Original Research Article

COMPARATIVE STUDY BETWEEN NASAL ATOMIZED DEXMEDETOMIDINE AND MIDAZOLAM AS PREMEDICATION IN CHILDREN

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Received : *06/09/2025*
Received in revised form : *19/10/2025*
Accepted : *05/11/2025*

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DOI: 10.70034/ijmedph.2025.4.299

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (4); 1660-1666

ABSTRACT

Background: Aims and objectives: The aim of our study was to compare the effects of atomized intranasal midazolam with intranasal dexmedetomidine for preoperative sedation in children undergoing surgery.

Materials and Methods: The present study was conducted in a prospective, randomized, double blinded and comparative manner in the Department of Anaesthesiology and Critical Care, Pt. B.D. Sharma PGIMS, Rohtak from October 2022 to March 2024. All patients were randomly allocated to one of the two groups: Group M (n=30): Children received atomized midazolam (0.2mg/kg) in supine position during inspiration, where we used nasal atomizer. It was administered at a dose of 0.2mg/kg. Group D (n=30) Children received intranasal Dexmedetomidine (1ug/kg). One ampule of dexmedetomidine contains 100µg of dexmedetomidine.

Results: In group M, among 30 children 26 children achieved satisfactory sedation (86.67%) and the mean time for satisfactory sedation was 13.18 minutes. In group D, 22 children achieved satisfactory sedation (73.30%) and the mean time for satisfactory sedation was 16.6 minutes. This shows that group M achieved slightly faster sedation levels than group D. Group M had a mean separation score of 1.33±0.65, while in group D the mean separation score was 1.66±1.07. This shows that group M had achieved slightly better child parent separation than group D which is statistically non- significant. (P=0.08). In Group M 18 patients (60 %) and in group D 14 patients (46.67%) had score 4 of mask acceptance which showed there is mild difference between the two groups which is statistically non-significant.

Conclusion: They conclude that atomized intranasal midazolam (0.2mg/kg) produces slightly superior sedation levels than intranasal Dexmedetomidine (1ug/kg) and equal separation and mask acceptance with non-significant changes in haemodynamics.

Keywords: Nasal Atomized Dexmedetomidine, Midazolam, Premedication.

INTRODUCTION

Anxiety in children undergoing surgery is characterized by subjective feelings of tension, apprehension, nervousness and worry that may be expressed in various forms.[1] Maladaptive behaviors such as new onset enuresis, feeding difficulties, apathy and withdrawal and sleep disturbances, may also result from anxiety before surgery.[2] In fact, studies have indicated that up to 60% of all children undergoing surgery may present with negative behavioral changes at 2 weeks postoperatively.[3,4] Variables such as age, temperament and anxiety of the child and parent in the preoperative holding area have been identified as predictors for these behavioral changes. Extreme anxiety during induction of anesthesia is also associated with an increase of these postoperative negative behavioral changes. In addition to behavioral manifestations, preoperative anxiety activates the human stress response, leading to increased serum cortisol, epinephrine and natural killer cell activity. This stress response can be activated by many different noxious stimuli including fear anxiety, pain, cold, major surgery and infection.

The main components of the stress system are the corticotropin-releasing hormone and the locus ceruleus- norepinephrine/autonomic systems and their peripheral effectors, the hypothalamic pituitary-adrenal axis and the limbs of the autonomic nervous system. [5] There is also evidence for a bidirectional communication between the neuroendocrine system and the immune system. Stress activates the hypothalamic pituitary-adrenal axis, increases circulating glucocorticoids and is associated with alterations of immune function and susceptibility to infection and neoplastic disease. The human response to surgical stress is characterized by a series of hormonal, immunological and metabolic changes that together constitute the global surgical stress response. [6] This perioperative response is considered a homeostatic mechanism for adapting to the perioperative injury. The effects of the surgical stress response, however, may be detrimental: neuroendocrine hormones (e.g., cortisol, catecholamines) and cytokines (e.g., interleukin-6) provoke a negative nitrogen balance and catabolism, delay wound healing and cause postoperative immunosuppression.[7] Children are particularly vulnerable to the global surgical stress response because of limited energy reserves, larger brain masses and obligatory glucose requirements. [8] Because acute psychological stress, such as preoperative anxiety, is associated with immediate stress hormone release, the contribution of perioperative psychological factors to the global perioperative stress response cannot be ignored. In adults, increased preoperative anxiety is associated with poor postoperative behavioral and clinical recovery. As an indicator of the importance of preoperative anxiety, a panel of 72 anesthesiologists recently ranked various anesthesia low-morbidity clinical outcomes based on importance and frequency. [9] The five clinical outcomes with the highest combined score were incisional pain, nausea, vomiting, preoperative anxiety and discomfort from IV insertion. Thus, consensus isevident among anesthesiologists about the need to treat anxiety before surgery. [10]

Identifying risk factors for development of preoperative anxiety is important, as more resources can be directed toward vulnerable children. Children 1–5 year old are at the highest risk for developing extreme anxiety. This is not surprising considering the psychobiology of separation anxiety. [11] Children who are shy or inhibited and those who have a high intelligence quotient and lack good adaptive abilities are also at increased risk. Previous surgery or hospitalization and poor response to visits to the pediatrician's office are also predictors for the development of preoperative anxiety. Finally, parental anxiety has also been identified as a predictor for increased child's anxiety. [12]

Preoperative anxiety in children can be managed with behavioral (nonpharmacological) modalities and pharmacological modalities. Behavioral Modalities include the development of coping skills, modeling, play therapy, operating room tour, by viewing a picture or video and printed materialand Parental Presence during Induction of Anesthesia. Pharmacological Modalities include midazolam, ketamine, transmucosal fentanyl, meperidine, clonidine, triclofos, hydroxyzine and many other drugs through various routes such as oral, intranasal, rectal and intramuscular.

Midazolam has been compared with many drugs such as clonidine, triclofos, hydroxyzine through various routes including oral and nasal routes. [13] Intranasal Midazolam has got some advantages. Midazolam is rapidly absorbed through the nasal mucosa, resulting in a rapid and reliable onset of action, avoidance of painful injection and first-pass metabolism in liver. However, with the recent availability of the Nasal Mucosal Atomization Device (MAD, Atomizer), which facilitates the effective delivering of the drug in the form of droplets which measure 30–100 micronin size, helps in a larger dispersion of the drug over the mucosa and hence results in better absorption. [14]

Dexmedetomidine is an alpha-2 agonist. It has been successfully used through various routes in children including intravenous and nasal routes. Because of its sedative and analgesic effects, it is gaining popularity in anesthesiology. It has several applications in pediatric anesthesia as a premedication and as an adjuvant in general as well as regional anesthesia. [15]

The aim of our study was to compare the effects of atomized intranasal midazolam with intranasal dexmedetomidine for preoperative sedation in children undergoing surgery.

MATERIALS AND METHODS

Study Design

The present study was conducted in a prospective, randomized, double blinded and comparative manner in the Department of Anaesthesiology and Critical Care, Pt.

B.D. Sharma PGIMS, Rohtak after obtaining approval from institutional ethical committee and the written & informed consent from patients.

Study Period: October 2022 to March 2024

Study Subjects: Following patients will be enrolled;

Inclusion Criteria

- Children belonging to both the sex.
- Children aged between 2-8 years.
- Children with American Society of Anesthesiologists' (ASA) physical status I and II.

- Children scheduled to undergo various elective surgical procedures like hernia surgeries, adenoidectomy, adenotonsillectomy, endoscopy procedures, major abdominal surgeries, syndactyly release, release of tongue tie, skin grafting, orchidopexy and fracture reduction surgeries.

Exclusion Criteria

- Children with active or recent upper respiratory tract infection.
- Children with systemic illness like - Cardiac diseases, neurological, liver and renal disease.
- Parents refusing to give consent.
- Known allergy or hypersensitivity to dexmedetomidine or midazolam.

Sample Size

The sample size was calculated based on a previous study by Yuen et al[16] where the sedation score at mask induction was 21.9% in midazolam group and 75% in dexmedetomidine group. The average % was noted to get 95% confidence and 80% power. The calculation showed that 30 patients per group would be required for the study and therefore, 60 patients were selected for our study.

Clinical Examination:

All the patients were evaluated one day prior to surgery. The purpose and protocol of the study was explained to the parents in detail. An informed and written consent of the parents were taken for participation in the study. A detailed clinical history was taken and all the patients were subjected to complete general, physical as well as systemic examination.

Preparation of the patient:

Patients were kept nil per oral six hours prior to surgery for solids and two hours for clear fluids. On the day of surgery, in the preoperative room, baseline recordings of heart rate, respiratory rate, systolic blood pressure and activity of child were noted. After shifting the patient to operating room, standard vital monitors were attached including heart rate (HR), electrocardiography (ECG), non-invasive blood pressure (NIBP) and Pulse oximetry (SpO2).

Group allocation and Randomization

All patients were randomly allocated to one of the two groups comprising of 30 Patients each using computer generated random number table.

1. Group M (n=30): Children received atomized midazolam (0.2mg/kg) in supine position during inspiration, where we used nasal atomizer. It was administered at a dose of 0.2mg/kg. The effective delivering of the drug through the atomizer in the form of droplets measures 30-100micron in size, which helps in a larger dispersion of the drug over the mucosa and hence results in better absorption.

2. Group D (n=30) Children received intranasal Dexmedetomidine (1ug/kg). One ampule of dexmedetomidine contains 100µg of dexmedetomidine. The drug was loaded in 1ml graduated syringe with 1µg/kg dexmedetomidine and instilled in separate nostrils with the patient in supine position.

- The child received the premedicant drug as per allocation of group. The study drug was prepared and administered by colleague anesthesiologist, while the observer was blinded for the study drug.
- The premedicant was administered approximately 30 minutes before induction of anesthesia in the preoperative holding room in presence of their parents.
- Heart rate, SpO2, respiratory rate, sedation score, child-parent separation score and mask acceptance score were evaluated perioperatively.

PARAMETERS MONITERED

Perioperatively the following parameters were monitored continuously and the readings were recorded every 5 minutes up to 30 minutes.

1. Sedation score
2. Separation score
3. Induction score/ Mask acceptance score
4. Standard vital monitors including heart rate (HR), electrocardiography (ECG), non-invasive blood pressure (NIBP) and Pulse oximeter (SpO2).

Sedation Score: The degree of Sedation was assessed and recorded every 5 minutes from the administration of drug with the six-point Ramsay sedation score for maximum of 30 minutes. When a sedation score of 4 or more was reached, the child was transferred to the operating room for induction and the time was noted. The time to reach score of 4 scale was also noted.

Separation Score

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 4-point scale. [17]

Induction Score

Ease of induction was assessed by mask acceptance by the child and recorded according to a 4-point scale during induction.

Statistical Analysis

Appropriate statistical analysis of data was done using Mann Whitney U test, Independent t test and chi square test. In our study, we compared the effects of atomized intranasal midazolam vs intranasal dexmedetomidine as premedication in 60 children undergoing various surgeries. Sedation score, separation score, time for satisfactory sedation, ease of mask acceptance, vital parameters and recovery scores were recorded and analysed. Statistical analysis was done by using IBM-SPSS version 25.0.

RESULTS

Among the 60 patients studied, 37 children were males (22 in group M and 15 in group D) and 23 were females (8 in group M and 15 in group D). Both the groups were comparable with respect to sex distribution (male children-73.33% in group M and 50.00 % in group D, female children -26.67% in group M and 38.33% in group D) with P=0.44 which is statistically not significant.

Table 1: Comparison of group M and group D in relation to sedation scores at different time intervals by Mann Whitney U test

Time (in minutes)	Group M			Group D			P-value
	Mean	SD	Mean rank	Mea n	SD	Mean rank	
0	1	0	39.5	1	0	39.5	1
5	1.76	0.67	47.63	1.34	0.48	31.78	0.01*
10	2.57	0.98	46.47	1.81	0.82	32.88	0.01*
15	2.76	0.96	42.47	2.46	1.11	33.28	0.07
20	2.61	0.86	26.67	2.44	0.72	25.64	0.81
25	2.67	0.82	22.67	2.41	0.89	23.9	0.77
30	2.52	0.67	16.2	2.33	0.71	15.15	0.76

****p<0.05***

There is a statistically significant difference in sedation scores between 2 groups at 5th minute (group M -1.76±0.67, group D- 1.34±0.48 with a P=0.01) and 10th minute (group M- 2.57±0.98, group D- 1.81±0.82 with a P=0.01). Group M achieved a statistically significant higher sedation levels than group D at 5th and 10th minutes while at other time intervals sedation levels were statistically non-significant.

Table 2: Children achieving satisfactory sedation in group M and group D

	Group M	Group D
Number of children Reaching adequate sedation levels (Ramsay sedation score of 3)	26/30	22/30
Percentage of children reaching adequate sedation levels	86.67%	73.30%
Time for reaching adequate sedation levels	13.18 minutes	16.6 minutes

In group M, among 30 children 26 children achieved satisfactory sedation (86.67%) and the mean time for satisfactory sedation was 13.18 minutes. In group D, 22 children achieved satisfactory (73.30%) and the mean time for satisfactory sedation was 16.6 minutes. This shows that group M achieved slightly faster sedation levels than group D.

Table 3: Comparison of group M and group D in relation to separation scores

Groups	N	Mean	SD	P-value
Group M	30	1.33	0.65	0.08
Group D	30	1.66	1.01	

****p<0.05***

Group M had a mean separation score of 1.33±0.65, while in group D the mean separation score was 1.66±1.07. This shows that group M had achieved slightly better child parent separation than group D which is statistically non- significant. (P=0.08)

Table 4: Comparison of group M and group D in relation to mask acceptance scores

Mask acceptance score	Group M		Group D		Total	
	N	%	N	%	N	%
Score 1	1	3.33	3	10.00	4	6.67
Score 2	2	6.67	3	10.00	5	8.33
Score 3	9	30.00	10	33.33	19	31.67
Score 4	18	60.00	14	46.67	32	53.33
Total	30	100	30	100	60	100
P = 0.26 (NS)						

****P<0.05= Significant, NS = Non-significant***

In Group M 18 patients (60 %) and in group D 14 patients (46.67%) had score 4 of mask acceptance which showed there is mild difference between the two groups which is statistically non-significant.

Table 5: Comparison of group M and group D in relation to mean mask acceptance scores in between the groups

Groups	N	Mean	SD	SE	P-value
Group M	30	3.43	0.77	0.12	0.89
Group D	30	3.13	0.96	0.21	

****p<0.05***

Group M had a mean mask acceptance score of 3.43 ± 0.77 and group D had slightly less mean score of 3.13 ± 0.96 score which is statistically non-significant. This shows that group M had mild more ease of induction than group D but it is statistically non-significant in relation to mask acceptance score.

Table 6: Comparison of group M and group D in relation to SBP values at different time intervals by independent t test

Time points	Group M		Group D		p-value
	Mean	SD	Mean	SD	
Baseline	116.84	6.85	115.63	6.21	0.41
0 minute	116.11	7.1	114.63	6.98	0.36
5 minutes	116.87	9.19	114.23	7.13	0.16
10 minutes	116.89	6.94	113.58	8.00	0.06
15 minutes	118.26	8.79	112.85	8.76	0.00*
20 minutes	117.13	6.22	113.88	9.02	0.067
25 minutes	118.53	5.56	113.9	9.95	0.01*
30 minutes	120.03	5.84	113.18	10.51	0.00*

****p<0.05***

The drop in mean systolic blood pressure was more in group D than group M at all the time intervals with a mean of 116.62 ± 7.1 in group M and a mean of 112.77 ± 7.94 in group D. There is statistically significant difference drop in blood pressure between the 2 groups at 25th minute to 30th minute with more drop in group D than group M. (P<0.05)

Table 7: Comparison of group M and group D in relation to DBP values at different time intervals by independent t test

Time points	Group M		Group D		p-value
	Mean	SD	Mean	SD	
Baseline	73.58	3.39	74.88	3.82	0.11
0 minute	73.34	2.89	73.9	3.08	0.41
5 minutes	73.76	2.84	74.25	2.88	0.45
10 minutes	75	3.18	74.95	2.51	0.94
15 minutes	74.71	2.89	75.63	3.06	0.18
20 minutes	75.61	3.00	75.00	2.52	0.33
25 minutes	75.03	3.04	75.25	3.40	0.76
30 minutes	74.97	3.35	74.8	3.58	0.82

The mean DBP in group M was 74.11 with a SD of 3.23 and in group D was 74.31 with a SD of 3.16. The results of the study showed the difference in mean diastolic blood pressure among the two groups was statistically not significant (p>0.05).

DISCUSSION

Midazolam is a water-soluble benzodiazepine known to have a rapid onset and short duration of action, as well as properties of amnesia and anxiolysis. Dexmedetomidine is a newer alpha 2-agonist with a more selective action on the alpha 2- adrenoceptor and short half-life, its bioavailability is when administered via the nasal mucosa.

The purpose of our study was to compare the effects of atomized intranasal midazolam 0.2mg/kg with intranasal dexmedetomidine 1 µg/kg for preoperative sedation in children undergoing surgery. The cardiorespiratory effects of two drugs in perioperative period were also compared.

DOSAGE OF DRUGS IN OUR STUDY

In our study, the dosage of drugs considered for intranasal midazolam 0.2mg/kg and intranasal dexmedetomidine 1µg/kg as a premedication in children. This dosage of drugs produced an effective anxiolytic and sedative response, which was comparable with other studies. Cheng et al,[11] used 0.2 mg/Kg intranasal midazolam and 2ug/Kg of intranasal dexmedetomidine as premedication in patients for deep sedation and found that 2ug/Kg of dexmedetomidine showed superior results than midazolam. In a study by Sundaram AM et al. [18] intranasal dexmedetomidine 1µg/kg as a premedicant produced satisfactory anxiolysis at 30 minutes, of which 83% achieved satisfactory sedation which is in accordance with our study. Fuks et al. [19] found no significant difference in the amount of dosage i.e. both 0.2 mg/kg and 0.3 mg/kg produces same effects regarding the parental separation score and children behaviour and hence 0.2 mg/kg can be used as intranasal method of premedication. Baldwa et al.,[20] also compared two different doses of intranasal midazolam 0.2mg/kg and 0.3mg/kg as premedication in children and they found that 0.3mg/kg intranasal midazolam achieves faster sedation and ease of separation from parents than 0.2mg/kg intranasal midazolam which is in contradiction with our study. Koppal R et al, [21] compared intranasal midazolam 0.3mg/kg with oral midazolam 0.3mg/kg as premedication in children. This dosage of drugs produces an effective sedation and ease of child-parent separation. While, the study by Akin A et al. [22] compared intranasal dexmedetomidine (1ug/kg) and midazolam (0.2 mg/kg) as premedication in children and observed that dexmedetomidine dose1µg/kg proved satisfactory mask induction in 60% children.

TIMING OF PREMEDICATION

In our study, the children were premedicated 30 minutes before induction, which was correlated with other studies: In a study by Sundaram et al,[18] compared intranasal dexmedetomidine (2 ug/kg) with intranasal midazolam (0.2 mg/kg) as premedication in children. They found that most of the children had satisfactory behavior at induction (30 minutes) of anaesthesia with no evidence of difference among groups. Koppal R et al,[21] compared intranasal and oral midazolam as premedication in children and they premedicated the children 30 minutes prior to induction. They observed that transnasal group achieved better sedation score at 30 minutes, which was significant.

SEDATION LEVELS

In our study, 26 children (86.67%) reached satisfactory sedation levels in group M and 22 children (73.30%) reached satisfactory sedation in group D. The time to reach satisfactory sedation was 13.18 minutes in group M and 16.6 minutes in group D which was correlated with other studies like: in a study by Baldwa et al,[20] most of the children (70%) reached satisfactory sedation at 10 minutes using 0.3mg/kg intranasal midazolam compared to 40% of children attains sedation using 0.2mg/kg intranasal midazolam. In another study by Sheta et al. [23] to evaluate the use of intranasal dexmedetomidine vs intranasal midazolam as premedication and observed that median onset of sedation was significantly shorter in group M (10-25) minutes than in group D (20-40) minutes and the results are comparable with our study. Our results are in accordance with the study conducted by Panda et al. [24] where they also found that 0.2 mg/kg of intranasal midazolam is more effective than 2 ug/kg of intranasal dexmedetomidine in terms of achieving sedation levels. However, in the study by Nagrajan et al. [25] intranasal dexmedetomidine (1 ug/kg) produced superior sedation scores than intranasal midazolam (0.2 mg/kg) in paediatric patients which is in disagreement with the present study which may be due to the longer period of observation before induction in their study.

SEPARATION SCORES

In our study, the mean separation scores were 1.33±0.65 in midazolam group and 1.66±1.07 in dexmedetomidine group. This shows that the group M had achieved slightly better child parent separation which was statistically non-significant. This is in contradiction with the study by Koppal R et al,[21] in which the mean separation scores at 30 minutes was 1.37±0.556 with oral midazolam and 1.73±0.740 with nasal midazolam. In a study conducted by Panda et al,[24] 0.2 mg/kg of intranasal midazolam is more effective than 2 ug/kg of intranasal dexmedetomidine in terms of achieving parental separation score and the results are in disagreement with the present study which may be due to the difference in the dosage of the drugs used.

MASK ACCEPTANCE SCORES

In our study, about 90 % children in midazolam group had satisfactory mask acceptance and 80% children in dexmedetomidine group had satisfactory mask acceptance score of 3-4. Hence group M achieved slightly better mask acceptance compared to dexmedetomidine which is statistically non-significant. Kumari et al,[12] found that children premedicated with oral midazolam (0.5 mg/kg) had slightly more satisfactory mask acceptance score than oral dexmedetomidine (4ug/kg) which was comparable to the score of our study. Therefore, it can be inferred that both the routes of administration produce same induction but the dose in oral routes is higher than intranasal route and hence intranasal route can be preferred. The results are in contradiction to the study conducted by Pareek et al. [26] where they found the slightly better mask acceptance score in the patients who had been given intranasal dexmedetomidine (1ug/kg) in comparison with intranasal midazolam (0.2mg/kg) but were statistically non-significant. In a study by Akin A et al,[22] 82.2% of children who received midazolam group and 60% of children who received dexmedetomidine group had satisfactory mask acceptance which is again slightly higher than the score observed in our study.

ADVERSE EFFECTS

In our study, we didn't find any adverse effects like nausea, vomiting, nasal stinging, shivering or bradycardia. This was consistent with various studies where they used intranasal midazolam and Dexmedetomidine intranasally. [27,28]

CONCLUSION

We conclude that atomized intranasal midazolam (0.2mg/kg) produces slightly superior sedation levels than intranasal Dexmedetomidine (1ug/kg) and equal separation and mask acceptance with non-significant changes in haemodynamics. Therefore, we recommend that both atomized intranasal midazolam and intranasal dexmedetomidine can be used as sedative premedication in paediatric patients and it is safe, effective and well tolerated by children.

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