Background: The intranasal route is a reliable way to administer preanesthetics and sedatives to children. The aim of this study was to compare the anxiolytic and sedative effect of intranasal dexmedetomidine and midazolam as a premedication in pediatrics with simple congenital heart disease undergoing cardiac catheterization. Patients and Methods: Sixty children 3–6 years old of either sex with simple congenital heart disease undergoing cardiac catheterization were randomly allocated into two groups: Dexmedetomidine group who received intranasal dexmedetomidine (0.1 µg/kg) and midazolam group who received intranasal midazolam (0.2 mg/kg) 30 min before induction. Heart rate, mean arterial blood pressure, and oxygen saturation were monitored up to 30 min after drug administration. The sedation score, anxiety score, and child-parent separation score were recorded until the child taken to the operating room. The postoperative agitation score was also observed. Results and Conclusion: The premedication of children with intranasal dexmedetomidine attained satisfactory and significant sedation and lower anxiety level with better parental separation than those who received intranasal midazolam.

Keywords: Cardiac catheterization, intranasal dexmedetomidine, intranasal midazolam, pediatrics, premedication

Introduction

One of the pediatric anesthesiologists’ challenges in the operating room (OR) environment is to minimize distress for children and to facilitate smooth induction of anesthesia. This is accomplished by administration of a sedation before transfer to the OR.[1] Deep sedation up to general anesthesia required during diagnostic and interventional cardiac catheterization to ensure immobility and blunt reflexes to painful stimuli. Depression of cardiovascular and respiratory function should be avoided in order for the cardiologist to obtain the most meaningful hemodynamic information.[2]

Anxiety and psychological trauma due to maternal deprivation are major challenges in pediatric anesthesia. Preanesthetic medication in children should aim to decrease the anxiety and psychological trauma and also to facilitate the induction of anesthesia without delaying the recovery. Several drugs have been tried to find the appropriate sedative agent and the best route of administration of these drugs in children. Hence, a drug use as premedicant should have an acceptable, nontraumatic route of administration in order not add extra stress to the child. Currently, the most commonly drugs are midazolam, ketamine, transmucosal fentanyl, and/or meperidine.[3]

The intranasal route is a reliable way to administer preanesthetics and sedatives to children and is a relatively easy noninvasive route with rapid onset of action and high bioavailability comparable to that of IV administration because of bypassing the first pass hepatic metabolism and the high vascularity of the airway mucosa.[4] Furthermore, it has the advantage of well tolerability, not requiring patient cooperation as would be in the case for drug swallowing or sublingual retention and does not have pungency or an unpleasant taste.[5]
In the pediatric patients, benzodiazepines are a mainstay of sedation as they provide sedation, anxiolysis and amnesia, and have muscular relaxation, hypnotic, and anticonvulsant properties. Midazolam is water-soluble and short-acting and is the most commonly used for sedation and premedication procedure in children. It is administered by many routes as follows: oral, nasal, intravenous (i.v.), or intramuscular. Midazolam may be administered orally to allay anxiety in children before the placement of i.v. lines.

Dexmedetomidine is highly selective and specific agonist for $\alpha_2$ adrenoceptor, commonly used for sedation ($<24$ h) in 1999. $\alpha_2$ adrenoceptor agonist exhibits sedative, hypnotic, analgesic, anxiolytic, and sympatholytic effect. It has a minimal effect on respiratory drive and it is more selective and shorter in duration than clonidine, also has reversal drug for its sedative action “Atipamezole,” and these properties render dexmedetomidine suitable for analgesia and sedation during perioperative period.

The aim of this study was to compare the anxiolytic and sedative effects of either intranasal dexmedetomidine or midazolam as a premedication in pediatrics with simple congenital heart disease; atrial septal defect (ASD) and ventricular septal defect (VSD) undergoing cardiac catheterization.

**Patients and Methods**

Our study was carried out in Mansoura University Children Hospital on 60 patients of either sex with age ranging from 3 to 6 years old with simple congenital heart disease (ASD, VSD) undergoing cardiac catheterization over 7-month period. The patients were divided according to the type of sedative drug used, after written informed consent obtained from their parents and approval of the local ethical committee of Mansoura faculty of medicine. Exclusion criteria were parent refusal or uncooperative patient, allergy to the study drug, any nasal disorder that may interfere with nasal administration of drugs as recurrent nasal bleeding or nasal masses, obstructive pharyngeal or laryngeal pathology, and mental retardation.

In the day before surgery, all details of the anesthetic plan were discussed with the parents of the child according to fasting hours, current medication and written consent was obtained. All patients were evaluated fulfilling full medical history, clinical examination with body weight, height, and body mass index (BMI), and airway assessment. Laboratory investigation were done in the form of complete blood count, arterial blood gas analysis, liver function test (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, bilirubin, and albumin), coagulation profile (international normalized ratio, prothrombin time), serum electrolytes (Na⁺, K⁺), and blood sugar level.

The patients were randomly divided using closed envelope method into:

- **Group 1** (dexmedetomidine group) $n = 30$: patients received intranasal dexmedetomidine (0.1 $\mu$g/kg) 30 min before induction.
- **Group 2** (midazolam group) $n = 30$: patients received intranasal midazolam (0.2 mg/kg) up to 15 mg, 30 min before induction.

All study drugs were prepared by the investigator anesthesiologist and were administered by other observer, and attending anesthesiologists were blinded to the given drug and responsible for further assessment and management of the patient. Children administered the study drug premedication in the presence of their parent after baseline heart rate (HR), oxygen saturation (SpO₂), and mean arterial blood pressure (MBP) were measured in the preoperative waiting area. The study drug was given to the child in the recumbent position by dripped into both the nostrils using a 2-mL syringe. HR, MBP, and SpO₂ were measured every 10 min after drug administration until transfer to OR. Child sedation state was assessed by a blinded observer every 5 min with Ramsay scale for sedation[6] [Table 1]. Anxiety was evaluated every 10 min with a four-point scale: 1 = cooperative and calm, 2 = anxious but could be reassured, 3 = anxious and could not be reassured, and 4 = resisting or crying. Child–Parent Separation score[9][10] was recorded at the time of transferring the patient to OR. Child–Parent Separation Score: 3 = patient crying and fearful, not quieted with reassurance; 2 = patient slightly crying and/or fearful; quieted with reassurance; 1 = patient unafraid, cooperative, or asleep.

Inhalation induction was initiated by face mask with sevoflurane 8% with O₂ 100% mixture. i.v. line was inserted after loss of consciousness, followed by administration of fentanyl 1–2 $\mu$g/kg slow i.v., propofol 1–2.5 mg/kg, and 0.9 mg/kg rocuronium to provide neuromuscular blockade and facilitates tracheal intubation. The patients were mechanically ventilated with 50% O₂, and the end tidal CO₂ was monitored by mainstream capnograph and maintained between 30 and 35 mmHg. The anesthetic level was delivered in a concentration that maintained a stable blood pressure, HR, and respiratory rate (baseline ± 20%). Standard monitoring was done using electrocardiogram, noninvasive blood pressure, pulse oximetry, and capnography. After the end of the surgery, anesthetic gases were discontinued to 0% and replaced with O₂ 100% ≥4 L/min. Endotracheal tube was removed when the patient is awake and then the patient was transferred to the postanesthetic care unit (PACU) for

| Table 1: Ramsay scale for sedation |
|-----------------------------------|
| Score   | Level of sedation                  |
| 1       | Patient agitated, anxious, or restless |
| 2       | Patient-oriented cooperative and tranquil |
| 3       | Patient responds to commands       |
| 4       | Asleep but with brisk response to light glabellar tap or loud auditory stimulus |
| 5       | Asleep, sluggish response to light glabellar tap or loud auditory stimulus |
| 6       | No response, asleep                |
monitoring of vital signs till discharge to the ward. In the PACU, a blinded anesthetist assessed the child’s agitation level according to a three-point scale: 1 = easily arousable, calm, follows commands; 2 = crying or restless but calms to verbal commands; and 3 = thrashing, combative, and disoriented.\[10\]

**Sample size calculation**
A priori G-power analysis was done to estimate study sample size. A power of 80% was estimated with a type I error of 0.05 to get a difference in sedation state at parent separation between groups of approximately 30% to yield of total sample size of 54 cases. A drop out of 10% of cases was expected. Therefore, a total number of 60 cases were needed (30 cases per group).

**Statistical analysis**
The statistical analysis of data was done using excel program for figures and Statistical Package for Social Science (SPSS, Inc., Chicago, IL, USA) program version 17. To test the normality of data distribution, Kolmogorov–Smirnov test was done only significant data revealed to be nonparametric. Unpaired student-t test was used for comparisons of numerical variables between-group, if its assumptions were fulfilled, otherwise for nonparametric; the Mann–Whitney test was used. The description of data done in the form of mean (±SD) for frequency and quantitative data. Chi square test was used for qualitative data. Any difference or changes having \( P < 0.05 \) was considered statistically significant at confidence interval 95%.

**RESULTS**
No significant difference regarding demographic data (age, gender, body weight, height, or BMI) was observed [Table 2].

Hemodynamic data showed that MBP and HR were significantly decreased 10, 20, and 30 min after drug administration in the dexmedetomidine group when compared with the midazolam group [Tables 3 and 4].

Peripheral arterial SpO₂ displayed no significant difference between the studied groups throughout the study period [Table 5].

Sedation score was significantly higher in the dexmedetomidine group when compared to the midazolam group after 15, 20, 25, and 30 min with no significant change at 5 and 10 min from drug administration [Table 6].

Anxiety score was significantly lower in the dexmedetomidine group when compared to the midazolam group after 20 and 30 min with no significant change at 10 min from drug administration [Table 7].

Separation score was significantly lower in the dexmedetomidine group when compared to the midazolam group [Table 8] while agitation score was not significantly differ between the two groups [Table 8].

**DISCUSSION**
This prospective, randomized, double-blind, controlled study compared the intranasal administration of dexmedetomidine and midazolam as premedication in children 3–6 years old with congenital heart disease undergoing cardiac catheterization. Intranasal dexmedetomidine premedication for children
Table 6: Sedation score at different time intervals after administration of the drug in the studied groups (n=30)

| Sedation score | Dexmedetomidine group | Midazolam group |
|----------------|-----------------------|-----------------|
| 5 min after drug administration | 1.8±0.5 | 2.0±0.6 |
| 10 min after drug administration | 2.2±0.6 | 2.1±0.6 |
| 15 min after drug administration | 3.1±0.9 | 2.2±0.6* |
| 20 min after drug administration | 4±0.9 | 2.9±1.0* |
| 25 min after drug administration | 4.4±1.2 | 3.1±1.1* |
| 30 min after drug administration | 4.7±1.2 | 3.3±0.9* |

Data were expressed as mean±SD. *P<0.05 is significant. SD=Standard deviation

Table 7: Anxiety score at different time intervals after administration of the drug in the studied groups (n=30)

| Anxiety score | Dexmedetomidine group | Midazolam group |
|---------------|-----------------------|-----------------|
| 10 min after drug administration | 2.2±0.7 | 2.3±0.6 |
| 20 min after drug administration | 1.1±0.3 | 1.9±0.5* |
| 30 min after drug administration | 1±0.2 | 1.8±0.4* |

Data were expressed as mean±SD. *P<0.05 is significant. SD=Standard deviation

Table 8: Child-parent separation score and postoperative agitation score in the studied groups (n=30)

|                         | Dexmedetomidine group | Midazolam group |
|-------------------------|-----------------------|-----------------|
| Separation score        | 1.21±0.4              | 2.09±0.51*      |
| Agitation score         | 1.13±0.35             | 1.33±0.48       |

Data were expressed as mean±SD. *P<0.05 is significant. SD=Standard deviation

attained satisfactory and significant sedation and lower anxiety level with better parental separation than those who premedicated with intranasal midazolam.

The intranasal application of preanesthetic drugs is a preferred route of administration and is an effective way to administer sedatives to children. The intranasal route does not require cooperation, convenient, noninvasive, well tolerated, and child would not be having an unpleasant taste or pungency. Wolfe and Braude suggested that intranasal drug administration offers a noninvasive, painless, quick way to give premedication drugs, with the rapid onset of action as drugs may access the venous blood of the systemic circulation because of the high vascularity of the subepithelial surface of the nasal cavity. Furthermore, it may penetrate the blood–brain barrier and reach the central nervous system directly and can avoid the first-pass metabolism in the liver.

Midazolam is the most widely used as a premedication before anesthesia. Intranasal administration of midazolam has the advantage of no first-pass effect with rapid absorption directly into the systemic circulation and a bioavailability of 55%–83%. Most children are better tolerated the intranasal than oral administration of midazolam. However, the nasal administration of midazolam is not favored in clinical practice as it has associated with a burning unpleasant sensation in the nasal cavity.

The clinical significant sedative effect of dexmedetomidine administered intranasally to healthy children and adult undergoing minor surgeries has been reported. while midazolam stimulates gamma-aminobutyric acid (GABA) receptors in the cerebral cortex to increase the conductance of chloride ions and hyperpolarization that inhibits normal function of neurons producing sedation.

The chosen dose of dexmedetomidine in the present study was 1 µg/kg intranasally according to Yuen et al., who reported that intranasal 1 and 1.5 µg/kg doses of dexmedetomidine have similar effects, and 1 µg/kg of is more effective than 0.5 µg/kg dexmedetomidine intranasally while the intranasal dose of midazolam of 0.2 mg/kg was determined according to Davis et al., who reported that there was no difference between intranasal dosage of 0.2 and 0.3 mg/kg midazolam. Furthermore, Tolksdorf and Eick have used an intranasal dose of midazolam of 0.2 mg/kg in their study for preanesthetic sedation.

The present study showed that the intranasal alpha2-agonists, dexmedetomidine, produced significant reduction in HR, and arterial blood pressure versus intranasal midazolam group. In a study comparing i.v. clonidine, dexmedetomidine, and midazolam for children preanesthetic medication, both dexmedetomidine and clonidine were shown to reduce HR and MBP before and during anesthesia. Dexmedetomidine i.v. in a dose of 1 µg/kg given over 10 min in children can produce a significant reduction of HR and MBP. Munro et al. reported that the reduction of HR and MBP were <20% of baseline in sedated children with 1 µg/kg i.v. dexmedetomidine, followed by a maintenance infusion during cardiac catheterization. However, these effects were not required medical intervention in both the groups.

In the current study, the peripheral arterial SpO2 was well maintained throughout the perioperative observation period in both groups. Dexmedetomidine does not suppress respiratory function, even at high doses while midazolam acts as GABA-mimetic drug, and therefore, it is known to decrease the respiratory drive in a dose-dependent manner.
Notably, respiratory depression was not observed in any of the midazolam-treated children.

In the present study, children in dexmedetomidine group achieved significant higher sedation score and lower anxiety score (more sedated) up to 30 min after drug administration in comparison to midazolam group. Furthermore, the children were satisfactorily separated from parents in dexmedetomidine group when compared to the midazolam group. The results of the present study are in consensus with Ghali et al.[27] who reported that intranasal dexmedetomidine is a better choice for preanesthetic medication than oral midazolam in children scheduled for adenotonsillectomy. Dexmedetomidine was associated with lower anxiety levels, lower sedation levels, and easier parent separation during transferring patients to the OR than children who received oral midazolam. The same result was confirmed by Yuen et al.[1] who found that children were more sedated during parent separation and at induction of anesthesia after intranasal dexmedetomidine than oral midazolam. Furthermore, Patel et al.[28] reported that children who were premedicated with intranasal dexmedetomidine had lower sedation scores and easier parent separation than children who received intranasal midazolam. On the other hand, the results of the present study are in contrast with Akin et al.[26] who found that intranasal midazolam and dexmedetomidine were equally effective in decreasing anxiety at parental separation. Furthermore, Schmidt et al.[29] did not find any difference in sedation between intranasal dexmedetomidine and oral midazolam. This could have resulted from the different scale used for sedation assessment.

The present results showed nonsignificant difference in the incidence of postoperative agitation between the dexmedetomidine and midazolam study groups. These results are in consensus with Akin et al.[26] who reported no evidence of difference in the postoperative agitation scores between the intranasal midazolam and dexmedetomidine as a preanesthetic medication in children scheduled for adenotonsillectomy. Furthermore, Bergese et al.[30] found no difference in the incidence of postoperative agitation between the midazolam and dexmedetomidine study groups during elective awake fiberoptic intubation. On the other hand, Mizrak et al.[31] and Munro et al.[2] found that dexmedetomidine was more effective than midazolam in reducing the incidence of postoperative agitation.

**CONCLUSION**

Premedication with intranasal dexmedetomidine 1 µg/kg attained significant and satisfactory sedation with better parent separation and lower anxiety levels without any adverse effects as compared with intranasal midazolam 0.2 mg/kg in children with simple congenital heart disease (ASD, VSD) undergoing cardiac catheterization.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: A double-blinded randomized controlled trial. Anesth Analg 2008;106:1715-21.
2. Munro HM, Tirotta CF, Felix DE, Lagueruela RG, Madril DR, Zahn EM, et al. Initial experience with dexmedetomidine for diagnostic and interventional cardiac catheterization in children. Paediatr Anaesth 2007;17:109-12.
3. Mostafa M, Morsy K. Premedication with intranasal dexmedetomidine, midazolam and ketamine for children undergoing bone marrow biopsy and aspirate. Egypt J Anaesth 2013;29:131-5.
4. Wang J, Bu G. Influence of intranasal medication on the structure of the nasal mucosa. Chin Med J (Engl) 2002;115:617-9.
5. Yuen VM, Hui TW, Irwin MG, Yap TJ, Wai GL, Yuen MK, et al. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. Anaesthesia 2010;65:922-9.
6. Tsichrict FT, Göpfert K, Fröhlich JM, Brunner G, Weishaupt D. Low-dose intranasal versus oral midazolam for routine body MRI of claustrophobic patients. Eur Radiol 2007;17:1403-10.
7. Talon MD, Woodson LC, Sherwood ER, Aarsland A, McRae L, Benham T, et al. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. J Burn Care Res 2009;30:599-605.
8. Davis PJ, Torre JA, McGowan FX Jr., Cohen JT, Latta K, Felder H, et al. Preanesthetic medication with intranasal midazolam for brief pediatric surgical procedures. Effect on recovery and hospital discharge times. Anesthesiology 1995;82:2-5.
9. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadalone. Br Med J 1974;2:656-9.
10. Almenrader N, Passariello M, Coccetti B, Haiberger R, Pietropaoli P. Premedication in children: A comparison of oral midazolam and oral clonidine. Paediatr Anaesth 2007;17:1143-9.
11. Feld LH, Champeau MW, van Steennis CA, Scott JC. Preanesthetic medication in children: A comparison of oral transmucosal fentanyl citrate versus placebo. Anesth Analg 1995;81:734-7.
12. Wolfe TR, Braude DA. Intranasal medication delivery for children: A brief review and update. Pediatrics 2010;126:532-7.
13. Taleagantkar S, Mishra P. Intranasal delivery: An approach to bypass the blood brain barrier. Indian J Pharmacol 2004;36:140-7.
14. Türker S, Onur E, Ozer Y. Nasal route and drug delivery systems. Pharm World Sci 2004;26:137-42.
15. Björkman S, Rigemar G, Idvall J. Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients. Br J Anaesth 1997;79:575-80.
16. Yıldırım SV, Guc BU, Bozdogan N, Tokel K. Oral versus intranasal midazolam premedication for infants during echocardiographic study. Adv Ther 2006;23:719-24.
17. Yuen VM, Irwin MG, Hui TW, Yuen MK, Lee LH. A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. Anesth Analg 2007;105:374-80.
18. Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, Scheinin M, et al. Bioavailability of dexmedetomidine after intranasal administration. Eur J Clin Pharmacol 2011;67:825-31.
19. Buck ML. Dexmedetomidine use in pediatric intensive care and procedural sedation. J Pediatr Pharmacol Ther 2010;15:17-29.
20. Pandharipande P, Ely E, Maze M. Dexmedetomidine for sedation and perioperative management of critically ill patients. J Crit Care 2006;21:43-50.
21. Unger RJ. General anesthesia with dexmedetomidine in a malignant hyperthermia-susceptible woman. Acta Anaesthesiol Scand 2006;50:1312-3.
22. Tolksdorf W, Eick C. Rectal, oral and nasal premedication using midazolam in children aged 1-6 years. A comparative clinical study. Anaesthesist 1991;40:661-7.
Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous
dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology
1992;77:1134-42.

Petroz GC, Sikich N, James M, van Dyk H, Shafer SL, Schily M,
et al. A phase I, two-center study of the pharmacokinetics and
pharmacodynamics of dexmedetomidine in children. Anesthesiology
2006;105:1098-110.

Hsu YW, Cortinez LI, Robertson KM, Keifer JC, Sum-Ping ST,
Moretti EW, et al. Dexmedetomidine pharmacodynamics: Part I:
Crossover comparison of the respiratory effects of dexmedetomidine
and remifentanil in healthy volunteers. Anesthesiology
2004;101:1066-76.

Akin A, Bayram A, Esmaoglu A, Tosun Z, Aksu R, Altuntas R, et al.
Dexmedetomidine vs. midazolam for premedication of pediatric
patients undergoing anesthesia. Paediatr Anaesth 2012;22:871-6.

Ghali AM, Mahfouz AK, Al-Bahrani M. Preanaesthetic medication
in children: A comparison of intranasal dexmedetomidine versus oral
midazolam. Saudi J Anaesth 2011;5:387-91.

Patel DD, Lisha M, Upadhayay MR. Pre-anaesthetic medication in
children: A comparison of intranasal dexmedetomidine versus intranasal
midazolam. J Med Res 2015;1:59-63.

Schmidt AP, Valinetti EA, Bandeira D, Bertacchi MF, Simões CM,
Auler JO Jr., et al. Effects of preanaesthetic administration of midazolam,
clonidine, or dexmedetomidine on postoperative pain and anxiety in
children. Paediatr Anaesth 2007;17:667-74.

Bergese SD, Patrick Bender S, McSweeney TD, Fernandez S,
Dzwonczyk R, Sage K, et al. A comparative study of dexmedetomidine
with midazolam and midazolam alone for sedation during elective
awake fiberoptic intubation. J Clin Anesth 2010;22:35-40.

Mizrak A, Koruk S, Ganidagli S, Bulut M, Oner U. Premedication
with dexmedetomidine and midazolam attenuates agitation after
electroconvulsive therapy. J Anesth 2009;23:6-10.