ORIGINAL ARTICLE

Comparative Evaluation of Efficacy of Midazolam and Dexmedetomidine as Premedicants in Children Undergoing Elective Surgery

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Abstract

Background: Drugs like midazolam and dexmedetomidine can allay anxiety when used as premedicants in children. Intranasal route offers the advantage of rapid and virtually complete absorption due to high mucosal vascularity. ***Objective:*** The aim of the study was to compare the effect of midazolam with dexmedetomidine for intranasal premedication in paediatric patients posted for elective surgery. ***Material and Methods:*** One hundred and five children of either sex, aged between 2-8 years undergoing elective surgery were randomly assigned to one of the three study groups. Group M (n=35) received 0.5 ml of 0.2 mg/kg midazolam, Group D (n=35) received 0.5 ml 1µg/kg dexmedetomidine and Group C (n=35) received 0.5 ml of normal saline in each nostril 40 minutes before induction of anesthesia. Heart rate, blood pressure, SpO_2, degree of sedation was measured every 10 minutes till 30 minutes according to the 5- point sedation scale. The reaction to intravenous (i.v.) cannulation was noted according to 4-point scale and face mask acceptance by the child was noted according to 5-point scale. After induction of anesthesia, vitals were noted every 10 minutes, intraoperatively. Postoperatively, level of sedation was assessed every 10 minutes for one hour using 3- point scale. ***Results:*** The difference in sedation score between group M and D was insignificant at 10 minutes but highly significant at 20 min, 30 min and 40 minutes with more sedation in dexmedetomidine group. Heart rate and blood pressure were lower in dexmedetomidine group. Children in group D had better reaction to i.v. cannulation and mask acceptance scores compared with group M (midazolam). Postoperative sedation was highest in group D and these children had better wake up scores than midazolam. ***Conclusion:*** Compared to midazolam, intranasal dexmedetomidine provides higher sedation level, better mask acceptance and better response to intravenous cannulation.

Key Words

Dexmedetomidine, Intranasal, Midazolam, Pediatric patients

Introduction

Children compound the sense of insecurity when they are separated from their parents for the induction of anesthesia or see unfamiliar faces inside the operating room (1). Preoperative anxiety can largely affect the smoothness of induction, emergence from anesthesia and the psychological and emotional state of the child (2).

Multimodal approach consisting of sedative drugs, parental presence during induction of anesthesia, play therapy, familiar environment and effective pain therapy is necessary to reduce preoperative anxiety (3). Certain drugs like midazolam and α_2 agonists like dexmedetomidine have been introduced in anesthesia practice as premedicants (4). Anterograde amnesia,

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reduced anxiety, rapid onset of sedation and reduced postoperative behavioral changes have been observed in children receiving midazolam as premedicant.

Premedication with dexmedetomidine produces preoperative sedation and anxiolysis in children. Furthermore, it has analgesic properties, decreases volatile anesthetic requirements and improves perioperative hemodynamics of the patient (5). Premedicant drugs can be administered through various routes. Intranasal route offers the advantage of rapid and virtually complete absorption due to high mucosal vascularity (6).

The primary outcome of the study was to evaluate the efficacy of intranasal midazolam and dexmedetomidine as premedicants to provide sedation by a noninvasive route. The secondary outcome was to compare their preoperative sedative and anxiolytic properties and assess side effects, if any.

Material and Methods

The study was conducted on one hundred and five children of either sex, aged between 2-8 years undergoing elective surgery under general anesthesia after approval from the Institutional Ethical Committee (Pharma/2010/2/541). Children with nasal pathology/ infection, allergy to any of the study drugs, compromised airway were excluded from the present study. Preoperatively, children were kept fasting for 6 hours. The study drugs were reconstituted according to per kilogram of body weight dosage and divided into two aliquots of equal volume for administration in both the nostrils. Variables like heart rate, blood pressure, SpO_2, degree of sedation were measured before administering the study drug. Each patient was randomly assigned to one of the three study groups:

Group M: 35 patients receiving midazolam 0.2 mg/kg, 0.5 ml in each nostril, 40 minutes before induction of anesthesia.

Group D: 35 patients receiving dexmedetomidine 1 μg/kg, 0.5 ml in each nostril, 40 minutes before induction of anesthesia.

Group C: 35 patients receiving normal saline as placebo, 0.5 ml in each nostril, 40 minutes before induction of anesthesia.

Drugs were administered into the nostrils with dropper in supine position after which the subjects were immediately shifted to lateral position, and then their nostrils were pinched. Heart rate (HR), blood pressure (BP), SpO_2, degree of sedation was measured every 10 minutes till 30 minutes according to the 5- point sedation scale: 1= Agitated (clinging to parent/crying); 2= Alert (aware, may whimper but not clinging/crying); 3= Calm (lying comfortably with spontaneous eye opening); 4= Drowsy (lying comfortably with eyes closed but responding to minor stimulation); 5= Asleep (eyes closed, arousable but does not respond to minor stimulation).

Once the sedation score of 2-3 was achieved, the child was taken inside the operating room and intravenous line with 5% dextrose started. The reaction to intravenous cannulation was noted according to 4-point scale: 1= fight without success; 2= fight with success; 3= minor resistance; 4= no reaction. Score 3 and 4 was considered satisfactory. Routine monitors were then attached to the child and HR, BP, SpO_2 and degree of sedation were noted at 40 minutes. Face mask acceptance (100% oxygen for 3 minutes) by the child was noted according to 5-point scale; 1= combative, crying; 2= moderate fear of mask, not easily calmed; 3= cooperative with reassurance; 4= calm, cooperative; 5= asleep, steal induction. Score 3 or more were considered satisfactory.

Induction was done with injection propofol 2 mg/kg. Tracheal intubation was done after administration of injection atracurium 0.6 mg/kg. Anesthesia was maintained with nitrous oxide 66%, oxygen 33% and 0.2-0.5% Halothane. Vitals were noted every 10 minutes, intraoperatively. Analgesia was provided with injection tramadol 0.5 mg/kg intravenous after induction of anesthesia. Any intraoperative complications were noted. At the end of the surgery, residual neuromuscular blockade was reversed by injection neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. Level of postoperative sedation was assessed using a 3- point scale: 1= agitated, crying; 2= crying but easily consoled; 3= calm/asleep. Postoperatively, patient was assessed at 10 minutes for one hour interval using the same scale.

Data was analyzed with the computer software SPSS version 17.0 for windows. Difference in mean values of sedation score and hemodynamic variables was assessed by One- way Analysis of Variance (ANOVA). Statistical significance of qualitative variables was assessed by chi-square test. Intergroup comparisons were made post-hoc by Bonferroni's t-test. p-value <0.05 was considered statistically significant. All p-values reported were two-tailed.

Results

All the three groups were comparable in terms of age, weight, sex and mean duration of surgery (*Table1*).

Table 1: Demographic Variables and Duration of Surgery

Group	Age (Years) Mean ± SD	Weight (Kg) Mean ± SD	Sex (M:F Ratio)	Duration of Surgery (Minutes)
M	5.47 ± 2.01	18.31 ± 4.86	17:18	50.00 ± 20.58
D	5.46 ± 2.01	18.68 ± 5.22	19:16	52.28 ± 19.57
C	5.57 ± 2.09	18.66 ± 4.79	18:17	53.43 ± 22.35
p value	0.959	0.986	0.97	0.834

Table 2: Sedation Score after Giving Premedication (Mean ± SD)

Group	Baseline	10 Minutes	20 Minutes	30 Minutes	40 Minutes
M	1.66 ± 0.48	2.17 ± 0.45	2.14 ± 0.55	2.23 ± 0.43	2.20 ± 0.58
D	1.74 ± 0.44	2.57 ± 0.61	3.63 ± 0.69	3.86 ± 1.46	3.66 ± 0.10
C	1.54 ± 0.50	1.43 ± 0.50	1.43 ± 0.56	1.31 ± 0.47	1.34 ± 0.48
p value	0.086	<0.001	<0.001	<0.001	<0.001

Table 3: Hemodynamic Variables after Giving Premedication (Mean ± SD)

Time (in minutes)	Group M	Group D	Group C	*p* value
Heart Rate				
Baseline	108.11 ± 15.06	100.37 ± 17.44	102.37 ± 12.56	0.084
10	107.46 ± 14.34	96.34 ± 17.97	108.46 ± 10.19	<0.001
20	106.06 ± 14.21	91.97 ± 16.42	108.63 ± 9.90	<0.001
30	105.54 ± 14.43	87.68 ± 14.90	109.06 ± 10.21	<0.001
40	105.46 ± 14.13	82.88 ± 13.74	110.20 ± 10.34	<0.001
Systolic BP				
Baseline	104.97 ± 10.86	101.08 ± 5.35	105.23 ± 6.74	0.082
10	104.20 ± 10.65	99.46 ± 4.62	106.08 ± 7.17	0.003
20	103.80 ± 10.67	95.20 ± 4.35	106.48 ± 6.79	<0.001
30	104.08 ± 10.07	90.83 ± 4.18	106.63 ± 6.79	<0.001
40	104.00 ± 10.40	86.57 ± 4.04	108.20 ± 7.37	<0.001
Diastolic BP				
Baseline	65.74 ± 5.68	64.51 ± 4.61	65.71 ± 4.66	0.051
10	63.03 ± 4.73	62.28 ± 4.38	67.74 ± 5.54	0.001
20	62.48 ± 4.62	59.28 ± 4.86	68.17 ± 5.75	<0.001
30	62.40 ± 4.49	56.91 ± 4.37	68.51 ± 5.65	<0.001
40	62.08 ± 4.55	54.37 ± 4.01	68.77 ± 5.56	<0.001

On intergroup comparison, the difference in sedation score between group M and D was insignificant at 10 minutes but highly significant at 20 min, 30 min and 40 minutes (*p*-value <0.001, Bonferroni's t-test) (*Table 2*). However, on intergroup comparison of group M and D with group C it was statistically highly significant at all time intervals (*p* value <0.001).

On intergroup comparison between group M and D the difference in heart rate and diastolic blood pressure was statistically highly significant at 10, 20, 30 and 40 minutes after giving premedication (*Table 3*). However, systolic blood pressure was found to be statistically significant at 10 minutes but highly significant at 20, 30 and 40 minutes after giving premedication (*p* <0.001).

The mean score for reaction to Intravenous cannulation and mask acceptance was highest for dexmedetomidine (*Table 4*). The difference was found to be statistically highly significant amongst all the groups (*p* <0.001). On intergroup comparison between group M and D the difference in Intraoperative mean heart rate, systolic and diastolic blood pressure was found to be statistically highly significant at 10, 30 and 60 minutes from the start of the surgery (*Table 5*) (*p* <0.001).

Table 6 shows the sedation score for the three groups

Table 4: Reaction to Intravenous Cannulation and Mask Acceptance Score

Group	Reaction to IV Cannulation Score (Mean ± SD)	Mask Acceptance Score (Mean ± SD)
M	2.51 ± 0.66	2.63 ± 0.88
D	3.37 ± 0.49	3.91 ± 0.44
C	1.86 ± 0.49	1.54 ± 0.66
p value	<0.001	<0.001

Table 5: Intraoperative Hemodynamic Variables Changes at Various Time Intervals from the Start of Surgery (Mean ± SD)

Time (in minutes)	Group M	Group D	Group C	*p* value
Heart Rate				
Baseline	108.11 ± 15.06	100.37 ± 17.44	102.37 ± 12.56	0.084
10	109.54 ± 14.7	85.57 ± 12.93	107.37 ± 10.44	<0.001
30	107.60 ± 13.21	84.88 ± 13.87	109.00 ± 13.81	<0.001
60	108.25 ± 12.65	85.06 ± 12.95	107.72 ± 12.96	<0.001
Systolic BP				
Baseline	104.97 ± 10.86	101.08 ± 5.35	105.23 ± 6.74	0.082
10	107.54 ± 10.26	92.66 ± 5.84	110.26 ± 9.37	<0.001
30	107.88 ± 10.64	88.53 ± 5.24	111.10 ± 8.15	<0.001
60	109.23 ± 12.47	89.06 ± 4.60	112.21 ± 6.35	<0.001
Diastolic BP				
Baseline	65.74 ± 5.68	64.51 ± 4.61	65.71 ± 4.66	0.051
10	65.26 ± 4.60	56.40 ± 4.80	71.34 ± 5.80	<0.01
30	64.74 ± 5.14	56.00 ± 4.18	72.83 ± 4.99	<0.01
60	66.69 ± 6.13	54.44 ± 5.46	74.67 ± 6.52	<0.01

Table 6: Postoperative Sedation Score (Mean ± SD)

Time (minutes)	Group M	Group D	Group C	*p* value
Emergence	2.11 ± 0.87	2.80 ± 0.40	1.34 ± 0.54	<0.001
10	1.97 ± 0.78	2.91 ± 0.28	1.28 ± 0.46	<0.001
20	1.83 ± 0.66	2.88 ± 0.32	1.40 ± 0.50	<0.001
30	2.03 ± 0.71	2.88 ± 0.32	1.60 ± 0.50	<0.001
40	2.23 ± 0.64	3.00 ± 0.00	1.60 ± 0.50	<0.001
50	2.37 ± 0.60	3.00 ± 0.00	1.68 ± 0.47	<0.001
60	2.43 ± 0.61	3.00 ± 0.00	1.83 ± 0.62	<0.001

at various time intervals from emergence till one hour, postoperatively. Using ANOVA, the difference was found to be statistically highly significant amongst the group (p <0.001) at all intervals.

Discussion

Preoperative anxiety can largely affect the smoothness of induction and emergence from anesthesia in children (2). Therefore, rapid and effective sedation is a prerequisite in pediatric population. A number of pharmacological agents have been used to provide sedation and promote smooth induction. These agents are melatonin, opioids (morphine, pethidine, fentanyl); barbiturates; phenothiazines (promethazine); chloral and related agents (chloral elixirs and triclofos); NSAIDS (diclofenac, piroxicam); anticholinergics (atropine, scopolamine); antiemetics; ketamine and α_2 agonists (clonidine, dexmedetomidine) (7-11).

Premedicant drugs can be administered through various routes. Intravenous and intramuscular routes lead to complete absorption of drugs but it is painful, traumatic, time consuming and potential source of infection. Oral route is associated with unpredictable absorption due to high first pass metabolism. Sublingual route is beneficial

but for desired effect drug must be held under the tongue for atleast 30 seconds which requires cooperation which is difficult in children. Bitter taste is also a limiting factor and cause for low compliance. Intrarectal route can make the patient uncomfortable, can cause defecation and has unpredictable absorption. Intranasal route is advantageous in various regard as it offers painless, rapid and virtually complete absorption due to high mucosal vascularity (12,13). Direct absorption through olfactory mucosa into CSF gives rapid brain levels of the drug (6).

Till date, few studies have been conducted using midazolam and dexmedetomidine as intranasal premedicants and many have recommended further evaluation. It is in this context that the present study was undertaken to compare the safety and efficacy of these drugs when used as premedicants via the intranasal route in pediatric patients.

In our study, children experienced sedation 10 minutes after the study drug was given. The sedation achieved with dexmedetomidine was more than midazolam and it increased significantly at 20, 30 and 40 minutes. In our study, sedation score was higher for dexmedetomidine than midazolam. However, the difference was statistically insignificant at 10 minutes, but significantly lower in midazolam at 20, 30 and 40 minutes.

Similarly, Sheta *et al.* (14) stated that intranasal dexmedetomidine was more capable of inducing sleep preoperatively than intranasal midazolam at 20 and 30 min and in the Operating Room. Talon *et al.* (15) and Patel *et al.* (16) compared dexmedetomidine with midazolam and reported that intranasal dexmedetomidine was more effective in inducing sleep preoperatively at 30 and 45 min after drug administration (p <0.0001). Similar to our finding, sedation score was significantly higher 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 in other studies as well (17,18). In the study done by Abdelmoneim *et al.* (19), the sedation scores were statistically significantly lower in the midazolam group at 10 and 20 min after the administration of the drug. But at 30 min after drug administration, there was a statistically significant decrease in sedation score in the dexmedetomidine group.

In our study, parental separation of the child was easier with dexmedetomidine than midazolam. Satisfactory sedation at parental separation in our study was seen in 22.86% children of midazolam and in 74.29% of dexmedetomidine group. Control group had no sedation and parental separation was difficult in these children. Our results are in accordance with those of Sundaram and Mathian (20) who reported satisfactory parental separation in 83% of the children after intranasal 1 µg/kg dexmedetomidine. Similar findings were reported in other studies as well (21-24). This is in contrast to the findings of Akin *et al.* (25) and Schmidt *et al.* (26) who did not find any difference in sedation in children premedicated with dexmedetomidine and midazolam. This could have resulted from different scales used for sedation assessment.

In the current study, the decrease in heart rate after giving midazolam was minimal. The mean values for SBP and DBP remained comparable throughout the preoperative period, that is, 40 minutes after premedication. This is in accordance with the Bhakta *et al.* (27) who noted that heart rate did not alter after 0.2 mg/kg intranasal midazolam premedication. This could be attributed to more rapid onset of action of midazolam.

Heart rate was significantly lower in dexmedetomidine group at all intervals after giving the premedication. Systolic blood pressure was statistically significantly lower in dexmedetomidine group at 20, 30 and 40 minutes and diastolic blood pressure at 30 and 40 minutes. Our results are supported by many other studies who have found a significant decrease in heart rate and SBP from baseline (13,21,22,24). The mean values for intraoperative hemodynamic parameters remained comparable to their preoperative values in each group.

Amongst the three groups, reaction to i.v. cannulation score was best observed for dexmedetomidine followed by midazolam and control group. This is in agreement with other studies who observed no or mild reaction to i.v. cannulation in children receiving dexmedetomidine (19,28). This can be explained by the sedative, anxiolytic and analgesic properties of dexmedetomidine while, midazolam does not have any analgesic action. As regards to mask acceptance in the present study, dexmedetomidine group had better mask acceptance scores than midazolam group. This is in agreement with many other previous studies (14,21-23,27).

Finally, postoperative sedation score was highest in dexmedetomidine and lowest in control group. Children were either calm cooperative or could be easily consoled in the postoperative period. This was in accordance with the studies of Mizrak *et al.* (29) and Munro *et al.* (30) who found better wake up score and significantly lower emergence agitation in dexmedetomidine than midazolam. In the present study, side effects such as teary eyes,

nasal irritation, bradycardia or respiratory depression were not recorded in any of the patients.

Limitations: Our study was designed to compare the efficacy of two drugs for premedication in children. Therefore, further studies with higher sample size are required to establish the usefulness of intranasal dexmedetomidine as perioperative anxiolytic in children. We have administered the drug with the help of a needle less syringe; it is possible to use atomizer for this purpose. Midazolam atomizer is available but it is not available for dexmedetomidine. If we would have used only Midazolam atomizer the process of blinding would have been adversely affected in our study.

Conclusion

Intranasal dexmedetomidine results in higher sedation level, better parental separation, better acceptance of mask and better response to intravenous cannulation than intranasal midazolam. Hence, intranasal dexmedetomidine is superior to intranasal midazolam for premedication in pediatric patients.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

References

1. Gupta A, Dalvi NP, Tendolkar BA. Comparison between intranasal dexmedetomidine and intranasal midazolam as premedication for brain magnetic resonance imaging in pediatric patients: A prospective randomized double blind trial. *J Anaesthesiol Clin Pharmacol* 2017;33(2):236-40.
2. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. *Pediatrics* 2006;118(2):651-58.
3. Kain ZN, Caldwell-Andrews AA. Preoperative psychological preparation of the child for surgery: an update. *Anesthesiol Clin North Am* 2005;23(4):597-614.
4. Malde AD. Dexmedetomidine as premedication in children: Status at the beginning of 2017. *Indian J Anaesth* 2017;61(2):101-02.
5. Lin Y, Chen Y, Huang J, Chen H, Shen W, Guo W, *et al.* Efficacy of premedication with intranasal dexmedetomidine on inhalational induction and postoperative emergence agitation in pediatric undergoing cataract surgery with sevoflurane. *J Clin Anesth* 2016;33:289-95.
6. Almenrader N, Larsson P, Passariello M, Haiberger R, Pietropaoli P, Lönnqvist PA, *et al.* Absorption pharmacokinetics of clonidine nasal drops in children. *Paediatr Anaesth* 2009;19(3):257-61.
7. Faghihian R, Eshghi A, Faghihian H, Kaviani N. Comparison of oral melatonin and midazolam as premedication in children undergoing general anesthesia for dental treatment. *Anesth Pain Med* 2018;8(2):e64236.
8. Chen Z, Lin M, Huang Z, Zeng L, Huang L, Yu D, *et al.* Efficacy of chloral hydrate oral solution for sedation in pediatrics: a systematic review and meta-analysis. *Drug Des Devel Ther* 2019;13:2643-53.
9. Chatrath V, Kumar R, Sachdeva U, Thakur M. Intranasal fentanyl, midazolam and dexmedetomidine as premedication in pediatric patients. *Anesth Essays Res* 2018;12(3):748-53.
10. Poonai N, Canton K, Ali S, Hendrikx S, Shah A, Miller M, *et al.* Intranasal ketamine for procedural sedation and analgesia in children: a systematic review. *PLoS One* 2017;12(3):e0173253.
11. Sidhu GK, Jindal S, Kaur G, Singh G, Gupta KK, Aggarwal S. Comparison of intranasal dexmedetomidine with intranasal clonidine as a premedication in surgery. *Indian J Pediatr* 2016;83(11):1253-58.
12. Mukherjee S, Ray M, Ray A, Khanra M, Mandal PK, Pal R. Clonidine premedication for paediatric patients: a comparison of the oral & nasal route. *J Anaesth Clin Pharmacol* 2010;26(3):319-22.
13. 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(2):374-80.
14. Sheta SA, Al-Sarheed MA, Abdelhalim AA. Intranasal dexmedetomidine vs midazolam for premedication in children undergoing complete dental rehabilitation: a double-blinded randomized controlled trial. *Paediatr Anaesth* 2014;24(2):181-89.
15. Talon MD, Woodson LC, Sherwood ER, Aarsland A, McRae L, Benham T. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. *J Burn Care Res* 2009;30(4):599-605.
16. Patel DD, Lisha, Upadhyay MR. Pre anaesthetic medication in children: a comparison of intranasal dexmedetomidine versus intranasal midazolam. *J Med Res* 2015;1(2):59–63.

17. Nitturi S, D'souza O. A comparative evaluation of intranasal dexmedetomidine and intranasal midazolam for premedication in pediatric surgery. *Int Arch Integr Med* 2018;5(1):82-94.

18. Messeha MM, El-Morsy GZ. comparison of intranasal dexmedetomidine compared to midazolam as a premedication in pediatrics with congenital heart disease undergoing cardiac catheterization. *Anesth Essays Res* 2018;12(1):170-75.

19. Abdelmoneim HM, Hamouda SA, Mahfouz GA, Hashem AE. Intranasal dexmedetomidine versus midazolam in preoperative sedation for noncomplex pediatric congenital cardiac surgeries. *Res Opin Anesth Intensive Care* 2016;3(3):129-37.

20. Sundaram AM, Mathian VM. A comparative evaluation of intranasal dexmedetomidine and intranasal midazolam for premedication in children: a double blind randomized controlled trial. *J Indian Dent Assoc* 2011;5:777-81.

21. 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(6):1715-21.

22. Sun Y, Lu Y, Huang Y, Jiang H. Is dexmedetomidine superior to midazolam as a premedication in children? A meta-analysis of randomized controlled trials. *Paediatr Anaesth* 2014;24(8):863-74.

23. Singla D, Chaudhary G, Dureja J, Mangla M. Comparison of dexmedetomidine versus midazolam for intranasal premedication in children posted for elective surgery: a double-blind, randomised study. *South Afr J Anaesth Analg* 2015;21(6):12-15.

24. Ghali AM, Mahfouz AK, Al-Bahrani M. Preanesthetic medication in children: a comparison of intranasal dexmedetomidine versus oral midazolam. *Saudi J Anaesth* 2011;5(4):387-91.

25. 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(9):871-76.

26. Schmidt AP, Valinetti EA, Bandeira D, Bertacchi MF, Simões CM, Auler JO Jr. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. *Paediatr Anaesth* 2007;17(7):667-74.

27. Bhakta P, Ghosh BR, Roy M, Mukherjee G. Evaluation of intranasal midazolam for preanasthetic sedation in paediatric patients. *Indian J Anaesth* 2007;51(2):111-16.

28. Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial. *J Anesth* 2014;28(1):12-18.

29. Mizrak A, Koruk S, Ganidagli S, Bulut M, Oner U. Premedication with dexmedetomidine and midazolam attenuates agitation after electroconvulsive therapy. *J Anesth* 2009;23(1):6-10.

30. 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(2):109-12.