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# Intranasal dexmedetomidine vs midazolam for premedication in pediatric patients undergoing surgery.

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## Abstract

**Introduction:** Preoperative period is stressful for pediatric patients. This leads to physical resistance during preoperative preparation, at the time of parental separation, vene puncture, mask applications and can cause late postoperative behavioral problems. Effective premedication minimizes preoperative stress, enhance patient cooperation for smoother induction of general anesthesia. In this study, we compared effect of intranasal dexmedetomidine and midazolam as premedication in pediatric patients undergoing surgery.

**Materials and method:** Ninety patients, aged 1-6 years of either sex of ASA I-II, undergoing elective surgery were randomly divided equally into three groups. Group-D patients received dexmedetomidine 1mcg/kg, group-M patients received midazolam 0.2mg/kg, group-C patients received normal saline 1ml intranasally as premedication 30min before transferring to operating room. The patients scores on the Ramsay Sedation Scale (RSS), parental separation anxiety scale (PSAS), vene puncture reaction, mask acceptance scale (MAS) were recorded. Hemodynamic parameters were measured before and every 10min after drug administration, intraoperative and till 2hrs in post-operative period. Patients were observed for any adverse effects.

**Results:** RSS score were significantly higher in the group-D than group-M and group-C at 30min ($p< 0.05$). PSAS was successful in 76% of patients in Group-D compared with 53.3% and 10% of patients in Group-M and C, respectively. Intravenous cannulation score and MAS was best achieved in group-D. Perioperative hemodynamic parameters were significantly lower in group-D than group-M and group-C at all time intervals.

**Conclusion:** Intranasal dexmedetomidine and midazolam provided effective sedation, parenteral separation, vene puncture reaction, better mask acceptance with minimal

hemodynamic changes. Intranasal dexmedetomidine(1mcg) provides better sedation than intranasal midazolam (0.2mg) as a premedication in pediatric patients.

**Keywords:** Premedication, Intranasally, Paediatrics, Midazolam, Dexmedetomidine.

## Introduction

Unfamiliar environment and Fear of separation from parents [1] leads to physical resistance during preoperative preparation, at the time of parental separation, mask applications, venipuncture and postoperative behavioral problems in preoperative period. Currently pharmacological agents like midazolam, chloral hydrate, ketamine, promethazine and opioids are used alone or in combination for premedication. Despite their efficiency, associated adverse effects limit their use in pediatrics procedures.[2]

The ideal premedicant for children should [3] be available in a preparation that is readily accepted by the children, have a rapid onset, provide anxiolysis with mild sedative effects, without side effects and provide a rapid recovery. Oral and rectal routes showed delays in onset, whereas intravenous (IV) and intramuscular (IM) medications are painful and frightening. Intranasal route is relatively easy, well tolerated, non-invasive and bypasses first-pass hepatic metabolism which give high bioavailability. The high blood supply in the nasal mucosa [4] causes relatively rapid delivery of drug to the bloodstream and the central nervous system (CNS).

Dexmedetomidine is a newer, highly selective α2-adrenergic agonist,[5] has produces analgesic, anxiolytic and sedative effects with minimum risk of respiratory depression. Dexmedetomidine had poor bioavailability and absorption is better through mucosal route.

Midazolam a benzodiazepine most commonly used preanesthetic medication among children provides anterograde amnesia, anxiolysis, hypnotic, anti-convulsant, sedative effect with risk of respiratory depression [6] and with no analgesic effect.

G Mostafa et al. [7], studied premedication with intranasal dexmedetomidine (1mcg/kg), midazolam(0.2mg/kg) and ketamine(5mg/kg) for children undergoing bone marrow biopsy and aspiration and concluded through all three drugs produced adequate sedation midazolam was more effective and safer and also cheaper with easy availability. Aman Priyanka et al. [8], compared intranasal midazolam spray (0.2mg/kg) verses oral midazolam syrup (0.5mg/kg) and concluded intranasal route was superior.

## Materials and Methods

### Study design

Approval from the Institutional Ethics Committee and an informed and written consent from parents was obtained. This prospective, randomized double blinded, controlled study was conducted on 90 patients in the age group of 1–6years of either sex, ASA I-II scheduled for elective surgery under general anesthesia.

The exclusion criteria included Parent's refusal, ASA >II, known allergic or hypersensitivity reaction to Midazolam or Dexmedetomidine, difficult venous access, developmental delay or mental retardation, congenital anomalies, intranasal pathology or active respiratory tract infection, any previous reaction to anaesthesia, difficult intubation, any cardiac and respiratory disease, emergency surgery and patients on sedative drugs.

Children were randomly allocated to one of the three groups by a computer-generated table of random numbers (30 each). Since the previous study of healthy adults has shown that the mean onset time for significant sedation after 1mcg/kg intranasal dexmedetomidine was approximately 45-60min [5] All children received intranasal medication or placebo at 60min before

induction of anaesthesia. Group-D received intranasal Dexmedetomidine hydrochloride 1mcg/kg, Group-M received intranasal Midazolam 0.2mg/kg and Group-C received 1ml of 0.9% normal saline.

**Study procedure**

Preanesthetic check-up was conducted; a detailed history and complete physical examination was done. Heart rate (HR), non-invasive blood pressure (NIBP), respiratory rate (RR), oxygen saturation ($spo_2$) at room air with other systemic examination were done and recorded. A cannulation sites were noted. Routine investigations like complete blood count (CBC), serum electrolyte(S/E), random blood sugar (RBS), renal function test (RFT), liver function test (LFT), chest x-ray(PA view) and electrocardiogram(ECG) were done. The patients were kept nil by mouth for 6hrs for solids and 2hrs for liquid prior to surgery. Dexmedetomidine was prepared from 100mcg/ml ampule, Midazolam from 5mg/ml ampule with respective doses in total volume of 1ml with normal saline.

All the study drugs were prepared by an independent investigator not involved in the observation or administration of anesthesia to children. Observers and attending anesthesiologist were blinded to the study drug given.

**Induction**

Children were premedicated in the preoperative holding area in the presence of one parent with resuscitation and monitoring equipment ready. Baseline HR, NIBP, spo2 and RR were recorded before study drug administration.

Total dose of study drug was dropped, into both nostrils equally using a needleless 2ml syringe with the child in the recumbent position, 30min prior to shifting to operating room (OR). HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure(MAP), SPO2 and RR were measured every 10mins until transfer to OR. Sedation status was assessed by observer every 10mins with Ramsay Sedation Scale [9].. All the patients were watched for side effects such as hypotension, bradycardia, hypoxemia, apnea, nasal irritation, vomiting, itching, etc.

Parental separation anxiety scale score (PSAS)[10] were recorded at the time of transferring the patient to OR. Monitor for pulse oximetry, electrocardiography, NIBP and ETCO2 were applied with Drager Fabius plus multipara monitor. Intravenous access was secured and reaction to intravenous cannulation was noted.[11]

All the patients were uniformly premedicated with intravenous Inj. Glycopyrrolate 0.004mg/kg, Inj. Fentanyl 2mcg/kg and antibiotic.

The patients were pre oxygenated with 100% oxygen by face mask for 3mins and mask acceptance scale (MAS)[10] was noted. Anesthesia was induced with intravenous Inj. Thiopentone 6mg/kg, Inj. Atracurium 0.5mg/kg and intubation done with an appropriately sized portex endotracheal tube. Maintenance of anesthesia was done with (50:50) O2:N2O with sevoflurane 1%-2% and intermittent dose of Inj. Atracurium 0.05 mg/kg intravenously. In the end, sevoflurane was discontinued plus N2O was switched off. Neuromuscular blockade was reversed with glycopyrrolate 0.01 mg/kg and neostigmine 0.04 mg/kg intravenously. The children were extubated after achieving spontaneous regular breathing with adequate tidal volume and respiratory rate, adequate neuromuscular recovery, return of protective reflexes after thorough suctioning of oral cavity.

HR, SBP, DBP, MAP, spo2 and RR were recorded at baseline, after study drugs instillation, at the time of shifting to OR, at vene puncture, after application of face mask, after induction, immediately after intubation, at every 10minute interval, at the time of reversal, at the

time of extubation and in postoperative period till 2hrs. The children were monitored for any signs of adverse effects, including respiratory depression (RR <14/min), desaturation (spo2<95%) and bradycardia(<80beats/min).

**Statistical analysis**

Statistical analysis was carried out using the graphpad prism 8.0 statistical software. Results of continuous measurements were presented as Mean±SD and results of categorical measurements are presented in number and percentage (%). Patients' characteristic data were analysed with one-way analysis of variance (ANOVA) for continuous variables. Intergroup comparison of Ramsay sedation scores, parenteral separation anxiety scale, reaction to cannulation, mask acceptance scores was done with a Mann- Whitney u-test. P-value<0.05 was considered statistically significant.

In the previous study, 21.9% patients in the midazolam group and 75% in the dexmedetomidine group had satisfactory sedation scores at separation.[12] Targeting the same difference, with a 95% confidence level and 80% power, the minimum sample size was calculated as 17 in each group. We included 30 patients in each group.

For statistical analysis, Ramsay sedation score was considered as satisfactory sedation, PSAS score and MAS score of 1-2 was considered "satisfactory." Vene puncture score of 3-4 was considered "satisfactory."

Although much research has been conducted on different sedation methods in children, ideal sedative drugs with ideal route has yet to be discovered. Therefore, we thought to compare the efficacy of intranasal dexmedetomidine(1mcg/kg) and intranasal midazolam(0.2mg/kg).

Our aim was to compare intranasal dexmedetomidine(1mcg/kg) and midazolam(0.2mg/kg) for sedation quality, ease of parental separation, reaction to vene puncture and mask acceptance. Our Secondary objective were to compare hemodynamic stability and possible adverse events during study period in pediatric patients undergoing surgery.

**Observation and Results**

Patients of all the groups were comparable with respect to age, sex, weight, duration and type of surgery. (Table - 1)

There was no significant difference between the three groups as regards HR and MAP before sedation. After administration of the study drugs, there was a significant decrease in HR and MAP in group-D as compared to group-M and group-C($p<0.05$) at all time interval. (Figures 1 &2) Hemodynamic data showed that HR, MAP was significantly decrease at 10, 20 and 30mins after drug administration in group-D compared to group-M and group-C. Immediately after intubation there was increase in HR in group-C and group-M. No episodes of bradycardia and hypotension was seen throughout observation period.

We did not observe SPO2 <95% and decrease in RR during the observation period in any study group after premedication. There were lower RR values in group-D than group-M and group-C but the difference was not significant.

The sedation score was statistically significantly higher in the midazolam group at 10 and 20min after the administration of the drug while at 30min it was lower than Group-D. But we observed that group-D and group-M achieved a comparable sedation score at 10, 20 and 30min. At 30min both dexmedetomidine (2.76±0.43) and midazolam (2.33±0.66) group had satisfactory sedation score while control group had unsatisfactory sedation score (1.23±0.43). None of the patients of any group showed score ≥5. (Figure 3)

The percentage of children who had satisfactory parental separation was 76%, 53.3% and 10% in group-D, M and

C, respectively. There was a statistically significant difference in response to cannulation between the three groups with no or mild reaction to cannulation in 56.6% of children in group-D compared with 33.3%in group M and in group-C. Satisfactory mask acceptance was seen in group-D (83.3%) compared with group-M (70%) and group-C (13.3%). (Figure 4)

Incidence of nausea and vomiting was lower in group-D (6.67%) and group-M (13.3%) compare to group-C (20%). It was treated with ondansetron 0.1mg/kg. None of the children included in the study had significant bradycardia, hypotension, nasal irritation or hypoxia (<95%

**Discussion**

Paediatric patients undergoing surgery can experience significant anxiety and distress during perioperative period which can lead to negative response postoperatively. Kain demonstrated that 54% of their patients had negative behavioral patterns at 2 weeks and 20% continued to have these patterns up to 6 months.[13] Dexmedetomidine produces sedation by stimulating α2-adrenergic receptors in the locus coeruleus, apart from the brain stem involved in the sleep–wake cycle, which reduce central sympathetic outflow, resulting in increased stimulation of inhibitory neurons.[14] Therefore, it causes analgesia and sedation without causing respiratory depression. While midazolam stimulates gamma-aminobutyric acid (GABA) receptors in the cerebral cortex to increase the conductance of chloride ions and hyperpolarization that inhibits normal function of neurons producing sedation.[15]

Midazolam is the most widely used as a premedication before anesthesia.[12] Intranasal administration of midazolam and dexmedetomidine has the advantage of no first-pass effect with rapid absorption directly into the systemic circulation and a bioavailability of 55%–83%.[16] Most children better tolerated the intranasal than oral administration.[17] So we aimed to compare the intranasal application of both agents.

According to Yuen et al. [5] who reported that intranasal 1 and 1.5mcg/kg doses of dexmedetomidine have similar effects. 1mcg/kg dexmedetomidine was found more effective than 0.5mcg/kg dexmedetomidine intranasally.[12] Davis et al. [18], reported that there was no difference in efficacy between intranasal dosage of 0.2 and 0.3mg/kg midazolam for premedication of Paediatric patients. So, in our study, we had taken intranasal dexmedetomidine 1mcg/kg and intranasal midazolam 0.2mg/kg as premedication in Paediatric patients.

In our study, we found mean sedation score after 1mcg/kg intranasal dexmedetomidine is (2.76±0.43) which was satisfactory level of sedation. The sedation score was statistically significantly higher in the midazolam group at 10 and 20min after the administration of the drug while at 30min it was lower than Group-D. None of the patients in group-C was sedated. Similar to our study, Patel et al. [19] reported that patients who were premedicated with intranasal dexmedetomidine had lower sedation score and easier parental separation than who received intranasal midazolam.

Ghali et al. [20] found statistically significant difference (P<0.05) in parental separation between children who received intranasal dexmedetomidine 1mcg/kg (Group-D) and oral Midazolam 0.5mg/kg (Group-M) at approximately 60 and 30min, respectively before induction of anaesthesia. They concluded child parental separation was easier in intratranasal dexmedetomidine group than oral midazolam group. Similar to that in our study we observed parental separation (PSAS) ≤2 in 76% of patients in Group-D compared with 53.3% of patients in Group-M and 10% in Group-C.

Gyanesh et al. [21] stated that in children given intranasal dexmedetomidine 30min before undergoing an MRI showed no or mild reactions to intravenous cannulation in 90.4% compared with the children given intranasal ketamine. Similarly in our study, we found that there was a statistically significant difference in response to cannulation between the three groups with no or mild reaction to cannulation in 56.6% of children in group-D compared with 33.3%, in group-M and 6.6% in group-C.

Faritus et al. [22], analysis of the mask acceptance behaviour at anaesthesia induction time revealed that children receiving dexmedetomidine were calm and cooperated well in terms of mask acceptance than children receiving midazolam. Similarly, Sun et al. [23] compared midazolam and dexmedetomidine intranasally and stated that the dexmedetomidine group was associated with more satisfactory sedation upon mask acceptance compared with the midazolam group. In our study, we found satisfactory mask acceptance by 83.3% of the patients in group-D, 70% of those in group-M and 13.3% in group-C which is similar to above studies.

Kumari et al. [24] compared the effect of 4mcg/kg of oral clonidine, 4mcg/kg of oral dexmedetomidine, and 0.5mg/kg of oral midazolam on preoperative cooperation and showed that the mean HR in all groups decreased significantly from the baseline by 30 minutes postoperatively. In our study, the HR in the dexmedetomidine group decreased significantly 20 minutes after drug administration than group-M and group-C. Despite this decrease, the values of HR remained within normal limit.

In our study, we found that patients receiving dexmedetomidine (group-D) had significantly lower MBP after drug administration in comparison to group-M and group-C. Similarly, Medhat et al. [15] had found that MBP decreased significantly in children after intranasal dexmedetomidine, compared with that in children who received intranasal midazolam. In our study, the fall in blood pressure and HR was within acceptable limits for the age of the child and did not require the use of chronotropic agents, fluids or inotropes.

Akin et al. [25] stated in their study that there was no statistically significant decrease in respiratory rate or $SpO_2$ below 95%. Similarly, in our study none of the patients in three groups had SpO2< 95% and decrease in RR at any point of time during patients monitoring.

None of the children in study groups had complications, such as bradycardia, hypotension, hypertension and respiratory depression after premedication. Similarly, no complication was noted in other studies.[12]

**Limitations of our study**

This study was done on patients belonging to ASA I-II so effects in high-risk patients have not been seen. We did not evaluate the peak effect of intranasal dexmedetomidine and midazolam or the blood concentrations. We did not study the effects of study drugs premedication on the analgesic and an aesthetic requirement during surgery.

**Conclusion**

We concluded that Intranasal dexmedetomidine and midazolam provides effective sedation, parenteral separation, lower reactivity to intravenous cannulation, better mask acceptance with minimal hemodynamic changes. Intranasal dexmedetomidine(1mcg) provides better sedation than intranasal midazolam(0.2mg) as a premedication in pediatric patients without significant adverse events.

The following study tools were used in this study:

**RSS-The Ramsay Sedation Scale [9]**

| Sn. | Criteria | Score |
|---|---|---|
| 1. | Patient is anxious and agitated or restless or both. | 1 |
| 2. | Patient is cooperative, oriented, and tranquil. | 2 |
| 3. | Patient responds to command only. | 3 |
| 4. | Patient exhibits brisk response to light glabellar tap. | 4 |
| 5. | Patient exhibits sluggish response to light glabellar tap. | 5 |
| 6. | Patient exhibits no response. | 6 |

**PSAS – Parental separation anxiety scale [10]:**

| Sn. | Criteria | Score |
|---|---|---|
| 1. | Easy separation. | 1 |
| 2. | Whimpers, but easily reassured, not clinging. | 2 |
| 3. | Cries & cannot reassured, not clinging to parents. | 3 |
| 4. | Crying & clinging to parents. | 4 |

**Reaction to intravenous cannulation [11]:**

| Sn. | Criteria | Score |
|---|---|---|
| 1. | Marked movements that make the procedure impossible. | 1 |
| 2. | Reactions that disturb the procedure. | 2 |
| 3. | Mild reactions that do not disturb the procedure. | 3 |
| 4. | No reaction. | 4 |

**MAS - Mask acceptance scale [10]:**

| Sn. | **Criteria** | **Score** |
|---|---|---|
| 1. | Excellent (unafraid, co-operative, accept mask readily) | 1 |
| 2. | Good (slight fear of mask, easily reassured) | 2 |
| 3. | Fair (moderate fear of mask, cannot reassured) | 3 |
| 4. | Poor (terrified, crying or combative) | 4 |

Table 2: Comparison of demographic data and type of surgery

| Variables | Group-C Mean±SD | Group-D Mean±SD | Group-M Mean±SD | P-value |
|---|---|---|---|---|
| Age (years) | 3.5±1.6 | 3.5±1.8 | 4.1±1.5 | 0.25 |
| Sex (Male: Female) | 23:7 | 15:15 | 14:16 | |
| Weight (kg) | 11.3±3.9 | 11.7±4 | 12.1±4.2 | 0.76 |
| Duration of surgery (mins) | 66.33± 10.33 | 69.33 ±15.18 | 67.67 ±12.44 | 0.66 |
| Type of surgery<br>Hickmen insertion<br>Lap. Splenectomy<br>Wide local excision | 26<br><br>1<br>3 | 25<br><br>1<br>4 | 27<br><br>1<br>2 | |

(Values are expressed as Mean±SD. P value <0.05 was considered as significant)

Figure 1: Comparison of heart rate at various time interval.

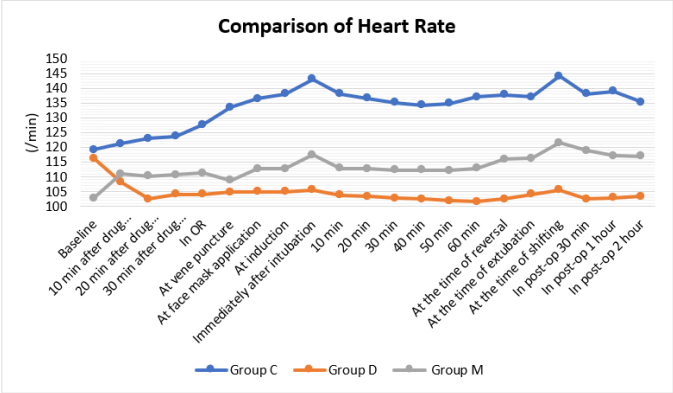



Figure 1: shows there was decrease in HR in group-D compared to group-M and group- C throughout the observation time.

Figure 2: Comparison of MAP at various time interval.

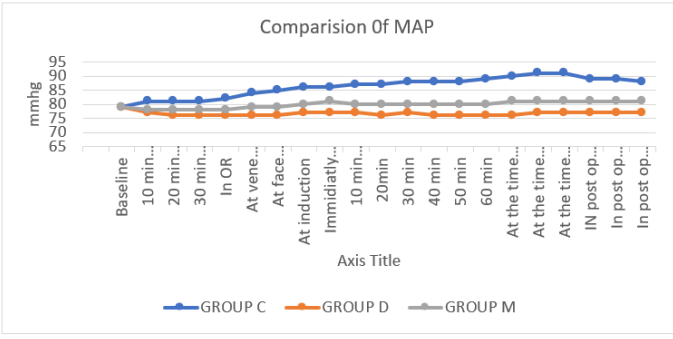
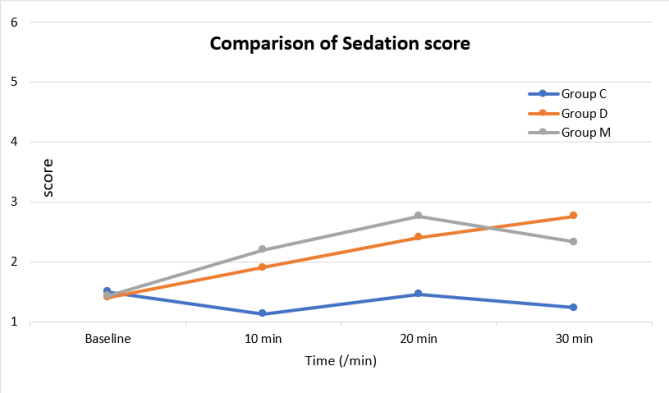


Figure 3: Comparison of sedation scores between study groups




SPO2 dose not fall below 98% at any time interval.

RR does not fall below 22/min at any time interval.

Figure 4: Comparison of different scores in study groups

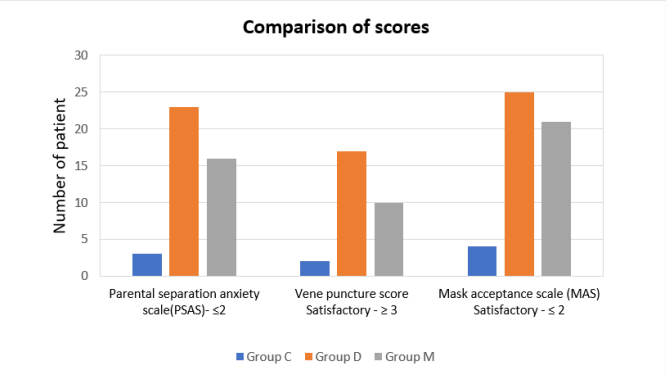



Table 2: Comparison of complications between study groups

| Complications | Group C N (%) | Group M N (%) | Group D N (%) |
|---|---|---|---|
| PONV | 6 (20%) | 4 (13.3%) | 2 (6.67%) |
| Hypotension | 0 (0%) | 0 (0%) | 0 (0%) |
| Bradycardia | 0 (0%) | 0 (0%) | 0 (0%) |
| Hypoxia ( <95% ) | 0 (0%) | 0 (0%) | 0 (0%) |
| Nasal irritation | 0(0%) | 0(0%) | 0(0%) |

(N – number)

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