Original Article

Indian Journal of Anesthesia and Analgesia
Volume 8 Number 1 January-February 2021
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.8121.2

To Compare the Effects of Atomized Intranasal Midazolam with Intranasal Dexmedetomidine as Premedication in Children

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Abstract

Background: Successful conduct of anaesthesia in children depends on adequate premedication which comforts the anxious child. Children are vulnerable to stress response because of limited energy reserves, larger brain masses and obligatory glucose requirements. This feeling of worry and nervousness is also seen in the parents of the children undergoing the surgery. Hence premedication becomes important in children in order to avoid anxiety in both children and parents.

Methods: A prospective observational study was conducted in 78 pediatric patients aged between 2 to 10 years of age in our institution. One group received atomized intranasal midazolam 0.3mg/kg (Group M) and the other group received intranasal dexmedetomidine 1mcg/kg (Group D) 30 minutes before the surgery.

Results: Mean sedation score was higher in Group M (1.58 ± 0.55) than in Group D (1.15 ± 0.36) with P value 0.002 at 5 minutes. Similarly the mean sedation score at 10 minutes for Group M was 2.34 ± 0.97 and Group D was 1.75 ± 0.71 with P value 0.008. Separation score and mask acceptance were better with Group M compared to Group D.

Conclusion: We conclude that in children, atomized intranasal midazolam produces better sedation levels, child parent separation and mask acceptance compared to intranasal dexmedetomidine.

Keywords: Children; Sedation; Premedication; Atomized; Intranasal; Midazolam; Dexmedetomidine.

How to cite this article:

Bindu Thimmahanumaiah, Prashanth Jagadeesha Prabhu, Suvina Narendra Datti /To Compare the Effects of Atomized Intranasal Midazolam with Intranasal Dexmedetomidine as Premedication in Children. Indian J Anesth Analg. 2021;8(1):15-19.

Introduction

Anxiety in children is characterized by subjective feelings of tension, apprehension, nervousness and worry expressed in various forms.[1] Studies have indicated that upto 60% of all children undergoing surgery present with negative behavioral changes. Age, anxiety of child and parents in preoperative holding area and anxiety during induction of anaesthesia have been identified as predictors of

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Received on 14.12.20, **Accepted on** 22.01.2021.

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negative behavioral changes.[2] Preoperative anxiety activates human stress respone, leading to increased serum cortisol, epinephrine and natural killer cell activity. The stress activates the hypothalamic pituitary – adrenal axis, increases circulating glucocorticoids and is associated with alterations of immune function and susceptibility to infection and neoplastic diseases.[3] Surgical stress response may be detrimental, provoke a negative nitrogen balance and catabolism, delay wound healing and cause postoperative immunosuppression.[4]

Anxiety before surgery needs to be avoided and can be managed by pharmacological and non-pharmacological methods. To avoid stress to the child, drug must be easy to administer and non-painful. Intranasal administration of drugs is rapidly absorbed through the nasal mucosa, resulting in a rapid and reliable onset of action, with no painful injection and avoids first pass metabolism in liver.

Midazolam is one of the established drugs for premedication with high hepatic metabolism. Intranasal Midazolam atomizer / MAD (mucosal atomization device) delivers drug in form of droplets measuring 30-100 microns which helps in larger dispersion of drug.[5] Dexmedetomidine is an alpha 2 agonist having sedative, anxiolytic and analgesic effects, approved by Food and Drug Administration (FDA) in 1999. Few studies have been done comparing both these drugs as premedication, with different routes, different doses but with varied conclusions. Hence we wanted to compare midazolam and dexmedetomidine as premedication for children through intranasal route.

Material and Methods

After institutional ethical committee approval on 10th October 2016 (VIEC/2016/APP/126), a prospective randomized double blind study was conducted. Sample size was calculated based on onset of anxiolysis with alpha error of 5% and 20% beta error, sample size was calculated as 39 children in single arm.

78 children of both sex, aged between 2-10 years, ASA 1 & 2, scheduled for various elective surgical procedures like hernia, adenoidectomy, adenotonsillectomy, endoscopy procedures, major abdominal surgeries, syndactyly release, release of tongue tie, skin grafting, orchidopexy and fracture reduction surgery were included in the study.

We excluded children with active or recent upper respiratory tract infection, with known allergy or hypersensitivity and parents refusing to give consent.

All children were evaluated a day prior to surgery and informed written consent was obtained from parents or guardians after explaining the anesthetic plan and study details. Children were advised nil per oral as per standard guidelines. Children were then randomly assigned to one of the two groups of premedication.

Group M (n=39 children) - Children received atomized intranasal midazolam (0.3mg/kg), dispensed through proprietary drug atomizer in supine position during inspiration.

Group D (n=39 children) - Children received intranasal dexmedetomidine (1mcg/kg). The drug was loaded in a graduated syringe and sprayed in nostril with patient in supine position during inspiration.

The observer was blinded for the study drug. After IV cannulation, the premedicant was administered 30 minutes before induction of anaesthesia in the preoperative holding room, in presence of their parents. Perioperative pulse rate, blood pressure, electrocardiography, Spo_2, respiratory rate and sedation levels were monitored.

Six point Ramsay sedation score [Table I] was used to monitor sedation levels. When a sedation score of 4 or more was reached, child was transferred to operating room. At end of 30 minutes, even no satisfactory sedation level was achieved, anaesthesia induction was conducted.[6]

After achieving adequate sedation levels, the child was separated from its parents and was taken to the operating room. The response to the child parent separation was assessed and recorded according to a Four point scale [Table II].[7] A separation score of less than equal to 2 was considered relevant.

The ease of induction was assessed by mask acceptance by the child and recorded accordingly to a Four point scale during induction [Table III].[6] Induction / Mask acceptance score of greater than equal to 3 was considered satisfactory.

At the end of surgery the child was placed in the recovery position and allowed to wake up naturally. Behavior at awakening was assessed and recorded with a Four point wake up score [Table IV].[7] Wake up score less than equal to 2 was indicative of smooth recovery.

All observations and particulars of each child was recorded in the proforma. Statistical analysis was done using the following tests Mann Whitney

U test, Independent t test, Chi-square test and by using IBM SPSS version 21.0. P<0.05 was considered statistically significant.

Results

There was no significant difference between the two groups in terms of age, sex, pulse rate, blood pressure, respiratory rate and saturation.

Table I: Ramsay Sedation score[6]

Condition of the patient	Score
Patient anxious and agitated / restless or both	1
Patient cooperative, oriented and tranquil	2
Patient responds to commands only	3
A brisk response	4
A sluggish response	5
No response	6

Score >=4 is significant

Table II: Separation score.[7]

Child condition during seperation	Grade	Score
Child unafraid, cooperative, asleep	Excellent	1
Slight fear or crying, quite with reassurance	Good	2
Moderate fear, crying, not quite with reassurance	Fair	3
Crying and need for restraint	Poor	4

Score <=2 considered relevant

In Group M, 84.61% (33/39) of children reached adequate sedation compared to 64.10% (25/39) of Group D. The time taken to reach adequate sedation score in Group M was 13.18 minutes compared to 16.6 minutes in Group D.

Group M had a higher sedation score at 5 and 10 minutes. Group M had a lesser separation score and a higher induction or mask acceptance score as shown in Table V. In our study 89.74% children in midazolam group had satisfactory mask acceptance and 66.66% children in dexmedetomidine group had satisfactory mask acceptance. Hence Group M achieved better mask acceptance compared to Group D, with p value 0.0101. The wake up score between the two groups was statistically not significant. No adverse effects observed in our study.

Table III: Induction score / Mask acceptance score.[6]

Condition of the child during induction / mask application	Grade	Score
Afraid, combative, crying	Poor	1
Moderate fear of mask, not easily calmed	Fair	2
Slight fear of mask, easily calmed	Good	3
Unafraid, cooperative, accepts mask easily	Excellent	4

Score >=3 considered satisfactory

Table IV: Wake up score.[7]

Condition of the child while waking up	Score
Calm and cooperative	1
Not calm but could be easily calmed	2
Not easily calmed, moderately agitated or restless	3
Combative, Excited, Disoriented	4

Score <=2 indicative of smooth recovery

Table V: Comparison of Group M and Group D.

		Group M	Group D	P value
		Mean +/- SD	Mean +/- SD	
In relation to sedation score	Time (in minutes)	-	-	-
	5 minutes	1.58 +/- 0.55	1.15 +/- 0.36	0.0020[a]
	10 minutes	2.34 +/- 0.97	1.75 +/- 0.71	0.0081[a]
In relation to separation score	Separation Score (<=2 is relevant)	1.28 +/- 0.6	1.72 ± 1.02	0.0249[b]
In relation to induction / mask acceptance score	Induction score (>=3 is comfortable)	3.51 +/- 0.76	2.82 +/- 1.32	0.0056[b]

*Group M: Atomized intranasal midazolam group, Group D: Intranasal dexmedetomidine, SD: Standard Deviation, P<0.05 – statistically significant, [a]Mann Whitney U test, [b]Independent t test

Discussion

An ideal premedication in children, should sedate well, make the child quite on reassurance when separating from parent and easily calm the child during induction and wake up. Various drugs through different routes are used as premedication in children. Due to high first pass metabolism, oral midazolam have low bioavailability. In our study intranasal route of midazolam was used which has been preferred over oral midazolam as it has a rapid and reliable onset of action due to rich blood supply of airway mucosa. One study by Koppal R et al had used 0.5 mg/kg intranasal midazolam and concluded that it provided adequate sedation and separation scores with faster onset.[5] Studies suggested that atomized midazolam at 0.3mg/kg is safe, faster in action and better

separation scores compared to 0.2mg/kg[8] and recommended its use due to efficacy, cost, safety as well as availability.[9] One of the disadvantage of midazolam is, it can cause respiratory depression. Dexmedetomidine is an alpha 2 adrenergic agonist which provide sedation. We wanted to study the level of sedation, ease of child parent separation, ease of induction and condition of the child while waking up from surgery by comparing atomized intranasal midazolam (0.3mg/kg) and intranasal dexmedetomidine (1mcg/kg).

We premedicated the children 30 minutes before induction in preoperative holding room as done in other studies using dexmedetomidine.[5,12] Most of the children in our study were sedated by end of 10 minutes with intranasal midazolam which was similar to study done by Gupta et al. The study also claimed that intranasal dexmedetomidine yields a higher sedation level that intranasal midazolam. It is not clear whether they used atomized intranasal midazolam or not and their dose of midazolam was 0.2mg/kg compared to our 0.3mg/kg.[8]

In our study the separation score was better with intranasal midazolam compared to dexmedetomidine which is similar to study conducted by Arora et al. They had compared with oral administration of midazolam (0.5mg/kg) and dexmedetomidine (4mcg/kg). The dose of oral midazolam was not even twice the dose of our intranasal midazolam, but the dose of intranasal dexmedetomidine was four times our intranasal dose.[10]

Mask acceptance was also better in our intranasal midazolam group when compared to intranasal dexmedetomidine group. Similar results were observed by Akin et al when they compared intranasal dexmedetomidine (1mcg/kg) with intranasal midazolam (0.2mg/kg).[11] Kim et al did a meta-analyis on sedative effects of intranasal dexmedetomidine and other sedation methods.[13] He suggested that intranasal dexmedetomidine is associated with better sedative effects than oral benzodiazipines, which can be explained due to higher first pass metabolism.

In our study atomized intranasal midazolam has appeared to perform better than intranasal dexmedetomidine, though in some studies intranasal dexmedetomidine is better, it could be because we used atomized intranasal midazolam which help in better dispersion of drug over mucosa as compared to intranasal spraying from cut end of needle syringe for dexmedetomidine as atomized dexmedetomidine was not available.[10]

The draw back of our study is larger population of children need to be studied to rule out any adverse events and to compare atomized intranasal midazolam with atomized intranasal dexmeditomidine to achieve accurate results.

Conclusion

We conclude that atomized intranasal midazolam as a safe and effective sedative premedication for faster sedation levels, better child parent separation and better mask acceptance in children compared to intranasal dexmedetomidine.

References

1. McCann ME, Kain ZN. The management of preoperative anxiety in children: an update. Anesth Analg 2001;93:98-105. doi: 10.1097/00000539-200107000-00022. PMID: 11429348.
2. Kain ZN, Wang SM, Mayes CL, Caramico LA, Hofstadter MB. Distress during induction of anesthesia and postoperative behavioral outcomes. Anesth Analg 1999;88(5):1042-7. doi: 10.1097/00000539-199905000-00013. PMID:10320165.
3. AderR,CohenN,FeltenD.Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet 1995 Jan 14;345(8942):99-103. doi: 10.1016/s0140-6736(95)90066-7. PMID:7815892.
4. Weissman C. The metabolic response to stress: an overview and update. Anesthesiology 1990 Aug;73(2):308-27. doi: 10.1097/00000542-199008000-00020. PMID: 2200312.
5. Koppal R, Adarsh ES, Ambi U, Anilkumar G. Comparison of the midazolam transnasal atomizer and oral midazolam for sedative premedication in pediatric cases. Journal of Clinical and Diagnostic 2011 October; Volume 5(5):932-934. https://www.jdcr.net/article_fulltext.asp?id=1550.
6. 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 Jun;106(6):1715-21. doi: 10.1213/ane.0b013e31816c8929. PMID: 18499600.
7. Sundaram ALM, Mathian VM. A Comparative evaluation of intranasal dexmedetomidine and intranasal midazolam for premedication in children: A double blind randomised controlled trial. Journal of Indian Dental Association 2011;5(7):777-781.
8. 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. Apr-Jun 2017; 33(2): 236-240. DOI: 10.4103/joacp.JOACP_204_16. PMID: 28781452 PMCID: PMC5520599.

9. Mostafa MG, Morsy KM. Premedication with intranasal dexmedetomidine, midazolam and ketamine for children undergoing bone marrow biopsy and aspirate. Egyptian Journal of Anaesthesia 2013 April;29(2):131-5. https://doi.org/10.1016/j.egja.2012.10.006.
10. Arora S, Saini K, Bhardwaj N. A comparative evaluation of midazolam, clonidine and dexmedetomidine as oral premedicants in children: A double blind randomized clinical trial. Anaesth Pain & Intensive Care. Oct 2014;18(4):355-60. http://apicareonline.com/index.php/APIC/article/view/384.
11. Akin A, Bayram A, Esmaoglu A et al. Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anaesthesia. Paediatri Anaesth. 2012 Sep;22(9):871-6. doi: 10.1111/j.1460-9592.2012.03802.x. Epub 2012 Jan 23. PMID: 22268591.
12. Miller JW, Divanovic AA, Hossain M, Mahmoud MA, Loepke AW. Dosing and efficacy of intranasal dexmedetomidine sedation for pediatric transthoracic echocardiography: a retrospective study. Can J Anaesth 2016 Jul; 63(7): 834-41. doi: 10.1007/s12630-016-0617-y. Epub 2016 Feb 16. PMID: 26883963.
13. Kim HJ, Shin WJ, Park S, Ahn HS, Oh JH. The sedative effects of the intranasal administration of dexmedetomidine in children undergoing surgeries compared to other sedation methods: A systematic review and meta-analysis. J Clin Anesth 2017 May; 38: 33-39. doi: 10.1016/j.jclinane.2017.01.014. Epub 2017 Jan 15. PMID: 28372674.