Indian Journal of Clinical Anaesthesia 2022;9(1):66–70

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical Anaesthesia

Journal homepage: www.ijca.in

Original Research Article

A comparative study of intranasal dexmedetomidine and intranasal midazolam for premedication - A prospective randomized double-blind study in children posted for tonsillectomy

Girimurugan Nagarajan[1,*], Pavithira Sekar[2], Navaneetha Krishnan Srinivasan[1], Prem Kumar[1], Harish Kumar[1]

[1]*Dept. of Anaesthesiology, Saveetha Medical College & Hospital, Chennai, Tamil Nadu, India*
[2]*Dept. of Pharmacology, Sri Muthukumaran Medical College Hospital & Research Institute, Chennai, Tamil Nadu, India*

ARTICLE INFO

Article history:
Received 09-11-2021
Accepted 21-12-2021
Available online 12-02-2022

Keywords:
Dexmedetomidine
Midazolam
Intranasal
Paediatrics
Premedication

ABSTRACT

Background and Aim: Preanesthetic medication in paediatric patients is well known to be a challenge for anaesthesiologists. Premedication in paediatric population helps to produce a relaxed state with reduced anxiety and increased compliance as well as to ease separation from parent and allowing the patient to tolerate and co-operate with the necessary procedure. Our aim is to do a comparation of dexmedetomidine and midazolam given via intranasal route in children posted for tonsillectomy as premedication.

Materials and Methods: This study was conducted in 100 patients of 6 to 12 years posted for tonsillectomy. Patients were randomly allocated into Group M and D. Patient in group M (50) received 0.2mg/kg of midazolam administered intranasally as nasal drop using 1ml insulin syringe and similarly group D (50) received 1μg/kg of dexmedetomidine administered intranasally as nasal drops using 1ml insulin syringe. Sedation score, Anxiolysis score, mask induction score, post-operative agitation score was assessed.

Results: Satisfactory sedation was achieved by 86% and 68% of patient in dexmedetomidine and midazolam respectively p (0.03). Satisfactory mask induction was achieved by 84% and 70% of patient in dexmedetomidine and midazolam respectively p (0.09). In terms of post op agitation score there is no difference in both the group p (0.30). During the time between administration of pre op drugs and initiation of anaesthesia, no patient seems to develop hypotension, hypoxia or any other life-threatening complication

Conclusion: In our study we concluded that in terms of decreasing anxiety at parental separation both dexmedetomidine and midazolam were found to be equally effective. However, Intranasal dexmedetomidine produced superior sedation scores at separation and induction compared to oral midazolam in paediatric patients.

This is an Open Access (OA) journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

1. Introduction

Preanesthetic medication in paediatric patients is well known to be a challenge for anaesthesiologists. Premedication in pediatric population helps to produce a relaxed state with reduced anxiety and increased compliance as well as to ease separation from parent and allowing the patient to tolerate and co-operate with the necessary procedure.[1–4] The aims of preanesthetic medication in pediatric population include decreasing fear, anxiety and facilitation of a smooth anesthetic induction[5,6] and preventing postoperative psychological sequel. Intranasal administration has shown to be very effective, easy, non-invasive route with high bioavailability

* *Corresponding author*.
E-mail address: drgirimurugan@gmail.com (G. Nagarajan).

https://doi.org/10.18231/j.ijca.2022.014
2394-4781/© 2022 Innovative Publication, All rights reserved.

and rapid onset of action due to the high vascularization of the nasal mucosa.[7]

A γ-amino-butyric acid (GABA) receptor inhibitor, Midazolam is the most widely employed sedative drug in children as a premedication. It is known to provide effective sedation, anxiolytic effect, and of antero-grade amnesia of varying degrees.[8,9] A recent clinical study shows that a dose of 0.2 mg/kg midazolam is effective in reducing both induction anxiety and separation from parent, with no effect on recovery time.[10,11]

A newer alpha 2-agonist, Dexmedetomidine has more selective action on the alpha 2-adrenoceptor and has a short half-life.[12,13] its bioavailability is around 80% when given via the nasal mucosa. Dexmedetomidine usage in paediatric population as preanesthetic is increasing because of its huge safety profile.[14] We hypothesized that dexmedetomidine can be used as an alternative to midazolam for intranasal premedication in children. This prospective randomized double-blind study was conducted to compare the efficacy of dexmedetomidine and midazolam as intranasal premedication in children undergoing tonsillectomy. The primary outcome was determined with correlation to preoperative sedation, response of child to parental separation, mask induction, and the incidence and severity of postoperative agitation. Secondary outcomes studied hemodynamic stability of both drugs.

2. Materials and Methods

This was a prospective double blinded study conducted after obtaining approval from institutional ethical committee. This study included children of age 6 to 12 years with ASA physical status I posted for tonsillectomy. Informed written consent was obtained from the parents of the patients after explaining the study protocol to them. Patients with known allergy to any of the study drugs, recent upper respiratory tract infection/ lower respiratory tract infection, congenital heart disease, mental retardation, or neurobehavioral problems were excluded from the study. Children were randomly assigned using simple randomization procedure (random numbers generated by computer) to 1 of 2 treatment groups. Intranasal study medication was given 60 min before inducting anaesthesia to all the children.

Patient in group M (50) received 0.2mg/kg of midazolam administered intranasally as nasal drop using 1ml insulin syringe and similarly group D (50) received 1μg/kg of dexmedetomidine administered intranasally as nasal drops using 1ml insulin syringe.

An investigator who doesn't have role in the giving anaesthesia was made to prepare the drug mixture. Anaesthesiologists attending the patients and the observers were blinded.

2.1. Pre-operative assessment

A blinded observer was made to assess the sedation status once in 10 min with a six- point sedation scale as shown in Table 1 and every 10 min the level of anxiety was evaluated using a four – point scale as shown in Table 2.

2.2. During anesthesia

All patients received general anaesthesia induced nasally by nitrous oxide, oxygen (50:50) and sevoflurane 2% via a primed face mask. The degree of mask acceptance was assessed using three-point Mask Induction scale. Standard ASA monitors (NIBP, ECG, SPO2) were connected.

2.3. Mask induction score

1. Calm, cooperative or asleep
2. Moderate fear of the mask, cooperative with reassurance
3. Combative, crying

2.4. Post-operative

At the end of surgery with adequate routine precautions post op agitation was assessed using a 3-point scale shown in Table 4. Postoperative agitation score after 10 min of extubation.

2.5. Postoperative agitation score

1. Calm, easily arousable and follows commands
2. Crying or restless but calms to verbal instructions
3. Disoriented, combative or thrashing.

2.6. Statistical analysis

Sample size was calculated based on a study by Akin A et al.[15] who mentioned that 82.2% of Group M and 60% of Group D (P = 0.01) achieved satisfactory mask induction. Taking this study as an example for calculating, in which a sample of 45 patients in each group provided 80% power at a 0.05 level of significance. We recruited 50 patients in each group in case of possible dropouts. The numerical data were compared using unpaired Student's t-test and reported as mean ± standard deviation. For sedation and anxiety scores nonparametric Mann-Whitney U-Test was used. Categorical variables were compared by Chi-square test and reported as median with interquartile range (IQR) and also numbers and percentages. For assessing statistical significance, a P value of 0.05 or less was set. Statistical Analysis was done using Epi info 3.5.4.

3. Results

During the entire study period, a total number of hundred patients met inclusion criteria and were involved in the study. The two groups selected were more or less similar

with regard to demographic characters like age, weight, gender, duration of surgery, duration of anaesthesia, and extubation time. The mean age in group dexmedetomidine 9.00 + 2.11 years and group midazolam was 8.98 + 2.18 years suggesting both the group had comparable demographic characteristics (p=0.962). In this study 52% were male and 48% female in group dexmedetomidine and 60% were male and 40% female in group midazolam, suggesting both the group had comparable demographic characteristics.

hows the mean of Duration of Surgery, Anaesthesia, extubation time in group Dexmedetomidine is 34.24, 47.44, 8.1 and group midazolam is 34.58, 47.04,8, suggesting mean value of both the group is comparable.

As shown in Table 4, separation from parent, a satisfactory sedation was achieved in 86% and 68% of patient in dexmedetomidine and midazolam respectively p (0.03). Mask induction was satisfactorily achieved by 84% and 70% of patient in dexmedetomidine and midazolam respectively p (0.09). In terms of post op agitation score there is no difference in both the group p (0.30).

hows that the Sedation score were statistically lower in dexmedetomidine group compared to midazolam group at the 50th and 60thmin after administered of drug and separation. The anxiety score is equal in both the group there is no statistically significant between the groups.

3.1. Haemodynamic parameters

In the dexmedetomidine group a 13.41% reduction was seen in Heart Rate compared with midazolam group there was 7.56% decrease at the end of 60^{th} minute. In our study, heart rate was significantly reduced in dexmedetomidine group when compared to midazolam group from the 20^{th} minute continuously intraoperatively. Peripheral oxygen saturation never went below 95% in any group in the preop, intraop and postop periods.

There was modest decrease in Blood pressure (13.19%) in dexmedetomidine group and 10.46% in midazolam group. There was no statistical significance in between groups both during preoperative and intraoperative period.

No patient developed hypotension, hypoxia during the time between administration of pre op medication and initiation of anaesthesia induction. None of the patient developed laryngospasm in the both groups.

4. Discussion

In this study, we intend to compare the effects of administering dexmedetomidine and midazolam via intranasal route on mask induction and satisfactory sedation upon separation from parents in children undergoing tonsillectomy and found that premedication with 1μg/kg of intranasal dexmedetomidine was superior to 0.2 mg/kg of intranasal midazolam in decreasing anxiety at parenteral separation. However, both drugs seem to have equal effectiveness in terms of achieving satisfactory sedation throughout mask induction.

Most frequently used drug as a premedication is Midazolam. The main drawback of using midazolam via intranasal route is that it causes an unfavourable irritation within the nasal cavity. Hence, the nasal route of administering midazolam isn't encouraged in regular practice. However, there are numerous studies that suggest that giving midazolam intranasally is best tolerated by children than its oral administration.[16]

Walbergh et al. studied the plasma concentration of Midazolam in children following intranasal administration and concluded that intranasal midazolam rapidly achieved sedative plasma concentration.

Malinovsky et al. studied the effect of intranasal, rectal and oral route on plasma midazolam concentration and observed that adequate sedation occurred within 10 min by giving midazolam intranasally.

As dexmedetomidine poses anxiolytic, sedation analgesic and sympatholytic properties, it's a useful adjunct for premedication, especially for patients vulnerable to preoperative stress. Yuen et al. studied the sedative

Table 1: Modified observer's assessment of Alertness/sedation score

Score	Criteria
6	Appears alert and awake, responds readily to name spoken in normal tone
5	Appears asleep but responds readily to name spoke 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

Table 2: Anxiolysis score

Score	Criteria
1	Calm and cooperative;
2	Anxious but could be reassured;
3	Anxious and could not be reassured
4	Crying or resisting

Table 3: Mean duration of surgery, anaesthesia and extubation time

Parameters (min)	Group D	Group M	p value
Duration of surgery (min) mean ± SD	34.24 + 3.52	34.58 + 3.32	0.620
Duration of Anaesthesia (min) mean ± SD	47.44 + 3.69	47.04 + 4.50	0.628
Extubation time (min) mean ± SD	8.10 + 1.52	8.00 + 1.41	0.733

Table 4: Separation from parents, quality of mask induction and agitation score

Score	Drugs		P Values
Separation from parents (Anxiolysis Score)	**Group D n(%)**	**Group M n(%)**	
Calm, cooperative	43 (86)	34 (68)	0.03
Anxious but could be Reassurable	5 (10)	10 (20)	0.16
Anxious and could not be Reassurable	1 (2)	4 (8)	0.16
Crying, or resisting	1 (2)	2 (4)	0.56
Quality of mask induction			
Calm, cooperative or asleep	42 (84)	35 (70)	0.09
Moderate fear of mask but cooperative with reassurance	4 (8)	10 (20)	0.08
Combative, crying.	4 (8)	5 (10)	0.72
Postoperative agitation score			
Calm, easily arousable, follows commands	35 (70)	30 (60)	0.30
Restless or crying but calms to verbal commands	14 (28)	18 (36)	0.39
Disoriented, Combative, thrashing	1 (2)	2 (4)	0.56

$p < 0.05$ is statistically significant.

Table 5: Preoperative sedation and anxiety score (median IQR)

Time	Sedation Score			Anxiety Score		
	Group D	Group M	P values	Group D	Group M	P values
Baseline	6 (6-6)	6 (6-6)	-	2 (1-4)	2 (1-4)	.680
10 min	5 (5-6)	5 (5-6)	.322	1 (1-4)	2 (1-4)	.065
20 min	5 (4-5)	5 (4-5)	.117	1 (1-4)	1 (1-4)	.349
30 min	4 (3-5)	4 (3-5)	.058	1 (1-4)	1 (1-4)	.192
40 min	3 (3-5)	3 (3-5)	.194	1 (1-4)	1 (1-4)	.244
50 min	3 (3-5)	3 (3-5)	.046	1 (1-4)	1 (1-4)	.244
60 min	3 (2-5)	3 (2-5)	.022	1 (1-4)	1 (1-4)	.244

Data are presented as median (IQR). z Mann-Whitney test,
p value < 0 05 was considered statistically significant

and analgesic effect of intranasal dexmedetomidine and concluded that intranasal route is more effective, well tolerated and convenient for the administration of dexmedetomidine.

L Kumar in 2017 has compared nasal instillation of Dexmedetomidine with oral Midazolam in various types of paediatric surgeries and has shown that both are effective premedication in paediatric practice.[17]

Another study clearly shows that intranasal 1 and 1.5 μg/kg doses of dexmedetomidine have similar effects on volunteers. Yuen et al reported that 1 μg/kg of dexmedetomidine is more effective in their study which compared 0.5 and 1 μg/kg intranasal doses. In children with burns, Talon et al. preferred using large doses of intranasal dexmedetomidine (such as 2 μg/kg) for preoperative premedication. Taking these references into consideration we choose 1 μg/kg dose of dexmedetomidine in our study. Davis et al. found that there's no difference in effects while using both 0.2 and 0.3 mg/kg intranasal midazolam. Numerous other studies have shown to use intranasal dose of midazolam of 0.2 mg/kg. The dose that we have used in our study was firm in light of these studies. Yuen et al. study shows that the sedative effect of intranasal dexmedetomidine is observed after 45–60 min while the best sedative effect occurs at 90–105 min in healthy volunteers. In a study of paediatric patients by the same authors, this duration was accepted approximately 60 min.[18] For intranasal midazolam Satisfactory separation from the parents has been found between 25 to 30 min[19] because midazolam has the benefit of being a fast-acting drug. In our study the time taken for onset of both drugs utilized was different, we kept the preoperative sedation time to be 60 min. In this investigation, it shows that 86% of paediatric patients in dexmedetomidine group attained a satisfactory sedation compared to 68% in midazolam group. Moreover 84% of those sedated patients allowed mask induction without signs of distress and awakening.

We may have seen the best sedative effect in the midazolam group if we had used the upper doses of 0.3mg/kg. In a previous study which compared the effects of Clonidine, dexmedetomidine, and midazolam as premedication in children proved that Oral preparation of midazolam is superior to clonidine, and oral dexmedetomidine with faster onset of sedation, higher sedation score, lower anxiety score, and greater number of children with easy separation and excellent mask acceptance.[20] Additionally, administering intranasal dexmedetomidine (0.5 and 1μg/kg) preoperatively shown

to reduce Heart rate and Blood pressure in healthy children during the first hour. The reduction in SBP and HR seen after giving 1 μg/kg of dexmedetomidine was 14.1% and 16.4%, respectively. In our study with dexmedetomidine, reduction in Systolic Blood Pressure was 13.19% and Heart Rate was 13.14%. These levels in comparison with midazolam group was 10.46% and 7.56%. In a study conducted by yuen et al also showed there was decrease in SBP & HR after 1μg/kg of dexmedetomidine was 14.1% and 16.4% respectively.

Postoperative agitation score, both the groups had better score and there's no statistical significance.

We found that there were no clear differences among both the groups with relevance to adverse effects, emergence from anaesthesia, or follow-up. The foremost limitation seen in this trail is that the timing of the drug administration, since peak onset of both the drug varied. So, fixing premedication time of both groups is also the reason for the difference and dose of midazolam could also be inadequate. The three- or four-point scales used in this study is unvalidated still, which again is considered as a limitation. There were some difficulties we encountered in evaluating paediatric patients while using these scales. For instance, if the child was crying but not combative, we found it hard to make a decision what rating to provide on the mask induction scale. More valid scales are to be used.

5. Conclusion

In our study we found that intranasal dexmedetomidine is a much better sedative than intranasal Midazolam so it can be preferred as a premedicant in young children. However, in providing satisfactory condition during mask induction, both the drugs midazolam and dexmedetomidine are equally effective.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

References

1. Kain ZN. Preoperative psychological trauma in children. In: Complications in Anesthesia. Philadelphia: W.B. Saunders Company; 1999.
2. Kain ZN, Caldwell-Andrews AA, Krivutza DM, Weinberg ME, Wang SM, Gaal D. Trends in the practice of parental presence during induction of anesthesia and the use of preoperative sedative premedication in the United States, 1995-2002: results of a follow-up national survey. *Anesth Analg*. 2004;98(5):1252–9.
3. Watson AT, Visram A. Children's preoperative anxiety and postoperative behavior. *Paediatr Anaesth*. 2003;13(3):188–204.
4. Dave NM. Premedication and Induction of Anaesthesia in paediatric patients. *Indian J Anaesth*. 2019;63(9):713–20.
5. Impellizzeri P, Vinci E, Gugliandolo MC, Cuzzocrea F, Larcan R, Russo T, et al. Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients. *Eur J Pediatr*. 2017;176(7):947–53.
6. Kain ZN, Mayes LC, Connor TO, Cicchetti DV. Preoperative anxiety in children: predictors and outcomes. *Arch Pediatr Adolesc Med*. 1996;150(12):1238–45.
7. Wang J, Bu G. Influence of intranasal medication on the structure of the nasal. 2002;115(4):617–9.
8. Almenrader N, Passariello M, Coccetti B, Haiberger R. Premedication in children: a comparison of oral midazolam and oral clonidine. *Pediatr Anesth*. 2007;17(12):1143–9.
9. Fazi L, Jantzen EC, Rose JB, Kurth CD, Watcha MF. A comparison of oral clonidine and oral midazolam as preanesthetic medications in the pediatric tonsillectomy patients. *Anesth Analg*. 2001;92(1):56–61.
10. Wang J, Bu G. Influence of intranasal medication on the structure of the nasal mucosa. *China Med J*. 2002;115(4):617–9.
11. Deshmukh PV, Kulkarni SS, Parchandekar MK, Sikchi SP. Comparison of preanesthetic sedation in pediatric patients with oral and intranasal midazolam. *J Anaesthesiol Clin Pharmacol*. 2016;32(3):353–8.
12. Giovannitti JA, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: review of current clinical applications. *Anesth Prog*. 2015;62(1):31–8.
13. Yuen VM. Dexmedetomidine: perioperative applications in children. *Paediatr Anaesth*. 2010;20(3):256–64.
14. Sajid B, Mohamed T, Jumaila M. A comparison of oral dexmedetomidine and oral midazolam as premedicants in children. *J Anaesthesiol Clin Pharmacol*. 2019;35(1):36–40.
15. 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):871–6.
16. Mehdi I, Parveen S, Choubey S, Rasheed A, Singh P, Ghayas M. Comparative Study of Oral Midazolam Syrup and Intranasal Midazolam Spray for Sedative Premedication in Pediatric Surgeries. *Anesth Essays Res*. 2019;13(2):370–5.
17. Kumar L, Kumar A, Panikkaveetil R, Vasu BK, Rajan S, Nair SG. Efficacy of intranasal dexmedetomidine versus oral midazolam for paediatric premedication. *Indian J Anaesth*. 2017;61(2):125–30.
18. Cao J, Shi X, Miao X. Effects of premedication of midazolam or clonidine on perioperative anxiety and pain in children. *Biosci Trends*. 2009;3(3):115–8.
19. Diwan G, Bharti AK, Rastogi K, Gupta PK. Comparison of Intranasal Dexmedetomidine and Midazolam as Premedication in Pediatric Surgical Patients: A Prospective, Randomized Double-Blind Study. *Anesth Essays Res*. 2020;14(3):384–9.
20. Kumari S, Agrawal N, Usha G, Talwar V, Gupta P. Comparison of Oral Clonidine, Oral Dexmedetomidine, and Oral Midazolam for Premedication in Pediatric Patients Undergoing Elective Surgery. *Anesth Essays Res*. 2017;11(1):185–91.

Author biography

Girimurugan Nagarajan, Assistant Professor

Pavithira Sekar, Assistant Professor

Navaneetha Krishnan Srinivasan, Professor

Prem Kumar, Associate Professor

Harish Kumar, Post Graduate

Cite this article: Nagarajan G, Sekar P, Srinivasan NK, Kumar P, Kumar H. A comparative study of intranasal dexmedetomidine and intranasal midazolam for premedication - A prospective randomized double-blind study in children posted for tonsillectomy. *Indian J Clin Anaesth* 2022;9(1):66-70.