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# A comparative study to evaluate the efficacy of intranasal midazolam and intranasal dexmedetomidine as pre-medication in paediatric patients

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**Abstract:** This study aimed to compare the efficacy of Midazolam and Dexmedetomidine as premedication agents in pediatric patients administered via the intranasal route. 100 children in ASA physical status I and II, aged 2-8 years, planned for surgery under general anesthesia, were randomly assigned to Group D, which received 1 mcg/kg of Intranasal dexmedetomidine, or Group M, which received 0.2 mcg/kg of Intranasal midazolam for premedication. The patients' sedation status, separation anxiety, and mask acceptance were evaluated using UMSS, PSAS, and MAS, respectively, along with hemodynamic parameters and side effects. The mean sedation score was higher in Group D than Group M, and the mean parental separation anxiety score and mean mask acceptance score were also higher in Group D than Group M. All hemodynamic parameters were comparable and stable in both groups. In conclusion, intranasal dexmedetomidine was found to provide better sedation, relieve preoperative anxiety, make parental separation easier, and promote better mask acceptance, without any significant side effects.

**Keywords:** Pediatric anesthesia; Premedication; Dexmedetomidine; Midazolam; Intranasal administration.

## 1. Introduction

Hospitalisation and surgery cause significant stress and anxiety in patients [1]. Due to limited cognitive capabilities and dependency, paediatric age group patients are most susceptible to anxiety during the preoperative period [2]. Preanaesthetic medication is an important component of anaesthesia management which helps alleviate the stress and anxiety of surgery, eases the child-parent separation, and promotes smooth induction of anaesthesia [3].

Midazolam is the most preferred premedicant used in children [4]. It produces anxiolysis, amnesia, and hypnosis but also causes respiratory depression in some patients [5].

Dexmedetomidine has selective action with rapid onset of action and shorter half, producing anxiolysis, sedation and analgesic effects without causing respiratory depression [6]. The ideal route of administration for premedication in children must be nontraumatic, well acceptable with good bioavailability and without significant side effects [7]. Premedication can be given through Oral, Transmucosal, parental (Intravenous and Intramuscular) and Rectal routes. The intranasal route of administration is relatively easy, painless and non-invasive. It produces rapid onset of action and has higher bioavailability due to the high vascularisation of mucosa and its ability to bypass first-pass metabolism

This study aims to assess the effectiveness of intranasal midazolam and intranasal dexmedetomidine as pre-medication in pediatric patients aged 2 to 8 years. The primary objectives are to compare the level of sedation and parental separation anxiety using UMSS and PSAS, respectively, before and 30 minutes after

premedication, between the two groups. The secondary objectives include comparing the mask acceptance score at induction, hemodynamic parameters (HR, MAP, SP02, RR) preoperatively (at 10-minute intervals till 30 minutes after premedication) and intraoperatively (at 15-minute intervals until the end of surgery), and any side effects between the two groups. This study aims to contribute to the understanding of the effectiveness of these pre-medication agents in pediatric patients, which can help in improving anesthesia management and patient outcomes.

## 2. Materials and Method

This prospective, randomized, controlled and comparative study was conducted in Department of Anaesthesiology, M.G.M. Medical College and M.Y Hospital, Indore, Madhya Pradesh over a period of 12 months, from 1 July 2021 to 30 June 2022, after approval from Ethics and Scientific Review Committee. 100 American Society of Anesthesiologists (ASA) I and II patients of either gender between 2-8 years, undergoing elective surgeries under general anesthesia were randomized into two groups. (1) Patients parent refusal (2) Patients with allergy to the study drugs. (3) Patients with any intranasal pathology or congenital anomaly (4) Children with a history of: a. Upper airway disease. b. CNS dysfunction. c. CVS dysfunction were excluded. Children(2-8year) admitted in the Department of Pediatric Surgery planned for elective surgery under general anesthesia fulfilling the inclusion criteria were included for the study. Pre-operative visit was made and written informed consent from the parents was obtained. The patients were randomly divided into two groups - Group D and Group M using simple randomisation numbers with closed envelop method. Premedication with Intranasal Dexmedetomidine 1$\mu$g/kg (Group D) or Intranasal Midazolam 0.2mg/kg (Group M) was given 30minutes prior to surgery according to group allotted. Total volume of drug was calculated and half of the volume of the drug was administered in one nostril and remaining half of the volume of the drug was administered in another nostril in the presence of his/her parent, using a needleless syringe. Intravenous cannulation was done and intravenous Ringer's lactate was administered as maintenance fluid through intravenous canula and all the multipara monitors were attached.

### 2.1. Sedation score assessed by UMSS

Score 0 for alert, Score1 for minimally sedated, Score 2 for moderately sedated, Score 3 deep sedated, Score 4 for unarousable patients.Sedation score of 2 was considered satisfactory.

### 2.2. Child-parent separation score assessed by PSAS

Score 1 for unafraid patient, Score 2 for slightly afraid, Score 3 for moderately afraid, Score 4 for crying patients. Score of 2 was considered satisfactory Sedation score and child parent separation score noted preoperatively (baseline) and 30 minutes after premedication. Hemodynamic parameters [Heart rate (HR), Mean arterial pressure (MAP), SpO2)] were monitored pre-operatively (baseline) and at interval of 10, 20, 30 minutes after premedication. Children were shifted to the operating room after 30 minutes. 100% oxygen was given via facemask and the mask acceptance score of the child was noted.

Mask acceptance score was assessed as : Score 1 for crying patients, Score 2 for moderate fear of mask, Score 3 for cooperative patients, Score 4 for calm patients, Score 5 for asleep patients.Mask acceptance score of 3 was regarded as satisfactory.

General anesthesia was given to patient as per standard protocol. Intra operative hemodynamic parameters [Heart rate (HR), Mean arterial pressure (MAP), SpO2)] were recorded every 15 min till the end of surgery. Any side effects like bradycardia, hypoxemia, nasal irritation, vomiting, if encountered was managed as per standard medical care.

## 3. Statistical Analysis

Statistical software IBM SPSS 20.0.0.0 (trial version) was used for calculating the P values. Comparison of mean heart rate, systolic blood pressure, diastolic blood pressure at different time points was done using unpaired 't' test. Chi-square test was used for categorical data. A p value of$<0.05$ was taken as statistically significant. The final data was presented in the form of tables.

## 4. Results

Two groups were comparable with respect to age and body weight. In Group D, the Mean sedation score was increased from 0 to 2.94 ± 0.24 ,30minutes after premedication. In Group M, the Mean sedation score was increased from 0 to 1.02 ± 0.141, 30minutes after premedication (Table 1). In Group D, the sedation was satisfactory as compared to Group M and the difference in both the groups was found to be statistically significant($p<0.001$). In Group D, the Mean parental separation anxiety score was decreased from 2.96 ± 0.28 to 1.90 ± 0.46, 30 minutes after premedication. In Group M, the Mean parental separation anxiety score was decreased from 2.98 ± 0.31 to 2.2 ± 0.27, 30 minutes after premedication (Table 2). In Group D, there was easy child parent separation as compared to Group M and the difference in both the groups was found to be statistically significant ($p=0.001$). In Group D the mask acceptance score was 3.94 ±0.24 and in Group M it was 2.4 ± 0.49 (Table 3) and the difference in both the groups was found to be statistically significant ($p=0.001$). Children in Group D showed better mask acceptance as compared to children of Group M. The Mean heart rate in both the groups was lower than baseline at various time intervals after premedication preoperatively and intraoperatively (Table 4) and was comparable and the difference was found to be statistically insignificant ($p>0.05$). The Mean MAP in both the groups was lower than baseline at various time intervals after premedication preoperatively and intraoperatively (Table 6) and was comparable and the difference was found to be insignificant ($p>0.05$). The Mean Spo2 in both the groups was stable and comparable at various time intervals preoperatively and intraoperatively (Table 7) and difference was found to be statistically insignificant ($p >0.05$). The Mean RR in both the groups were comparable at various time interval preoperatively (Table 5) and the difference was found to be statistically insignificant ($p>0.005$). There were no incidences of any side effects in both the groups.

**Table 1.** Comparison of Mean Sedation score between both groups [by University of Michigan sedation Scale (UMSS)

| Sedation Score | Group D | | Group M | | p-value (unpaired T test applied) |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Before premedication | 0 | 0 | 0 | 0 | NA |
| 30 Min. after premedication | 2.94 | 0.24 | 1.02 | 0.141 | <0.001, significant |
| Mean Difference | 2.94 | | 1.02 | | |
| p-value (paired T test applied) | 0.000 significant | | 0.000 significant | | |

T test applied. P value < 0.05 was taken as statistically significant.

**Table 2.** Comparison of parental separation anxiety score between both groups [by Parental separation anxiety scale (PSAS)]

| Parental separation anxiety score | Group D | | Group M | | p-value (unpaired T test applied) |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Before Pre-Medication | 2.96 | 0.283 | 2.98 | 0.31 | 0.73 |
| 30 Min. After Pre-Medication | 1.9 | 0.463 | 2.2 | 0.274 | 0.001, significant |
| Mean difference | 1.06 | | 0.78 | | |
| p-value (paired T test applied) | 0.000 significant | | <0.001 Significant | | |

T test applied. P value < 0.05 was taken as statistically significant.

**Table 3.** Comparison of mask acceptance score between both groups

| | Group | N | Mean | SD | p-value (un-paired T test applied) |
|---|---|---|---|---|---|
| Mask | Group D | 50 | 3.94 | 0.24 | 0.001 |
| Acceptance Score | Group M | 50 | 2.4 | 0.495 | Significant |

T test applied. P value < 0.05 was taken as statistically significant.

**Table 4.** Comparison of Heart rate between both groups (Mean ± SD)

| Time(min.) | Group D | Group M | P value |
|---|---|---|---|
| Heart rate(preoperatively) | | | |
| Baseline | 119.67±9.13 | 117.9±9.81 | 0 .473 |
| 10 | 115.77±8.69 | 117.6±9.3 | 0 .433 |
| 20 | 115.1±9.29 | 115.8±9.39 | 0.773 |
| 30 | 111.53±9.57 | 115.83±8.87 | 0 .076 |
| Heart rate (intraoperatively) | | | |
| Baseline | 109.5±9.25 | 111.57±9.6 | 0.27 |
| 15 | 109.43±9.86 | 112.57±9.07 | 0.10 |
| 30 | 107.97±9.64 | 110.53±8.82 | 0.16 |
| 45 | 107.23±10.52 | 110.03±8.27 | 0.27 |
| 60 | 108.88±10.98 | 109.10±8.72 | 0.91 |
| 75 | 106.50±10.44 | 109.50±6.70 | 0.09 |
| 90 | 104.73±9.79 | 107.11±8.88 | 0.20 |

T test applied. P value < 0.05 was taken as statistically significant.

**Table 5.** Comparison of pre-operative RR (Respiratory Rate) between both groups

| | Group D | | Group M | | |
|---|---|---|---|---|---|
| Time (min) | Mean RR (/min.) | SD | Mean RR (/min.) | SD | p-value (un-paired T test applied) |
| 0 min. | 21 | 3 | 20 | 2 | >0.05 |
| (baseline) | | | | | |
| 10 min. | 20 | 2 | 19 | 2 | >0.06 |
| 20 min. | 19 | 2 | 19 | 2 | >0.07 |
| 30 min. | 19 | 2 | 18 | 2 | >0.08 |

T test applied. P value < 0.05 was taken as statistically significant

**Table 6.** Comparison of MAP (Mean arterial pressure) between both groups (Mean ± SD)

| Time(min.) | Group D | Group M | P value |
|---|---|---|---|
| MAP (preoperatively) | | | |
| Baseline | 64±3 | 63±3 | >0.05 |
| 10 | 63±3 | 62±3 | >0.05 |
| 20 | 62±3 | 62±3 | >0.05 |
| 30 | 62±3 | 62±3 | >0.05 |
| MAP (intraoperatively) | | | |
| Baseline | 62±3 | 62±3 | >0.05 |
| 15 | 62±3 | 61±3 | >0.05 |
| 30 | 63±3 | 62±3 | >0.05 |
| 45 | 63±3 | 62±3 | >0.05 |
| 60 | 63±3 | 63±3 | >0.05 |
| 75 | 63±3 | 64±3 | >0.05 |
| 90 | 62±1 | 65±0 | >0.05 |

T test applied. P value < 0.05 was taken as statistically significant

**Table 7.** Comparison of Spo2 between both groups (Mean ± SD)

| Time(min.) | Group D | Group M | P value |
|---|---|---|---|
| Sp02(preoperatively) | | | |
| Baseline | 100±1 | 99±1 | >0.05 |
| 10 | 100±1 | 99±1 | >0.06 |
| 20 | 99±1 | 99±1 | >0.07 |
| 30 | 99±1 | 99±1 | >0.08 |
| Spo2 (intraoperatively) | | | |
| Baseline | 100±1 | 100±1 | >0.05 |
| 15 | 99±1 | 99±1 | >0.05 |
| 30 | 99±1 | 99±1 | >0.05 |
| 45 | 99±1 | 100±1 | >0.05 |
| 60 | 99±1 | 99±1 | >0.05 |
| 75 | 100±0 | 100±0 | >0.05 |
| 90 | 100±0 | 100±0 | >0.05 |

T test applied. P value < 0.05 was taken as statistically significant.

## 5. Discussion

Sedative premedication is more reliable and one of the most widely used method to mitigate the anxiety of a child during the preoperative period. Among various sedative drugs available, Midazolam is the most commonly used because it produces anxiolysis, amnesia, hypnosis and has anticonvulsant and skeletal muscle relaxant properties but sometimes it is associated with respiratory depression and is devoid of analgesic properties. Dexmedetomidine an alpha-2 receptor agonists has recently been found to be a promising premedicating agent in children due to its anxiolytic, sedative and analgesic properties. Premedication can be given through Oral, Intranasal,

Parentral (Intravenous and Intramuscular) and Rectal routes. Intranasal route is found to be advantageous as it has rapid onset, is painless and nearly complete absorption due to high mucosal vascularity. So, we aimed to compare the effects of Dexmedetomidine and midazolam administered through intranasal route to draw the inferences on their efficacy as premedicant in children.

In this prospective, randomised, comparative and double blind study, 100 patients of age group 2 to 8 years of either sex of ASA grade I and II undergoing elective surgery under GA up to 90 minutes were included in the study. They were randomly divided into two groups of 50 each, by closed envelope method using computer generated randomised numbers. 1. Group D (n = 50): The patients received intranasal dexmedetomidine 1$\mu$g/kg (through needleless syringe) 30 min before surgery. 2. Group M (n = 50): The patients received intranasal midazolam 0.2 mg/kg (through needleless syringe) 30 min before surgery.

## 6. Demographic data

In our study, demographic parameters like age, sex and weight were taken and all the parameters were comparable in both the groups and our findings were comparable to studies done by Mostafa G.Mostafa *et al.*, [11] and Li Wang *et al.*, [6]. They were also comparable in group distribution as they were divided equally into two groups of 50 each.

## 7. Patient sedation score

In our study, we found that the Mean sedation score in Group D was 2.94 ± 0.24 and in Group M was 1.02 ± 0.14, 30 minutes after premedication and the difference was found to be statistically significant($p<0.001$) (Table 1). Children in Group D showed satisfactory and better sedation as compared to Group M in our study. Our finding regarding the sedative effect of dexmedetomidine was comparable with the studies done by Dr.Shweta Nitturi *et al.*, [11] and Anupriya Gupta *et al.*, [8]. Our study finding was in disagreement with the study done by Aynur Akin *et al.*, [3], in which both Dexmedetomidine and Midazolam Group provided equivalent and comparable level of sedation in children.

The sedative effect of dexmedetomidine is probably due to its stimulating effect on alpha2-adrenergic receptors in the locus coeruleus in the brain stem, thereby increasing the activity of inhibitory GABA neurons in the ventrolateral preoptic nucleus and thus produces a cooperative form of sedation (children can be easily arousable with light touch stimulation).

## 8. Parental separation anxiety

In our study we found that mean parental separation anxiety score in Group D was 1.90 $\pm$ 0.46 and in Group M was 2.2 $\pm$ 0.27, 30 minutes after premedication and the difference was found to be statistically significant (p=0.001) (Table 2). In Group D, children were easily separated from their parents as compared to Group M.

Our finding regarding the anxiolytic effect of dexmedetomidine was comparable with the studies done by Dr Shweta Nitturi *et al.,* [11] and Josemine Davis *et al.,* [5].

Children who were premedicated with intranasal dexmedetomidine were easily separated from their parents as compared to children who were premedicated with intranasal midazolam probably because children were better sedated in dexmedetomidine group as compared to midazolam group.

MAS (MASK ACCEPTANCE SCORE) :In our study we found that the mean mask acceptance score in Group D was 3.94 $\pm$ 0.24 and in Group M was 2.40 $\pm$ 0.49 (Table 3) and the difference was found to be statistically significant (p=0.001). Children in Group D showed better mask acceptance as compared to children of Group M.

Our finding regarding the mask acceptance in both the groups were comparable with the studies done by Dr Shweta Nitturi *et al.,* [11] and Anupriya Gupta *et al.,* [8].

Better mask acceptance was seen with intranasal dexmedetomidine probably due to its better anxiolytic and sedative property.

Haemodynamic parameters :In our study, hemodynamic parameters such as heart rate, mean arterial pressure, respiratory rate and SpO2 were comparable and stable in both the groups, at different time intervals during preoperative and intraoperative period.

### 8.1. Heart rate (HR)

In our study, the mean heart rate was comparable at baseline (0min) preoperatively between the two groups which was 119.67$\pm$9.13 per minute in Group D and 117.9$\pm$9.81 in Group M (P>0.05).The mean heart rate was lower in Group D as compared to Group M at various time intervals preoperatively and intraoperatively the difference was found to be statistically insignificant (p >0.05) (Table 4).

Our findings regarding heart rate were comparable to the studies done by Anita Pareek *et al.,* [12]. Our study findings were in partial disagreement with the studies done by Josemine Davis *et al.,* [7] and Bassem B. Saad *et al.,* [9]. In their study they found that intranasal Dexmedetomidine caused significant decrease in mean heart rate preoperatively and intraoperatively as compared to intranasal Midazolam.

The decrease in mean heart rate in Dexmedetomidine group was probably due to its sympatholytic effect leads to decrease in the circulating catecholamine levels and increases cardiac vagal activity. The decrease in mean heart rate in Midazolam group was probably due to its GABA facilitating action that leads to decrease anxiety and sympathetic activity in body.

### 8.2. Mean arterial pressure (MAP)

In our study, the MAP was comparable at baseline (0min) preoperatively in both the groups which was 64$\pm$3 mmHg in Group D and 63$\pm$3 mmHg in Group M (P>0.05). The Mean MAP in both the groups was comparable and lower than baseline at various time intervals after

premedication preoperatively and intraoperatively and the difference was found to be statistically insignificant (p>0.05) (Table 6). Our findings regarding MAP were comparable to the studies done by Anita Pareek *et al.,* [12]. In their study they also found that the mean MAP was comparable in both groups during preoperative and intraoperative period. Our study finding was in disagreement with study of Dr Shilpa Agarwal *et al.,* [15]. In their study, they found that intranasal Dexmedetomidine caused significant decrease in MAP (preoperatively and intraoperatively) as compared to intranasal Midazolam.

### 8.3. Respiratory Rate (RR)

In our study the Mean Respiratory rate (RR) preoperatively at baseline(0min) in Group D was 21±3 per min and in Group M was 20±2 per min. The Mean RR in both the groups were comparable at various time interval preoperatively and the difference was found to be statistically insignificant (p>0.005) (Table 7).

Our findings regarding Respiratory rate were comparable to the studies done by Anita Pareek *et al.,* [12].

Midazolam acts on GABA receptors and can lead to decrease in respiratory drive in a dose-dependent manner and may cause decrease in respiratory rate. In our study we used midazolam (0.2mg/kg) which did not cause the decrease in respiratory rate.

### 8.4. Arterial oxygen saturation (Spo2)

In our study the Mean Spo2 in both the groups was stable and comparable at various time intervals preoperatively and intraoperatively and the difference was found to be statistically insignificant (p>0.05) (Table 7).

Our findings regarding Sp02 were comparable to the studies done by Aynur Akin *et al.,* [3], Ayushi Gupta *et al.,* [13], Darshna D Patel *et al.,* [2] they all compared intranasal dexmedetomidine(1mcg/kg) and midazolam(0.2mg/kg) for premedication in children. They also found that Spo2 were comparable and stable in both the groups at various time intervals (preoperatively and intraoperatively) and difference was found to be statistically insignificant (p >0.05).

### 8.5. Side effects

In our study, none of the patients in either group (intranasal dexmedetomidine 1mcg/kg and intranasal midazolam 0.2mg/kg) showed any side effects like nasal irritation, bradycardia, hypoxemia, nausea/vomiting.

Our findings regarding side effects were comparable to the studies done by Anupriya Gupta *et al.,* [8] and Anita Pareek *et al.,* [12]. Our study finding was in disagreement with study of Manjunath C Patil *et al.,* [14]. In their study they found that, seven children become euphoric and restless after premedication with intranasal midazolam.

## 9. Limitations of study

In our study, both midazolam and dexmedetomidine were administered in the form of intranasal drops by needleless syringe. The use of spray or metered dose atomizer might have shown better absorption and greater bioavailability of intranasal drugs. Our study was conducted to compare the efficacy of two drugs for premedication in children with smaller sample size. Therefore, further studies with larger sample size are required to draw more inferences on their efficacy as premedicating agent. We compared single dose of both the drugs to evaluate their effectiveness as a premedicating agent. Further studies with different doses of drugs are required to throw more light on their efficacy as premedicating agent.

## 10. Conclusion

Overall, it can be concluded from our study that intranasal dexmedetomidine provides better sedation, relieves preoperative anxiety, easy parental separation and provides better mask acceptance. It provides stable hemodynamics (preoperatively and intraoperatively) and no side effects. Hence, intranasal dexmedetomidine can be an effective and safe alternative as compared to intranasal midazolam for premedication in children undergoing elective surgery under general anaesthesia.

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