A study to evaluate the effects of intranasal dexmedetomidine as a premedicant in paediatric patients undergoing cardiac surgeries

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Background
Premedication is defined as the administration of drugs before anaesthesia to allay apprehension, produce sedation and facilitate the administration of anaesthesia to the patient. The current study is a prospective randomized double-blinded trail conducted to evaluate the effects of intranasal dexmedetomidine over placebo (0.9% saline) as a premedicant in paediatric cardiac surgeries.
Patients and methods
A total of 60 children of ASA physical status I and II, between the ages of 2 and 8 years undergoing various cardiac surgeries were assigned randomly into two groups. In group D, patients received intranasal dexmedetomidine (2 μg/kg), and in group P, patients received intranasal saline. At intervals of 10, 20, 30 and 45 min after intranasal administration of the study drug, parameters such as heart rate, blood pressure, respiratory rate and SpO_2 (oxygen saturation) were monitored. At 45 min, sedation, the ease of separation and intravenous cannula acceptance were evaluated.
Results
Statistically significant reductions in heart rate and blood pressure were observed from 30 min onwards in group D ($P < 0.05$) when compared with the placebo group. In the study, the sedation score in group D was 3.23 ± 0.568 when compared with 1.13 ± 0.345 in the placebo group ($P = 0.0001$). The ease of parental separation was 2.63 ± 0.614 in group D compared with 1.1 ± 0.305 in the saline group ($P = 0.0001$). The intravenous cannula acceptance score in group D was 2.1 ± 0.547 when compared with 1.06 ± 0.253 in group P ($P = 0.0001$).
Conclusion
Intranasal dexmedetomidine (2 μg/kg) provided better sedation, parental separation and intravenous cannula acceptance than placebo in children undergoing cardiac surgeries.

Keywords:
dexmedetomidine, intranasal, paediatric cardiac surgery, premedicant

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Introduction

Increased anxiety of a child in the preoperative holding area predicts an increased incidence of negative postoperative behavioural problems. Parents and children prefer to stay together during medical procedures. Therefore, parent separation and sedation before the induction of anaesthesia are important aspects of premedication in children. Premedication in children can decrease anxiety and facilitate their separation from parents [1]. The ideal premedicant in children should be readily acceptable and have a rapid and reliable onset of action with minimal side effects. These premedication drugs can be administered in different ways such as intravenous, intramuscular, intranasal, oral, rectal, etc. [2–6]. Earlier, drugs such as meperidine and promethazine were commonly used, but now-a-days the commonly used drugs are ketamine, midazolam and dexmedetomidine [4–7].

Many studies have been undertaken to study the effectiveness of these drugs as a premedication in children. They have been used intravenously, intranasally and through the rectal route [3]. Dexmedetomidine is the dextroenantiomer of medetomidine; the methylated derivative of etomidine was selected as our study drug. Its specificity for the a-2 receptor is eight times that of clonidine, with an a-2 : a-1 binding affinity ratio of 1620 : 1.

Acyanotic congenital heart disease is characterized by a left-to-right intracardiac shunt. Increased anxiety

and crying causes sympathetic stimulation, thereby increasing systemic vascular resistance. These changes produce an increase in the magnitude of left-to-right shunts, leading to pulmonary hypertension and congestive heart failure. Hence, the need to allay anxiety in these paediatric cardiac patients is of utmost importance.

Although dexmedetomidine has been used as a premedicant in various surgeries, there are only a few studies performed to assess the premedicant effects of intranasal dexmedetomidine in paediatric cardiac surgeries. Therefore, this study was conducted to compare the premedicant effects of intranasal dexmedetomidine with that of intranasal 0.9% saline.

Patients and methods

After approval of the institutional ethical committee and written informed consent from patients' parents were obtained, 60 paediatric patients of ASA I and II aged between 2 and 8 years were included in the study. The various surgical conditions included in the present study were uncomplicated atrial septal defects, patent ductus arteriosus and ventricular septal defects. Children with hepatorenal dysfunction, mental retardation, nasal and oral deformities and severe pulmonary hypertension were excluded from the study. Patients were divided into two equal groups by computer-generated random tables. Patients in group D received intranasal dexmedetomidine (2 μg/kg), which was prepared from a parenteral formulation of dexmedetomidine (50 μg/0.5 ml) ampoules, and group P received equal volumes of 0.9% saline intranasally.

Children were kept in the holding area in the comforting presence of their parents and were connected to all standard monitors. Their baseline heart rate (HR), blood pressure (BP) and oxygen saturation were measured before premedication. An intranasal dose of the drug was administered in the supine position after seeking consent from the parents. After calculating the dose of dexmedetomidine, the drug was diluted to 1 ml and was administered to both nostrils, 0.5 ml in each. Children were observed constantly for their HR, BP and saturation and possible side effects such as nausea and vomiting. Readings were taken at 10-min intervals until 45 min, when the child was separated from the parents. At 45 min after the intranasal dose, sedation, the ease of separation and intravenous cannula acceptance were evaluated on a four-point score scale.

The scoring scales [7] that were used are as follows (Table 1):

Children with scores of 3 or 4 were considered as satisfactory sedation or separation from parents. Scores 1 or 2 were considered as unsatisfactory sedation or separation. In the operation theatre, intravenous cannulation was performed before the induction of anaesthesia. A four-point evaluation system was used to evaluate the acceptance of the intravenous cannula. Children with scores of 3 or 4 were taken as satisfactory acceptance, whereas scores of 1 or 2 were taken as unsatisfactory acceptance. The onset of action is defined as the time from the administration of the drug to the beginning of drowsiness, that is, attaining sedation score scale 3.

Statistical analysis

Descriptive and inferential statistical analyses were carried out in the present study. Results of continuous measurements are presented as mean ± SD (minimum–maximum) and results of categorical measurements are presented as number (%). Significance is assessed at a 5% level of significance. The following assumptions on the data were made:

(a) Dependent variables should be normally distributed;
(b) Samples drawn from the population should be random;
(c) Cases of the samples should be independent.

The Student *t*-test (two-tailed, independent) was used to determine the significance of the study parameters on a continuous scale between the two groups (intergroup analysis) of metric parameters. Leven1s test for the homogeneity of variance was performed to assess the homogeneity of variance. The χ^2-test/Fisher exact test was used to determine the significance of the study parameters on a categorical scale between two or more groups.

The statistical softwares, namely SAS 9.2 (Johannesburg, South Africa), SPSS 15.0 (Acquired by IBM 2009, Chicago), Stata 10.1 (Stata corp, Texas, US), MedCalc 9.0.1 (Belgium), Systat 12.0 (San Jos, California, US) and R environment ver.2.11.1 (Bell

Table 1 The scoring scale

Scores	Sedation score	Separation score	Intravenous cannula acceptance score
1	Agitated	Poor (crying, clinging)	Poor (terrified, crying)
2	Awake	Fair (crying but not clinging)	Fair (fear of needle, not reassured)
3	Drowsy	Good (whimpers, easily reassured)	Good (slight fear, easily reassured)
4	Asleep	Excellent (easy separation)	Excellent (readily accepts cannula)

Labs, John Chambers), were used for the analysis of the data, and Microsoft Word and Excel were used to generate graphs, tables, etc.

Results

This study was carried out on a total of 60 paediatric patients undergoing cardiac surgeries. In the present study, sedation scores and hemodynamics were compared between the dexmedetomidine (group D) and the placebo groups (group P). Both the groups were comparable with regard to the age, the sex, the weight and the height. The diagnosis and the surgical procedure were also comparable between the two groups (Tables 2 and 3).

There was no statistically significant difference between the two groups with respect to baseline readings of HR (P = 0.839), systolic blood pressure (SBP) (P = 0.132), diastolic blood pressure (DBP) (P = 0.879) and mean arterial pressure (MAP) (P = 0.378).

There was a gradual reduction in HR in the dexmedetomidine group, which was statistically significant from the 30th minute till the 45th minute. There was not much change in HR in the placebo group throughout the study period (Fig. 1).

There was a statistically significant decrease in SBP, DBP and MAP from the 30th minute till the 45th minute in group D when compared with group P (Figs. 2–4).

There was no difference between the groups with respect to the respiratory rate and SpO_2.

Table 2 Demographic data

Demographic data	Group D	Group P	*P* value
Age (years)	4.83 ± 2.12	5.17 ± 1.89	0.523
Sex (M : F)	14:16	15:15	0.796
Weight (kg)	13.87 ± 4.61	15.83 ± 4.80	0.111
Height (cm)	103.57 ± 11.62	106.57 ± 13.22	0.354

All values expressed in mean ± SD, except the sex, expressed as the male-to-female ratio.

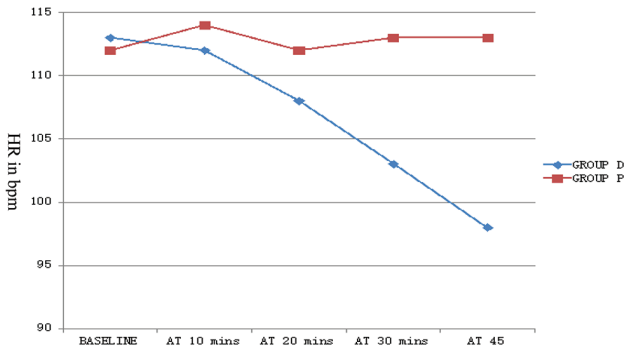
Table 3 Diagnosis and procedure

Procedure	Group D [*n* (%)]	Group P [*n* (%)]
ASD closure	4 (13.33)	7 (23.33)
VSD closure+repair	5 (16.66)	7 (23.33)
PDA ligation	21 (70.0)	16 (53.3)
Total	30 (100.0)	30 (100.0)

ASD, atrial septal defects; PDA, patent ductus arteriosus; VSD, ventricular septal defects.

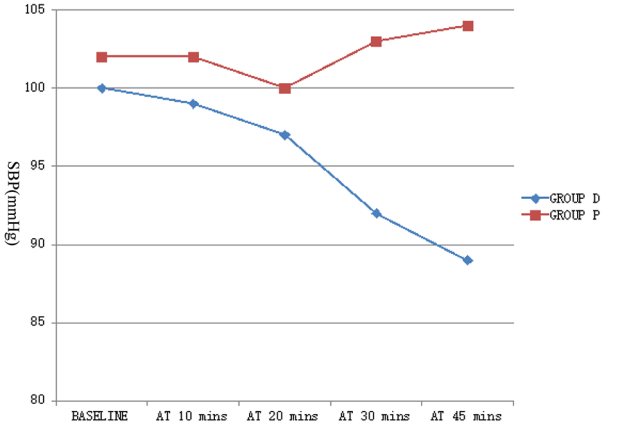
On comparing the sedation score, parental separation and the intravenous cannula acceptance score showed the following results as in Fig. 5. The sedation score in group D was 3.23 ± 0.568 when compared with 1.13

Figure 1



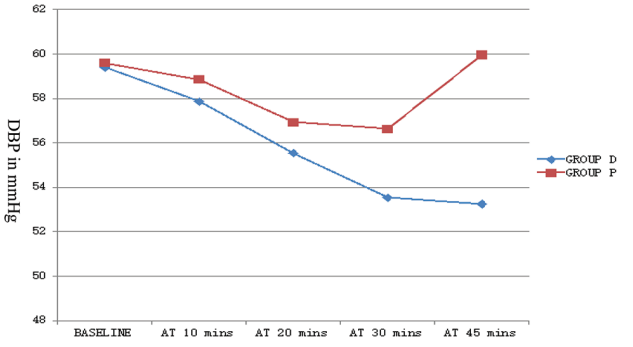
A line diagram showing heart rate (HR) changes in two groups (bpm) at various time intervals (min).

Figure 2



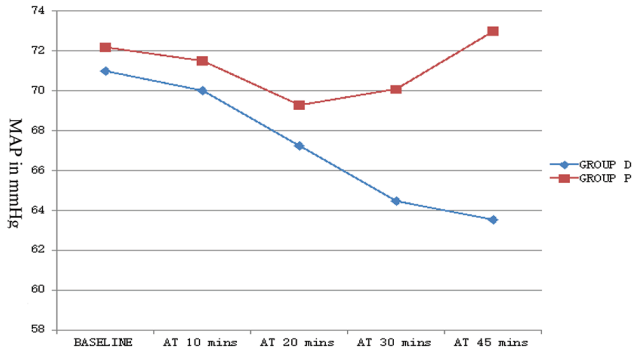
A line diagram showing systolic blood pressure (SBP) changes in two groups (mmHg) at various time intervals (min).

Figure 3



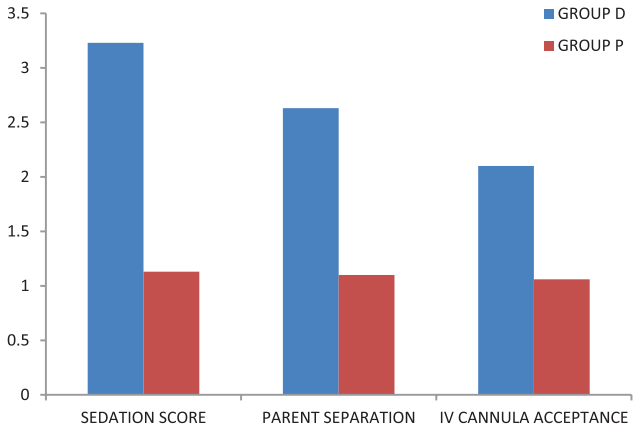
A line diagram showing diastolic blood pressure (DBP) changes in two groups (mmHg) at various time intervals (min).

Figure 4



A line diagram showing mean arterial pressure (MAP) changes in two groups (mmHg) at various time intervals (min).

Figure 5



A bar diagram showing the sedation score, the parental separation score and the intravenous cannula acceptance scale. The sedation score at the time of shift to the operation theatre revealed a significant *P* value of 0.001. The parent separation score showed a *P* value of 0.001, which was also statistically significant. The intravenous cannula acceptance score showed a significant *P* value of less than 0.001. Therefore, on comparison, it shows the dexmedetomidine group to have a better sedation, parent separation and intravenous cannula acceptance score.

± 0.345 in the placebo group (*P* = 0.0001). The ease of parental separation was 2.63 ± 0.614 in group D compared with 1.1 ± 0.305 in the saline group, which was statistically significant (*P* = 0.0001). The intravenous cannula acceptance score in group D was 2.1 ± 0.547 when compared with 1.06 ± 0.253 in group P, which was also statistically very significant (*P* = 0.0001). Therefore, on comparison, it shows the dexmedetomidine group to have a better sedation, parent separation and intravenous cannula acceptance score.

The side effects found in our study, in both groups, included a minimal amount of vomiting and salivation, which did not require any intervention. Out of 30 patients, four patients in group D (13.3%) and two patients in group P (6.7%) developed vomiting. Only two patients in group D (6.7%) and none in group P had salivation.

Discussion

Premedication is aimed to relieve anxiety, apprehension, fear and resistance to anaesthesia. It counteracts unwanted side effects of agents used in anaesthesia by reducing the anaesthetic requirement. The boon of using sedative drugs in paediatric patient is to control pain, fear and anxiety, thereby creating a behaviour that will facilitate the provision of quality medical care [1]. The fact that no single sedative drug has achieved universal acceptance suggests that the ideal drug has not yet been found.

In the quest to establish a gold standard for methodology and drugs, various routes of administration (intravenous, intramuscular, oral, rectal, intranasal, etc.) and combinations of drugs have been scientifically studied by numerous researchers. The intranasal administration of drugs is preferred as it works for a wide variety of drugs, and is more accessible, noninvasive and comfortable because the child cannot resist or spit it out. Apart from drug absorption over the nasal mucosa, significant parts of the medication will go to the pharynx where absorption through the pharyngeal mucosa occurs and the remaining volume will be swallowed. The intranasal route has a significant advantage of a noninvasive, quicker onset of action and relatively less or delayed side effects [6].

In our study, we used intranasal dexmedetomidine 2 μg/kg, which is an α-2 receptor agonist. Agonism at the α-2A receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection [8] and inhibition of insulin secretion [9]. Agonism at the α-2B receptor suppresses shivering centrally, promotes analgesia at spinal cord sites and induces vasoconstriction in peripheral arteries. α-2C receptors are associated with the modulation of cognition, sensory processing, mood and stimulant-induced locomotor activity and the regulation of epinephrine outflow from the adrenal medulla.

The mechanism of action of dexmedetomidine is unique. The presynaptic activation of α-2A adrenoceptor in the locus ceruleus inhibits the release of norepinephrine and results in the sedative and hypnotic effects [10]. In addition, the stimulation of α-2 adrenoceptors in the descending medullospinal noradrenergic pathway terminates the propagation of pain signals, leading to analgesia. The postsynaptic activation of α-2 receptors in the central nervous system results in a decrease

in sympathetic activity, leading to hypotension and bradycardia.

At the spinal cord, the stimulation of α-2 receptors at the substantia gelatinosa of the dorsal horn leads to the inhibition of the firing of nociceptive neurons and the inhibition of release of substance P. Also, α-2 adrenoceptors located at the nerve endings play a possible role in the analgesic mechanism by preventing norepinephrine release. The spinal mechanism is the principal mechanism for the analgesic action of dexmedetomidine even though there is clear evidence for both supraspinal and peripheral sites of action [11].

α-2 receptors are located on blood vessels, where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release [12].

We have conducted our study in paediatric cardiac surgery, especially acyanotic congenital heart disease such as patent ductus arteriosus, ventricular septal defects and atrial septal defects, as any increase in the sympathetic response and crying can increase the magnitude of the left-to-right shunt and cause pulmonary hypertension. Therefore, taking a calm and sedated child into the operating room allays anxiety and sympathetic stimulation in them.

The effectiveness of the premedicant in our study was assessed mainly by sedation, parental separation and intravenous cannula acceptance scores. The sedation score, the parental separation score and the intravenous cannula acceptance score were found to be better in the dexmedetomidine group when compared with placebo. About 93.3% of the patients were found to be sedated (sedation score 3 and 4), 66% had better parent separation (score 3 and 4) and 50% had good intravenous cannula acceptance (score 3 and 4) in the dexmedetomidine group.

In our study, the dose of intranasal dexmedetomidine was used at 2 μg/kg; similarly, Talon *et al.* [13] used intranasal dexmedetomidine (2 μg/kg) and compared it with oral midazolam (0.5 mg/kg) as a premedicant in burn children undergoing reconstructive surgery. Their study was carried out on 100 patients and the drug was administered 30–45 min before induction. They observed that dexmedetomidine was more effective than oral midazolam at inducing sleep preoperatively.

We observed that dexmedetomidine had an onset time of 30.47 ± 4.43 min in our study. Yuen *et al.* [4] showed that the onset of action between 1 and 1.5 μg/kg of intranasal dexmedetomidine was 45 min in their study.

Yuen *et al.* [4] studied the effects of intranasal dexmedetomidine at various doses such as 0.5 (group A), 1 (group B) and 1.5 μg/kg (group C) and inferred that intranasal dexmedetomidine was well tolerated. Both 1- and 1.5-μg/kg doses produced significant sedation and decreases in the bispectral index, SBP, DBP and HR when compared with the placebo ($P < 0.05$). The onset of sedation occurred at 45 min, with a peak effect at 90–150 min. The maximum reduction in SBP was 6, 23 and 21% in groups A, B and C, respectively.

HR, SBP, DBP and MAP in the dexmedetomidine group of our study showed a significant decrease. HR in the dexmedetomidine group decreased by 14% and BP by 11%. In our study, we considered any decrease in the BP 20% from baseline as hypotension and a decrease in the HR below 100 bpm in children between 0 and 3 years and a decrease below 60 bpm in the age group between 3 and 8 years as bradycardia [14]. Although there was a decrease in HR and BP in the dexmedetomidine group, none of the patients met the criteria for gross hypotension or bradycardia, requiring any medical intervention.

Yuen *et al.* [4] showed that there was a significant decrease in SBP from baseline at 30 min after the administration of intranasal dexmedetomidine. There was also a significant time effect on HR and it decreased by 16.4% at 60 min after intranasal dexmedetomidine of 1 μg/kg.

In the present study, SpO_2 and the respiratory rate did not show any significant changes from baseline. Yuen *et al.* [4] in their study showed that there was no significant reduction in SpO_2 below 95% for dexmedetomidine with 1 and 1.5 μg/kg. Ghali *et al.* [15] showed that there were similar baseline values in SpO_2 when intranasal dexmedetomidine and midazolam were administered in two groups. At the time of transferring patients to the operation room, there was no statistically significant difference between the two groups. No SpO_2 reduction below 95% could be detected in both groups.

The limitations of this study are mentioned here. The number of children with congenital cardiac anomalies recruited in the study was small. It is preferable to study a larger population of children with diverse medical conditions to arrive at definite inferences. The duration of premedication of 45 min was found to be relatively short. A time period of 60 min or more would have been preferable to study the peak effects of the drug.

Hence, from this study, it can be concluded that intranasal dexmedetomidine at a dose of 2 μg/kg is a useful premedicant in paediatric patients undergoing cardiac surgeries. The intranasal route proves to be an effective alternative to other invasive routes, especially in paediatric patients. Dexmedetomidine provided excellent sedation, good parental separation and better intravenous cannula acceptance when compared with placebo. It also provides stable hemodynamics with minimal side effects.

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Nil.

Conflict of interest
There are no conflicts of interest.

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