses of 1mcg/kg and 2 mcg/kg along with normal saline as a control group in pediatric patients.

### III. Materials And Methods:

This is a prospective, randomised, double blinded control study undertaken in King George Hospital, Visakhapatnam after obtaining clearance from Institutional Ethics Committee. Informed consent was taken from parents and children aged 2 to 9 years of ASA classification 1 and 2 undergoing elective surgical procedures were included in this study. Children with known hypersensitivity to study drug, presence of any nasal pathology and children with congenital heart disease, including arrhythmias or heart blocks and respiratory illness were excluded from this study. Ninety Children were randomly allocated to one of three groups; normal saline (Group NS) intranasal dexmedetomidine 1mcg/kg. (Group SD) or intranasal dexmedetomidine 2mcg/kg (Group DD). The randomization list was generated by an independent statistician who was not involved in data collection or analysis. Preservative-free dexmedetomidine in a concentration of 100 mcg/ml parenteral preparation was used. The study drug was prepared in a 1-ml syringe by an independent anesthetist. If recruited children were assigned to Group SD, dexmedetomidine was diluted with an equal volume of 0.9% saline; if assigned to Group DD, then Dexmedetomidine was not diluted. The final volume of administered solution was 0.02 ml/kg. An equal volume of drug was dropped into each nostril by a blinded research assistant. The premedication time of 60 minutes<sup>3</sup> was taken. Baseline measurements of Heart rate, Spo2 were observed and thereafter every 10min after intranasal drug administration until transfer to the operating theatre. Following intranasal drug administration, Sedation score (modified from the Observer Assessment of Alertness and Sedation Scale) at the time of parenteral separation and at the time of induction and Behaviour score for mask or IV cannula acceptance were assessed by a blinded observer. Inhalational or intravenous mode of induction was decided by the attending anesthesiologist depending on the sedation and behaviour characteristics of the child.

Table 1: SEDATION SCORE (assessed during separation from parents and at induction)

1	Does not respond to mild prodding or shaking
2	Responds only mild prodding or shaking
3	Responds only after name is called loudly or repeatedly
4	Lethargic response to name spoken in normal tone
5	Appear asleep but respond readily to name spoken in normal tone
6	Appear alert and awake, response readily to name spoken in normal tone

Table 2: BEHAVIOUR SCORE (Assessed at the time of mask or IV cannula acceptance)

1	Calm and cooperative
2	Anxious but reassuring
3	Anxious and not reassuring
4	Crying, or resisting

For statistical analysis, sedation scores were categorized as being satisfactory when rated between 1 and 4 and unsatisfactory when rated 5 or 6. Behavior scores were categorized as satisfactory when they were 1 or 2, and unsatisfactory when they were 3 or 4. Demographic data and hemodynamic variables were analysed by analysis of variance (ANOVA). Sedation and behaviour scores were analysed using Chi-square test. A p value of less than 0.005 was considered to be statistically significant.

### IV. Results

The demographic data is summarised in table 3. Patients in all the three groups were similar with respect to age, weight, gender, and age distribution in the age groups of 2 to 5 years and 6 to 9 years. The heart rate variability was assessed and showed a statistically significant decrease in heart rate after administration of intranasal dexmedetomidine of 1mcg/kg and 2mcg/kg as shown in table 4, but there were no incidences of bradycardia necessitating any intervention. No child complained of pain or showed signs of nasal irritation.

TABLE 3:

	GROUP NS n=30	GROUP SD n=30	GROUP DD n=30
Age(in years)	5.4	5.2	5.4
Weight(in kg)	17.5	16.1	18.3
Male/female	17/13	18/12	17/13
Age distribution			
2-5	16	17	17
6-9	14	13	13

Dexmedetomidine had no effect on oxygen saturation levels. Table 5,6 shows the proportion of children who were satisfactorily sedated at the time of parenteral separation and at the time of induction. Table 7 shows the results for Behaviour Scoring. On comparison to the control group, satisfactory sedation status was achieved in both the drug groups with the p value being significant but the satisfactory sedation achieved in both groups receiving 1mcg/kg and 2mcg/kg were similar in results with no statistical significant difference between them. The results were similar when assessing the Sedation status at the time of parenteral separation and at the time of induction and also with the Behaviour scoring for either mask or intravenous cannula acceptance.

TABLE 4:

	GROUP NS	GROUP SD	GROUP DD
Min.	83	81	78
Max.	143	135	141
Mean	112.56	107.27	107.86
Std. dev.	17.24	12.35	14.50
p value	0.953	0.003	0.001

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TABLE 5:  
**SEDATION AT SEPARATION FROM PARENTS**

	GROUP SD	GROUP DD
N	17(54.8%)	14(45.2%)
S	13(44.8%)	16(55.2%)

p=0.303

	GROUP SD	GROUP NS
N	17(38.2%)	30(68.8%)
S	13(100%)	0(0.0%)

p=0.000

	GROUP DD	GROUP NS
N	14(31.8%)	30(68.2%)
S	16(100%)	0(0.0%)

p=0.000

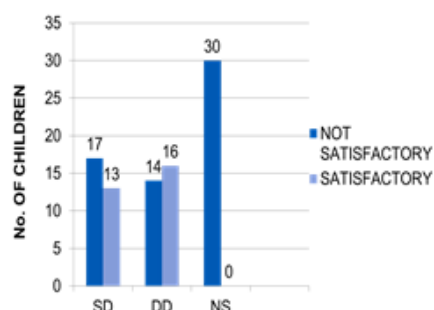


TABLE 6:

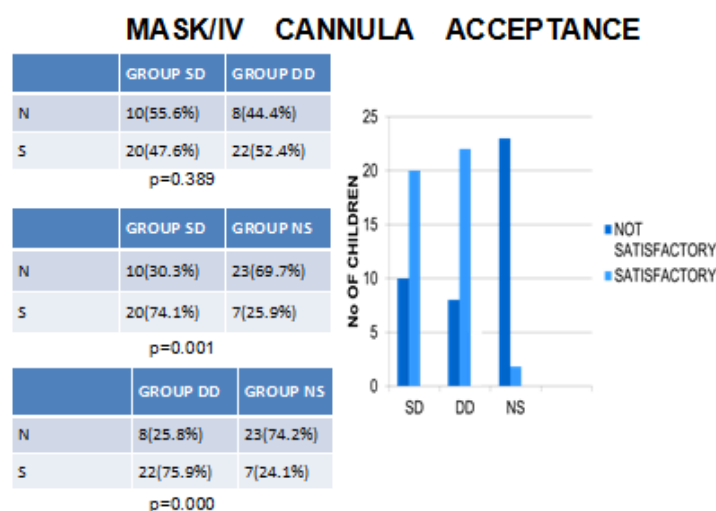
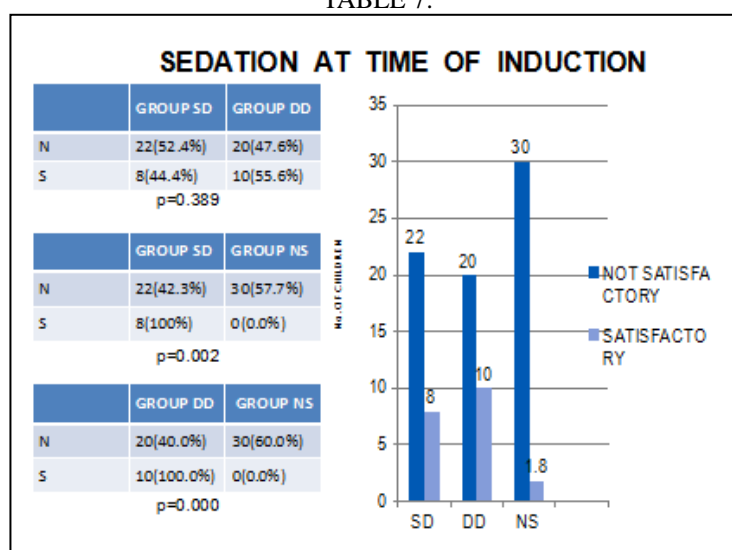


TABLE 7:



Intranasal Dexmedetomidine used pre-operatively in pediatric anaesthesia is especially useful in extremely anxious and uncooperative children as observed by Kain et al<sup>11</sup> in relation to post operative behaviour problems. Kain et al<sup>11</sup> determined that a patient's anxiety level influences their immediate postoperative outcomes as well as long-term outcomes after discharge. Previous studies<sup>1,2-8</sup> have shown that intranasal administration is an effective way to administer premedication and sedation to children. It is a relatively easy and noninvasive route with a high bioavailability. However, cooperation is still required and it may be more difficult in younger children. Oral administration may be even more difficult in uncooperative children and compliance is easier with intranasal route than oral. Intranasal midazolam produces local signs of nasal irritation<sup>9</sup>, which was avoided with intranasal dexmedetomidine, not seen in any of study children. The main advantage of dexmedetomidine lies in the fact that the patients are sedated but are easily arousable<sup>13</sup> which resembles natural sleep and also there were no incidences of bradycardia or respiratory depression or any untoward incidents.<sup>14</sup> However, the ideal premedication drug and the route of administration is still debatable. The onset time for intranasal Dexmedetomidine is relatively prolonged paralleling a prolonged premedication time. Yuen et al<sup>2</sup> used two doses of intranasal dexmedetomidine-0.5 and 1 mcg/ kg for premedication in healthy children aged 2 to 12 years. In their study, the premedication period was 45–60 min, and effective sedation was achieved within that time period in children who received 1 mcg/ kg. The optimal timing<sup>3</sup> for the administration of 1 mcg/ kg intranasal dexmedetomidine for premedication in children was judged based on intravenous cannulation attempts at different time points after premedication. The median time for sedation onset was found to be 25 (25–30) min. In Yuen et al<sup>4</sup>. study, children who received a dose of intranasal dexmedetomidine similar to the dose utilized in our study (1 mcg/ kg) were significantly more sedated when they were separated from

their parents and at the time of anesthesia induction compared to those who received oral midazolam 0.5 mg/ kg, We hypothesised that 2mcg/kg produces more satisfactory sedation when compared to 1mcg/kg based on previous studies<sup>10</sup>.The discrepancy between our results and theirs may be attributed to pharmacokinetic factors<sup>15,16</sup> including different age groups, children characteristics, and dissimilar sedation scores.We used simple nasal drops administration instead of nasal spray or mucosal atomisation device<sup>12</sup>We did not evaluate the onset time and peak effect of the two doses of intranasal dexmedetomidine or the blood concentrations.In this study, the premedication period was 60 min for intranasal dexmedetomidine.If a longer premedication period had been taken,possibly more subjects could have attained satisfactory sedation at separation from parents and at induction of anesthesia.The sedation produced by dexmedetomidine differs from other sedatives as patients may be easily aroused and cooperative. Some children who were premedicated with dexmedetomidine became distressed when they were aroused at the induction of anesthesia, despite being very much sedated at the time of parental separation. Anesthetic technique may need to be adjusted to provide optimal conditions for induction in children sedated with dexmedetomidine.

## VI. Conclusion

Intranasal Dexmedetomidine is well tolerated without producing any side effects.1mcg/kg and 2 mcg/kg produced similar levels of sedation in children premedicated with intranasal dexmedetomidine.The utility of Dexmedetomidine in clinical practice is expanding because of its unique sedative,anxiolytic and analgesic properties.However future studies are warranted to provide optimal dose,timing of administration and role of intranasal route in clinical settings.

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