Original Article

Comparison of intranasal and nebulized dexmedetomidine for premedication in pediatric patients: A non-inferiority randomized controlled trial

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Abstract

Background and Aims: Dexmedetomidine is a highly selective α-2 adrenoreceptor agonist and has been found to be an effective premedication agent when administered via the intranasal route. We aimed to compare the efficacy of dexmedetomidine premedication administered via intranasal route and through nebulization in pediatric patients.

Material and Methods: This non-inferiority randomized controlled trial was conducted after getting approval from institutes ethics committee and informed written parental consent. Sixty-four children aged 2-8 years scheduled for elective surgery under general anesthesia were enrolled and were divided into two groups. Group I (Intranasal, n = 33) received 2 mcg/kg dexmedetomidine via intranasal route and group N (Nebulized, n = 31) received 2 mcg/kg dexmedetomidine through nebulization. The primary outcome was number of patients with satisfactory sedation 30 minutes after premedication at separation from parent. The secondary outcome included ease of medication acceptance, anxiety at parental separation, acceptance of anesthesia mask, perioperative hemodynamics, emergence agitation during recovery and adverse effects. Data collected was analyzed using Chi-square test, Student "t" test and Mann-Whitney U test with the help of SPSS 22. A one tailed P value < 0.025 was considered significant.

Results: Demographic profile was comparable between groups. On arrival in OR 27 (81.8%) patients in group I and 21 (67.7%) patients in group N had satisfactory sedation score ($P = 0.19$). The median (IQR) sedation score was comparable between group I and group N ($P = 0.057$). Patients in Group I showed significantly better medication and mask acceptance scores ($P < 0.0001$, $P = 0.001$ respectively), parental separation anxiety score ($P < 0.0001$) and emergence agitation score ($P = 0.001$). There were no significant differences in hemodynamic parameters and adverse effects between the groups.

Conclusion: Although nebulized dexmedetomidine is non-inferior to intranasal dexmedetomidine in providing desired level of sedation but intranasal administration had better acceptance of medication and anesthesia mask with lesser anxiety at parental separation and postoperative emergence agitation.

Keywords: Dexmedetomidine, intranasal, nebulization, premedication

Introduction

Surgery and anesthesia may induce tremendous emotional stress upon children. Preoperative anxiety stimulates sympathetic, parasympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability.[1,2] Premedication facilitates smooth induction of anesthesia by reducing the child's stress and anxiety on

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separating them from their parent. An ideal premedicant should be easily acceptable, effective when administered via different routes, and have a rapid and reliable onset with minimal side effects. Various drugs have been used via different routes with varying degree of acceptability.[3-6]

Dexmedetomidine is a highly selective α-2 adrenoreceptor agonist and possesses sedative, analgesic and anxiolytic properties without respiratory depression.[7] Its colorless and odorless properties have made its use suitable for oral, buccal, transdermal and intranasal administration.[8] Various studies have evaluated the efficacy of intranasal administration of dexmedetomidine and have very well proven its role for premedication in the pediatric age group.[9,10] Administration of dexmedetomidine in a nebulized form is a relatively newer approach which allows rapid drug absorption through the nasal, respiratory and buccal mucosa.[11,12]

With the hypothesis that as a premedication agent, administration of dexmedetomidine via nebulization is not inferior to that when administered via intranasal route. The aim of this study was to compare the efficacy of dexmedetomidine premedication administered via intranasal route and through nebulization in pediatric patients.

Material and Methods

This study was conducted at AIIMS, Jodhpur, after obtaining approval by the institute's ethical committee (AIIMS/IEC/2016/675 dated 26/09/2016) and written informed consent from parents of all children participating in the trial. Sixty-four patients, aged between 2 to 8 years, belonging to American Society of Anesthesiologists (ASA) physical status I/II and scheduled for all types of elective surgery (through Dec 2016 to May 2018) lasting for less than 2 hours under general anesthesia (GA) were enrolled. Exclusion criteria included were parental refusal, children having chronic illness, difficult airway, congenital heart disease, surgery with more than two hours duration, known allergy to study drug, intraoperative or postoperative regional anesthesia and emergency and laparoscopic surgeries.

During preoperative assessment, detailed history, general physical and systemic examinations were done. Patient's particulars, demographics and baseline vital parameters were recorded. Investigations as per the individual requirement were carried out. Fasting as per institutional protocol (2 h for clear liquid and 6 h for semisolid and solid) was advised.

Patients were randomly divided into two groups using a computer-generated randomization sequence. Group I (Intranasal, n = 33), received 2 mcg/kg intranasal dexmedetomidine and Group N (Nebulized, n = 31), received 2 mcg/kg nebulized dexmedetomidine. To ensure allocation concealment, the opaque envelope method was used which was opened prior to surgery. Single blinding was ensured as the physician who administered the premedication was not involved in data collection and the person involved in the data collection was unaware of the group allocation and premedication administered.

The drug for intranasal route was instilled through a tuberculin syringe evenly into both nostrils. Volume administered in each nostril was 0.01 ml/kg of undiluted drug. Patients were made to lie supine for 10 minutes after instillation of drug. The drug for nebulization was prepared in 3 ml of 0.9% saline and was administered through a standard hospital jet nebulizer (with oxygen flow @ 6-8 L/min). Treatment was stopped after about 10 to 15 minutes when the nebulizer began to sputter. The study drug for both groups was prepared and administered by an independent observer not involved in the further assessment while the assessment of the child at predefined time interval was done by another observer who was unaware of the group allocation. The nature of the intervention did not allow us to make the patient blinded to the allocated intervention.

On the day of surgery in preoperative holding area, baseline parameters like heart rate (HR), mean blood pressure (MBP), peripheral oxygen saturation (SpO_2) and sedation score using Modified observer assessment of alertness score[13] (6-Appears alert and awake, responds readily to name spoken in normal tone; 5-Appears asleep but responds readily to name spoken in normal tone; 4-Lethargic response to name spoken in normal tone; 3-Responds only after name is called loudly or repeatedly; 2-Responds only after mild prodding or shaking; 1-Does not respond to mild prodding or shaking; 0-Does not respond to noxious stimulus) were recorded. The premedication was administered as per the group allocation. After premedication, acceptance of the medication was assessed using medication acceptance score[14] (1-Excellent, accepted medication without complaint; 2-Good, complained, was briefly tearful or unhappy, but then accepted medication; 3-Fair, complained, initially uncooperative but eventually accepted medication; 4-Poor, refused medication) and recorded. After premedication, patients were monitored continuously by a blinded observer. Thirty minutes after completion of premedication HR, MBP, SpO_2 and sedation score was recorded and patients were shifted to operating room (OR). Sedation level was considered satisfactory at a score of 3 or 4 on sedation scale. Anxiety score[15] (1-easy separation, 2-whimpers, but is easily reassured, not clinging, 3-cries and cannot be easily reassured, but not clinging to parents, and 4-crying and clinging to parents) at parental separation was also recorded.

In the OR, anesthetic technique was standardized in all patients. Anesthesia was induced with sevoflurane 8% in oxygen. An intravenous (IV) cannula was placed and balanced crystalloid solution was started at 4 ml/kg/hr. Patients then received IV fentanyl 2 mcg/kg, IV propofol 1 mg/kg and IV atracurium 0.5 mg/kg. Endotracheal tube (ETT) or laryngeal mask airway (LMA) of suitable size was inserted as per the choice of attending anesthesiologists. At induction HR, MBP, SpO_2 and face mask acceptance score using mask acceptance scale[15] (1-Excellent, accepted face mask without complaint; 2-Good, complained, was briefly tearful or unhappy, but then accepted face mask; 3-Fair, complained, initially uncooperative but eventually accepted face mask; and 4-Poor, refused face mask) was recorded. Anesthesia was maintained with sevoflurane in a 50% oxygen/air mixture. Intraoperative analgesia was maintained with intermittent boluses of IV fentanyl (1 mcg/kg/hr) and IV paracetamol (15 mg/kg). At the end of the procedure, residual neuromuscular blockade was reversed with a combination of IV neostigmine (0.05 mg/kg) and IV glycopyrolate (0.01 mg/kg) and the ETT or LMA was removed.

In the recovery room, vitals and emergence agitation using a four-point scale[14] (1-Calm and cooperative; 2-Anxious but reassurable; 3-Anxious and not reassurable; and 4-Crying, or resisting) was recorded at 0 and 30 minutes. Perioperative adverse events such as hypotension, bradycardia, respiratory depression and vomiting were noted and recorded. Significant hypotension or bradycardia was defined as more than 20% reduction of the baseline values. For bradycardia injection atropine 10 mcg/kg was administered and hypotension was treated by fluid boluses. Respiratory depression was defined as requirement of supplemental oxygen to maintain SpO_2 of ≥95%.

Sample size was calculated based on the primary outcome measure of our study, i.e., number of patients with adequate sedation at 30 min after the end of study drug administration. Based on a previous study,[13] the fraction of patients in whom intranasal dexmedetomidine provided satisfactory sedation on arrival to the operating room was 0.66. We assumed that to be clinically non-inferior, the fraction of patients in whom nebulized dexmedetomidine provided satisfactory sedation on arrival to the operating room would be 0.45. Thirty-one patients in each group were sufficient to detect this difference at noninferiority limit of 1 with a power of 90% and a one tailed type I error of 2.5%.[16]

Data collected during the study were compiled using Microsoft Excel spreadsheet and was analysed using Statistical Package for Social Sciences version 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp., NY, USA). Normality of data was tested with Kolmogorov–Smirnov one-sample test. Data were presented as mean ± standard deviation (SD) for normally distributed quantitative variables and as median (IQR) for ordinal variables and quantitative variables with non-normal distribution. Categorical variables were presented as absolute numbers or percentages. Student's *t* test and $\chi 2$ test was used to analyse continuous and categorical data respectively. Quantitative variables with non-normal distribution and ordinal variables were analysed with Mann-Whitney test. One tailed *P* value < 0.025 was considered as significant.

Results

A total of 85 participants were initially screened, out of them twenty-one (sixteen not meeting inclusion criteria and five refused to participate) were excluded [Figure 1]. Demographic profile (age, gender, ASA grading and weight), baseline parameters (HR, MBP, and SpO_2) and surgical duration were comparable between the groups [Table 1].

On arrival in OR 27 (81.8%) out of 33 patients in group I and 21 (67.7%) out of 31 patients in group N had satisfactory sedation score ($P = 0.19$). There was no difference in the median (IQR) sedation score on arrival in OR between group I [3 (3, 4)] and group N [3 (3, 4)] (p0.057) [Table 2]. However, patients in group I had significantly better acceptance of medication, parental separation anxiety, mask acceptance and emergence agitation scores [2 (1, 2); 2 (1, 3); 2 (2, 3) and 2 (2, 3) respectively] compared to those patients in group N [2 (1, 3); 3 (1, 3); 3 (2, 3) and 2 (1, 3) respectively] ($P < 0.025$) [Table 2]. Figure 2 compare the number of patients with individual score (sedation, medication and mask acceptance, parental separation anxiety and emergence agitation) between both groups.

The HR and MAP recorded at various time points were comparable between groups as well as within group ($P > 0.025$) [Figure 3]. None of the patient in both groups had any adverse effects during the period of observation.

Discussion

Our study demonstrated that administration of dexmedetomidine via intranasal instillation and nebulization for premedication in pediatric patients provide desired level of sedation (sedation score 3 or 4, 30 min after administration) in 81.8% and 67.7% patients respectively. Although most of the

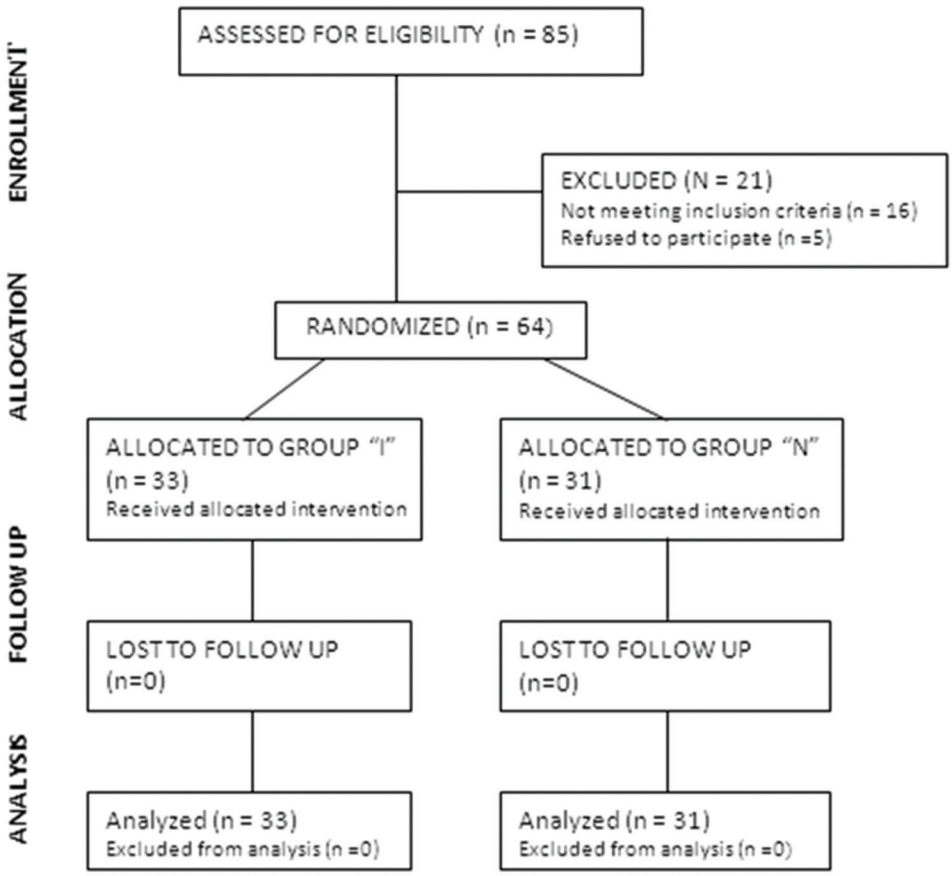

Figure 1: Consort flow diagram

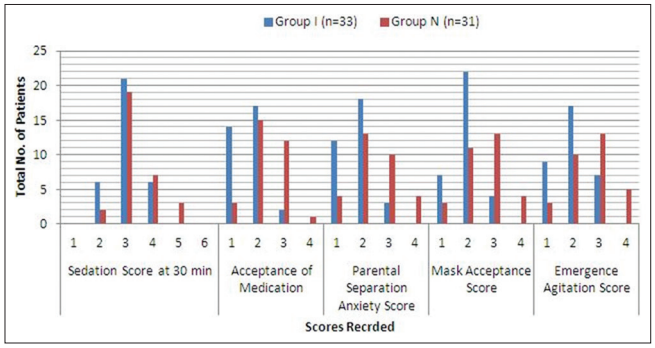

Figure 2: Comparison of various scores between two groups

Table 1: Comparison of demographic variables, duration of surgery and baseline vitals between groups

Parameters	Group I (*n*=33)	Group N (*n*=31)
Age (years)[a]	4.9±1.9	4.5±2.1
Gender (M/F)[b]	23/10	20/11
ASA (I/II)[b]	30/3	27/4
Weight (kg)[a]	15.0±3.3	13.8±3.8
Duration of surgery (in minutes)[a]	82.1±36.2	88.9±34.2
Baseline Heart rate (beats per minutes)[a]	104.1±17.1	106.9±17.1
Baseline mean arterial pressure (mmHg)[a]	72.6±7.6	71.6±8.3
Baseline Oxygen Saturation (%)[a]	99.2±0.7	99.0±0.9

[a]*Values presented in Mean±SD;* [b]*Values presented in numbers*

patients achieved desired sedation level in both groups, patients receiving intranasal dexmedetomidine had better medication and mask acceptance, and less parental separation anxiety and emergence agitation score compared to patients receiving nebulized dexmedetomidine. Both routes of administration were safe with regard to hemodynamic changes and adverse effects.

The preoperative period can be a traumatic time for children undergoing surgery. Pediatric anesthesiologists strive to minimize distress for children in the OR environment and to provide a smooth induction of anesthesia.[17] Premedication with various sedatives and analgesics administered through various routes for minimizing this distress have been studied, with varying degrees of patient acceptance, efficacy and safety.[2,18-20]

Dexmedetomidine might be considered as most suitable among the available premedication agents with its anxiolytic, sedative, and mild analgesic properties. It has been administered through various routes for pediatric sedation especially for non-painful procedures with each route having varying degree of acceptability.[5,6,8,9]

Table 2: Comparison of Baseline sedation score, Sedation score at 30 min, Acceptance of medication, Parental separation anxiety score, Mask acceptance score, and Emergence Agitation score between groups

Parameters	Group I (*n*=33)	Group N (*n*=31)	*P*	95% Confidence Interval
Baseline Sedation Score	6 (6, 6)	6 (6, 6)	0.43	(-0.211 to 0.284)
Sedation Score at 30 min	3 (3, 4)	3 (3, 4)	0.057	(-0.109 to 0.396)
Acceptance of Medication	2 (1, 2)	2 (1, 3)	<0.0001	(0.390 to 1.047)
Parental Separation Anxiety Score	2 (1, 3)	3 (1, 3)	<0.0001	(0.370 to 1.032)
Mask Acceptance Score	2 (2, 3)	3 (2, 3)	0.001	(0.311 to 1.032)
Emergence Agitation Score	2 (2, 3)	2 (1, 3)	0.001	(0.306 to 1.015)

Values are presented in Median (IQR)

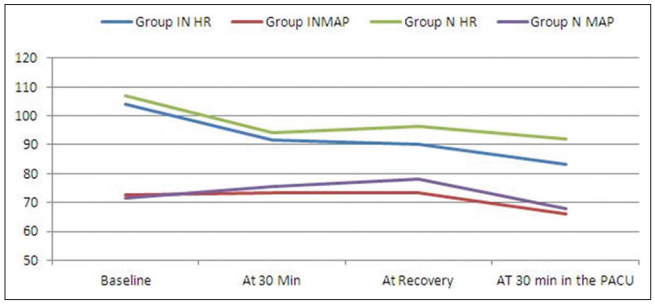

Figure 3: Comparison of heart rate and mean arterial blood pressure at different time interval between groups

Administration of a drug through intranasal route in pediatric patients is relatively easy, needle-free and effective that provide direct systemic absorption by bypassing hepatic first-pass metabolism and may also produce effects by direct nose to brain delivery, potentially via the olfactory and trigeminal nerves, bypassing the blood brain barrier.[21] The bioavailability of intranasal dexmedetomidine was found to be higher compared to bioavailability after oral and buccal administration but lower than those after intramuscular and intravenous administration.[22-24] The median absolute bioavailability of intranasally administered dexmedetomidine was reported to be 83.8% (69.5%-98.1%) in children.[24] The intranasal delivery can be accomplished by either atomizer or drops and both techniques have been found to be equally effective leading to increasing its use as a pediatric premedication and procedural sedation.[25] Recent systemic reviews and meta-analysis on sedative effects of the intranasal dexmedetomidine in children undergoing surgeries demonstrated that intranasal dexmedetomidine provided more satisfactory sedation at parent separation without producing respiratory depression and reduced the need for rescue analgesics compared to other sedation methods.[9-10] Various doses [(1 mcg/kg versus 2 mcg/kg)[26] and (2 mcg/kg versus 3 mcg/kg)[27]] of intranasal dexmedetomidine have been shown to provide satisfactory sedation in 53% versus 66% and 90% versus 93% patients respectively. Similar to our results Li *et al.*[25] also found successful sedation in 82.5% (95% CI 75.3–87.9%) and 84.5% (95% CI 77.7–89.5%) patients who received intranasal dexmedetomidine sedation either by an atomizer or by drops, respectively ($P = 0.569$). They reported similar sedation success rate in both groups proving that increasing the dose from 2 mcg/kg might not translate into higher success rate. Also, the use of higher doses of intranasal dexmedetomidine has been shown to significantly prolong length of stay in the PACU.[28] Behrle *et al.*[29] also reported similar success rate (92%) and a longer post procedure sleep time ($P < 0.001$) which had a significant effect on recovery time (p0.024) in patients receiving 3 mcg/kg intranasal dexmedetomidine.

Nebulization of dexmedetomidine for premedication is a relatively newer approach that provides rapid drug absorption through nasal, respiratory and buccal mucosa with a bioavailability of 65% through nasal mucosa and 82% through buccal mucosa.[8,24] Data on pharmacokinetics for nebulized route are limited. We selected the same dose of dexmedetomidine for administration through either route based on previous studies that proved the clinical effectiveness of this dose administered through intranasal route. Previous studies have compared the intranasal and nebulized route of drug administration for pediatric premedication using different drugs[18,19] but none of them have directly compared dexmedetomidine administered via both routes. Nebulized dexmedetomidine in a dose of 3 mcg/kg and 2 mcg/kg has been shown to produce satisfactory sedation leading to parental separation anxiety scale score of 1 in 63.3% and 65.5% patients respectively (p 0.861) and mask acceptance scale score of 1 in 53.3% and 55.2% patients respectively (p0.887).[30] Compared to nebulized ketamine (2 mg/kg) and midazolam (0.2 mg/kg), nebulized dexmedetomidine (2 mcg/kg) had more satisfactory sedation, shorter recovery time, and less postoperative agitation.[11] Addition of ketamine 1 mg/kg to nebulized dexmedetomidine (1 mcg/kg) has been shown to produce synergistic effect leading to more satisfactory sedation, more smooth induction of GA, with more rapid recovery and no significant side effects.[12] In a study on 17,948 pediatric patients receiving a combination of 2 mcg/kg of dexmedetomidine and 1 mg/kg of ketamine intranasally for procedural sedation demonstrated a sedation success was 93%.[31]

Both the routes of administration for dexmedetomidine were well tolerated as none of the patients in our study had any complication. However, intranasal dexmedetomidine administration is easy, convenient and well tolerated whereas for nebulization cooperation is still required especially in younger children as demonstrated by better medication acceptance score in patients receiving intranasal dexmedetomidine.

Dexmedetomidine possesses protective effects against postoperative emergence agitation however the degree of protection is dependent on the route of administration. We found that intranasal route provide better protection against postoperative emergence agitation compared to nebulized route. The reason for higher incidence of emergence agitation in nebulized group may be accounted for the lower bioavailability in comparison to intranasal route. Mc Cornick *et al*. compared the plasma concentration and sedation scores after nebulized and intranasal midazolam in healthy volunteers and concluded that comparative bioavailability of midazolam estimated by ratio (nebulized: intranasal) of area under 60 min plasma concentration curve was 1: 2.9.[20]

This study has several limitations. First, because of the intervention chosen, blinding was not possible and the risk of bias associated with non-blinding could not be neglected. Second, we enrolled patients aged between 2-8 years so the study results could not be extrapolated to children who are less than 2 years and more than 8 years of age. Furthermore, increasing age might have an influence on sedation score achieved; we didn't further subdivide our patients into specific age groups to evaluate the degree of variation in sedation with age. We did not measure plasma concentrations of dexmedetomidine thereby lacking the data regarding the bioavailability of both the routes. Further studies are required to clarify their efficacy and safety.

In conclusion, dexmedetomidine (2 mcg/kg) administered by nebulization is non-inferior to that when administered by intranasal route in providing satisfactory sedation. However, intranasal route had better medication and mask acceptance, and less parental separation anxiety and emergence agitation score. Non-parenteral administration of dexmedetomidine is a convenient and safe alternative to parenteral administration. The nebulized route may offer an alternative mode of administration of dexmedetomidine, but require further studies for evaluation of the dose required to produce a sedative effect, either by improving nebulizer delivery or by increasing the dose administered.

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Conflicts of interest
There are no conflicts of interest.

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