Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(3) (Part - II): 929-935
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6319.34

Comparative Study of Intranasal Dexmedetomidine v/s Midazolam as a Premedication in Pediatric Patients Undergoing Cardiac Surgery

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Abstract

Background: Intranasal midazolam is a novel technique for administering premedication in children. It has been shown to be more effective than parental presence or placebo in reducing anxiety and improving patient's compliance at induction of anesthesia. Dexmedetomidine is selective α2 agonist with sedative, anxiolytic and analgesic properties with favorable pharmacokinetics. We designed this prospective randomized double-blinded study to compare the safety and efficacy of midazolam and dexmedetomidine administered intranasally as premedication in children undergoing cardiac surgery for CHD. *Method:* Sixty-two children belonging to the American Society of Anaesthesiologists (ASA) class I and II, scheduled for elective cardiac surgery were divided into two groups by standard randomization technique. Patients belonging to group M received intranasal midazolam 0.2 mg/kg whereas patients in group D received intranasal dexmedetomidine 1 µgm/kg 30 min prior to surgery in an adequately monitored condition. Patient's sedation score, behaviour scores, attitude, heart rate, respiratory rate, oxygen saturation, intravenous cannula acceptance and face mask acceptance at the time of induction were studied by an observer till induction of anesthesia. *Results:* There was no significant difference in sedation score in both the groups except at 20 minutes, when it was significantly lower in patients belonging to Group D as compared to those of Group M. There was no significant difference inheart rate, respiratory rate, SpO_2, behavior score, parental separation acceptance, behavior at separation and level of sedation atinduction of anaesthesia between the two groups. There was a significant difference in the number of patients with a change of behaviour (6.4% v/s 34.4%) and change of sedation (7.1% v/s 37.5%) in Group M and Group D respectively. Patients inGroup M were calmer and allowed face mask application at the time of induction of anesthesia. *Conclusion:* Intranasal route is safe and effective for administering both, midazolam and dexmedetomidine as premedication in children undergoing corrective surgery for congenital heart disease. However, we observed better behaviour with midazolam at induction of anesthesia.

Keywords: Intranasal midazolam; Intranasal Dexmedetomidine; Cardiac Surgery.

How to cite this article:

Jigisha Pujara, Hitendra Kanzariya, Visharad Trivedi et al. Comparative Study of Intranasal Dexmedetomidine v/s Midazolam as a Premedication in Pediatric Patients Undergoing Cardiac Surgery. Indian J Anesth Analg. 2019;6(3):929-935.

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Received on 16.03.2019, **Accepted on** 16.04.2019

Introduction

For pediatric cardiac anaesthesiologist, it is a challenge to minimize distress among children and to facilitate smooth induction anesthesia in the operating room environment, particularly in presence of severe pulmonary artery hypertension or cyanosis is associated with congenital heart diseases. Each year approximately 10,000 infants require anesthesia for corrective or palliative surgery for congenital heart disease [1,2]. The surgical injury may be followed by stress-induced catabolism, which can lead to delayed convalescence and increased morbidity and mortality [3,4]. Furthermore, postoperative mortality is higher and recovery is slower in patients who have delirium after surgery, than in those without delirium, which leads to prolonged ICU stay and higher cost of treatment [5,6].

The pre-aesthetic management of infants and children undergoing surgery for congenital heart disease can be a challenge for the anesthesiologist. Fear of operation theatre, injections and separation from parents prior to anesthesia produces traumatic experiences in tender mind of young children [7].

Premedication by the atraumatic method can minimize such problems. To provide effective anxiolysis and conscious sedation and to facilitate parental separation, were the objective of our study. The ideal premedication for children should have a rapid and reliable onset, should be atraumatic, palatable with minimal side effects and rapid recovery [8,9].

Thus, the intranasal route was selected, as all the criteria for an Ideal\premedication were satisfied [10]. Midazolam has already been used aspremedication by various routes. Oral and rectal roots for midazolam [11] are wildly used in this age group. The onset of action is slow via oral route (15-30 min) [12], and its first pass metabolism results in lower and unpredictable systemic availability. [13,14]. Intranasal midazolam for premedication in preschool children was first described and advocated by Wilton and colleagues [15].

Clonidine, an alpha-2 agonist has been used as an effective premedication in paediatrics. Oral clonidine premedication has also been shownto reduce the incidence of sevofluraneinduced emergence agitation [16] Dexmedetomidine is a newer alpha-2 agonist with a more selective action on the alpha-2 adrenoreceptor and a shorter half-life. Its bioavailability is 81.8% (72.6-92.1%) when administrated via buccalmucosa [17].

Many studies have reported, dexmedetomidine tobe an effective agent for sedation in pediatric population when given intravenously (IV) or intramuscularly (IM) [18,19] or intra-nasally (IN) [20]. The primary objective of our study was to evaluate and compare the efficacy and safety of intranasal midazolam 0.2 mg/kg with intranasal dexmedetomidine 1 μg /kg in paediatric patients Posted for cardiac surgery for CHD. Our secondary objectives were to evaluate the effects of the two drugs on the level of sedation, behavioral changes, parental separation reaction, and face mask acceptance.

Materials and Methods

After approval from hospital's scientific and ethical committees and after obtaining written informed consent fromthe patient's parents, sixty -two Children in the age group of 1 to 12 years, belonging to ASA grade Ior II scheduled for elective cardiac surgery for CHD were selected for this prospective randomized double-blinded study. Patients with known allergy, organ dysfunction, cardiac arrhythmias, bradycardia and mental retardation were excluded from the study.

Children were randomly allotted to either of the two groups (Group-M and Group-D) by computer generated random numbers. Children in Group-M received intranasal midazolam (0.2 mg/kg) while Group D children received intranasal dexmedetomidine 1 μg /kg via 1 ml syringe 30 min prior to surgery in the preoperative holding area in the presence of one parent with monitored anesthesia care.

Intranasal midazolam was prepared from the 5 mg/ml parenteral preparation in a 1 ml syringe, after appropriate dilution with 0.9% saline to make a final volume of 0.4 ml. Intranasal dexmedetomidine was prepared from the 100 μg /ml parenteral preparation diluted with 0.9% saline to make the final volume of 0.4 ml. All drugs were prepared by an independent investigator not involved in the study or conduct of anesthesia. Observers and attending anaesthesiologist were blinded to the study drug given.

The drug was instilled into both nostrils using 1 ml syringe with the patient in recumbent position. Baseline heart rate (HR), Oxygen saturation (SpO_2) and Respiratory rate (RR) were recorded, and observations were made at 2.5 min, 5 min, 10 min, 20 min and 30 min after test drug administration. Sedation status was assessed by 5 point Wilton

and Colleagues sedation score [21] and behaviour was evaluated with a 4 point behaviour score [22] Table 1. Other parameters observed were attitude (co-operative or not), Separation reaction crying, apprehensive or good, change of behaviour from satisfactory to unsatisfactory at the time of parental separation and face mask acceptance. Adverse effects, if any, especially odd behaviour, excessive salivation, nausea, vomiting, pane, desaturation, bradycardia (20% decreases in baseline value), restlessness etc. were recorded.

Table 1: Sedation and behaviour scores

Wilton and Colleagues sedation score.
1. Agitated.
2. Alert
3. Calm
4. Drowsy
5. A sleep

Behaviour Score
1. Calm and co-operative
2. Anxious but reassurable
3. Anxious and non- reassurable
4. Crying and resisting

Outcome measures: Primary endpoints were behaviour and sedation status atseparation from the parent and at induction of anesthesia. Secondary end point included Heart rate, Respiratory rate and SpO_2.

Statistical Analysis

Statistical analysis was carried out using SPSS version 20.0 software (SPSS Inc., USA). This data was presented as mean ± SD or proportion as appropriate.Chi-square test and Independent sample t test was used to compare categorical and continuous variables respectively. The "p" value less than 0.05 was considered to be significant.

Results

Between July 2016 to January 2017 sixty-two (62) children posted for congenital heart surgery were enrolled for the study and evaluated for various parameters. All children accepted the intranasal drug instillation well without anyvomiting. All children were studied in two groups, group M (IN midazolam) and group D (IN dexmedetomidine). Demographiccharacteristics are summarized in Table 2. Patients in both the groups were comparable with respect to age, weight, height, BSA, gender and numbers. No children complained of pain or discomfort with intranasal drug administration.

There were no statistically significant differences in heart rate, respiratory rate and SpO_2 in both the groups during premedication sedation period (Fig. 1).

Assessment of sedation and behaviour score after intranasal drug administration (Table 3,4).

Table 3 shows the sedation score at various time points. There was no significant difference in sedation score between the groups except at 20 min when the sedation score was significantly lower in group D as compared to group M (P-value 0.010). The onset of sedation was at 5 min in both the groups (sedation score >2), and patients became calm at 20 min in group M (Mean sedation score 3.32 ± 0.65 min), while in group-D, it is at 30 min (Mean sedation score 3.22 ± 0.61 min).

Table 4 shows behavior score after IN premedication. Behavior scores were comparable in both the groups at various time periods with onset time within 5 min and accepted score at 10 minutes of IN premedication administration.

Table 2: Demographic details

	Group M	Group D	P value
Age	5.52 ± 2.84	4.42 ± 2.61	0.118
Weight	14.48 ± 4.09	12.36 ± 5.18	0.078
Height	108.26 ± 14.11	100.2 ± 19.98	0.071
BSA	0.66 ± 0.13	0.59 ± 0.17	0.094

Table 3: Sedation Score after IN Premedication

Willton score	Group M	Group D	p value
2.5 willton score	1.48 ± 0.50	1.48 ± 0.50	1.000
5 willton score	2.38 ± 0.61	2.25 ± 0.63	0.412
10 willton score	2.83 ± 0.52	2.64 ± 0.48	0.140
20 willton score	3.32 ± 0.65	2.93 ± 0.51	0.010
30 willton score	3.54 ± 0.72	3.22 ± 0.61	0.063

Table 4: Behaviour Score after IN Premedication

Behaviour score	Group M	Group D	p value
2.5 Behaviour score	1.90 ± 0.59	2.19 ± 0.60	0.059
5 Behaviour score	1.19 ± 0.40	1.35 ± 0.48	0.159
10 Behaviour score	1.06 ± 0.24	1.19 ± 0.40	0.126
20 Behaviour score	1 ± 0	1.03 ± 0.17	-------
30 Behaviour score	1 ± 0	1 ± 0	--------

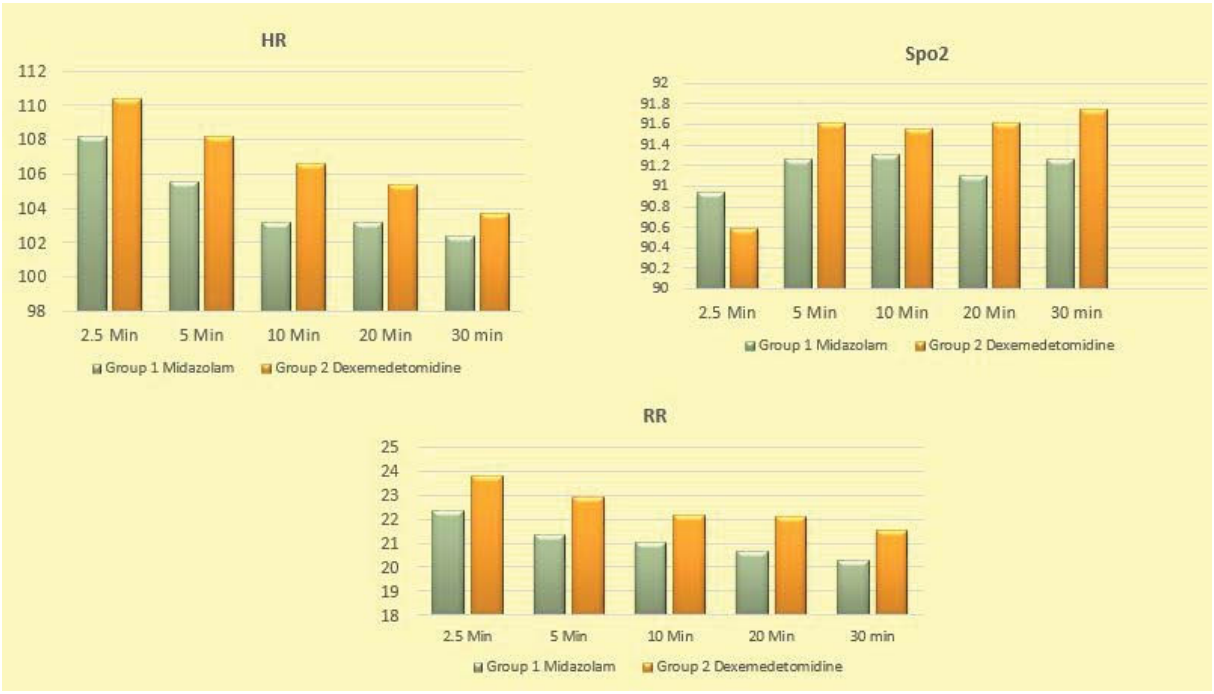

Fig. 1: Comparison of Heart Rate, Respiratory rate and SpO_2

Table 5: Behaviour and sedation status at parental separation and at induction

	Group M (No %)	Group D (No %)	p value
Sedation at Separation	31 (100%)	30 (96.7%)	1.000
Behaviour at Satisfactory	30 (96.7%)	29 (93.5%)	1.000
Sedation at Induction	30 (96.7%)	26 (83.8%)	0.197
Change of Behaviour	02 (6.4%)	10 (32.2%)	0.024
Change of Sedation	02 (6.4%)	09 (29.03%)	0.046

Assessment of sedation and behaviour at separation and at Induction: (Table 5).

We observed sedation at separation in 28 children (90.32%) in group M, while in 24 children (77.4%) in group D, but it was not statistically significant. The behavior seemed to be satisfactory in 30 children (96.7%) in group M and in 29 children (93.5%) in group D. There was no statistically significant difference in behaviour score at separation in both the groups.

We observed that in 96.7% patients (no=30) in group M, there was sedation at induction of anesthesia, while in group D 83.8% patients (no=26) had sedation at induction time (no significant difference between the groups).

During induction change of behaviour from satisfactory to unsatisfactory was observed to be significantly lower in group M (6.4%/2 patients) as compared to group D (32.2% / 10 patients). Similar changes in the level of sedation during induction, from satisfactory to unsatisfactory was also significantly lower in group M (6.4% / 2 patients) as compare to group D (29.03% / 9 patients). Children in group M were significantly calmer during induction of anesthesia. Face mask acceptance was without cry in 22 children in group M, while in 14 children in group D.

Discussion

There is a continuous search for safe premedication for children posted for congenital cardiac surgery, which would make separation of children from parents peaceful. As suggested by weksler et al. [23], ideal premedication for children should be easy to administer, with rapid onset and faster recovery. Ketamin, midazolam, clonidine, dexmedetomidine etc possess ideal criteria for premedication such as rapid onset, good anxiolysis, sedation and rapid recovery [24].

Oral, rectal, intravenous and intranasal routes are documented for premedication in children. The problem with the oral route is delayed and unpredictable effect due to first-pass hepatic metabolism, while for the intravenous route, intravenous line should be required and chances of respiratory depression are there.

Previous studies have shown that in administration is an effective way to administer premedication and it provide rapid and reliable onset of action,

predictable effect, good quality of sedation to children, it's relatively easy and non-invasive route with high bioavailability (25, 26, and 27).

Intranasal midazolam and intranasal dexmedetomidine are safely used as premedicant in various paediatric surgeries. In this prospective, randomized double-blinded study, we compared IN dexmedetomidine with IN midazolam as premedication in 62 paediatric cardiac surgery patients in the age group of 1 to 12 years.

Dexmedetomidine is an alpha-2 agonist, can beadministrated intranasally or transbuccally, has recently been introduced as a sedative in paediatric patients [28]. Primarily it has been used forpaediatric sedation by intravenous route [29]. It has minimal effects on the respiratory drive and upper airway dynamics [30]. It is odourless, intranasal administration is not irritating and well tolerated by children [28]. Limited animal studies suggested dexmedetomidine may not be associated with neurodegeneration [29]. Dexmedetomidine has a half-life of 2 hours, which may lead to faster recovery. However, as an alpha-2 adrenergic receptor agonist, it decreases heart rate and blood pressure [31].

Most children tolerated the intranasal study drugs. Primary end points were behaviour and sedation status at separation from the parent and at induction of anesthesia. We observed onset of sedation at 5 min in both the groups with little delay in group D but without statistical significance. Satisfactory sedation achieved at 20 min in group M (3.32 ± 0.65 minat 20 min in group M), while it is at 30 min in the group- D (3.22 ± 0.61 min at 30 min in group-D), which was statistically significant. Behaviour score was satisfactory at all time intervals in group M, while it was satisfactory at 5 min, 10 min, 20 min and 30 min in group D, but there was no statistical difference at 2.5 min interval in both groups. We observed good sedation and satisfactory behaviour at separation of children from parents in both the groups.

When compared with group D, the number of patients with change of behaviour and change of sedation were significantly lower in group M. Change of behaviour 6.4% (2 patients) in group M v/s 32.2% (10 patients) in group D, which is statistically significant (p=0.024). Change of sedation 6.4% (2 patients) in group M v/s 29.03% (9 patients) in group D, that is statistically significant (p=0.046). These observations were also noted by A L Menakshi et al. (32a), unlike conventional gabaminergic sedative drugs, such as midazolam dexmedetomidine's site of action in thecentral nervous system is primarily in the locus coeruleus where it induces electroencephalogram activity Similarto natural sleep [32]. Dexmedetomidine induces arousable sedation, undereffect of which, the patient can be awakened by background noise and movement [33] and patients are less likely to become disoriented and uncooperative. Attitude and facemask acceptance were excellent in group M as compared to group D. Secondary end point like intraoperative pulse rate, oxygen saturation, respiratory rate had no significant difference in group M and group D.

Post-operative oral secretions were minimal in both groups. Nystagmus and other sideeffects like vomiting and increased salivation were not observed in any patients. None of the patients had any reaction in our study, consistent with the study done by Agrawal Nidhi et al. [34].

Conclusion

Intranasal drug administration for premedication in children posted for congenital heart surgery is simple, rapid and with predict sedation. We have observed that this route is feasible for dexmedetomidine and midazolam–both the drugs are safe and effective premedicants in pediatrics with better sedation and behaviour at induction of anesthesia in midazolam group as compare to dexmedetomidine group.

In summary, 0.2 mg/kg intranasal midazolam and 1 μg/kg intranasal dexmedetomidine both produce significant sedation in children between 1 and 12 years of age. The behavior of the children at parental separation and at induction of anesthesia was satisfactory inboth the groups.

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