**ORIGINAL ARTICLE**

# Comparison of Intranasal Midazolam and Oral Midazolam as Premedication for Pediatrics patients

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**ABSTRACT**
**BACKGROUND AND OBJECTIVES:** Preoperative anxiety in children causes difficulty in separating the child from parents, can affects the smoothness of induction. It can also cause postoperative negative behavioural responses needs better pre anaesthetic sedation. Midazolam hydrochloride is world widely accepted benzodiazepine for premedication in paediatric patients. It has been proved to be an excellent premedication in children for various routes like oral, rectal, intravenous, intramuscular, sublingual and now nasal with its own merits and demerits. This present study compares oral Midazolam syrup (0.5mg/Kg) and intranasal Midazolam spray(0.2mg/Kg) as painless and needleless system of drug administration as premedication in paediatric patients posted for general surgeries. **METHODS:** A prospective, randomized, single bind clinical study was conducted on 60 paediatric patients posted for elective surgery during November 2012to November 2013. Patients were randomly assigned into two groups, Group-N: received intranasal Midazolam spray 0.2mg/Kg and Group-O: received oral Midazolam syrup 0.5mg/Kg. Every child was observed for sedation score, parental separation, acceptance to mask, recovery and side effects of drug. Data were analysed using Student's t-test for quantitative data and Chi-square test for qualitative data. **RESULTS:** At 5minutes after premedication mean sedation score in Group-N and Group-O were 2.83 ± 0.64 and 2.26 ± 0.52 respectively, which was highly significant (P<0.001). In both the groups, sedation score at 20 minutes after pre medication (Group-N: 3.96±0.55 and Group-O: 3.86±0.64), parental separation and acceptance to mask were comparable (p>0.05). **CONCLUSION:** Separation from parents and mask acceptance were satisfactory in both groups. Achievement of sedation was earlier in intranasal group than oral midazolam group. So, we concluded that, Intranasal Midazolam is a safe and effective alternative as a sedative premedication in paediatric patients.
**Keywords:** children, intranasal midazolam atomized spray, oral midazolam syrup, sedative pre medication

## INTRODUCTION

Anxiety & apprehension are main factors causing considerable stress in children before operation. Most of the children suffer from moderate to severe anxiety when they are separated from their parents. This preoperative anxiety in children can affect smoothness of induction, emergence from anaesthesia and also psychological and emotional state of child. Behavioural responses such as general anxiety, crying, nightmare can occur in up to 44% of children two weeks after surgery.[1]

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So the anaesthesiologist should always consider the child's emotional needs and create an environment that will abolish or minimise fear and stress. This paediatric age group demands a search for safe and ideal pre medication that can alleviate anxiety and fear of surgery and administered by convenient route. Midazolam hydrochloride is widely accepted benzodiazepine for premedication in paediatric patient. It has been used for the last two decades as a premedication in children. It is unique and has property of good premedication because of its sedative and anxiolytic properties. It has been proved to be an excellent premedication in children for various routes such as oral, rectal, intravenous, intramuscular, sublingual and now intranasal route. Intravenous and intramuscular route are painful and

children however dislike needles. Rectal route is associated with unpredictable absorption and discomfort. Sublingual route requires lot of co-operation of the patient. Oral route is most popular and commonly used now but studies have shown that it has disadvantage of low bioavailability (15% to 27%) hence larger dose is required. The peak effect is delayed and also the bitter taste adds upon to limiting factor. Use of intranasal midazolam as premedication has come in to practice from early 90's.Owing to high nasal mucosal vascularity intranasal route offers rapid and complete absorption of drug. Atomised or fine aerosol preparations are available now a day. Bjorkman showed that aerosol would allow greater contact with the absorbing surface and application would be less pleasant than drops.[2] The problems of volume retention in nasal cavity is solved using concentrated, atomized spray.[3,4] It has greater systemic bioavailability (50% to 80%), faster onset and rapid recovery from anaesthesia. We used atomized spray for nasal and syrup formulation for oral route to administer Midazolam for premedication. So considering all these aspects the present study was planned to compare safety and efficacy of intranasal midazolam(0.2 mg/kg) with oral midazolam(0.5mg/kg) as premedication in paediatric patients posted for general surgical procedures.

**AIMS AND OBJECTIVE**

The present study is done to compare Intranasal Midazolam and Oral Midazolam as premedicationin paediatric patients with aimed to compare Sedation score, parental separation and mask acceptance of Intranasal Midazolam spray and Oral Midazolam syrup.We also compared the hemodynamic parameters (PR,BP) , respiratory parameters (RR,$SPO_2$) and observed for any side effect and complication in both the groups.

**MATERIALS AND METHODS**

After ethical committee approval this Prospective Randomised Comparative clinical study conducted on 60 paediatric patients posted for elective surgery at S.S.G Hospital, Vadodara from November 2012 to November 2013. From reference study we had taken mean and standard deviations of both groups (for group O 4±0.871 and for Group N 4.63±0.669 ) for the parameter "Sedation Score at 30min".[5] With power of study 80% and alpha error 0.05, sample size derived 24 in each group. To generalize the results, we selected a larger size of 30 children in each group with Age group 2 – 7 years of either sex with ASA status I or II undergoing elective surgery like Herniotomy, circumcision, hypospadiasis, dressing & colostomy. Patients with upper respiratory tract infection, taking any other sedatives, with any cardiac or respiratory diseases, having allergy to study drug and with nasal infection & nasal pathology were excluded from our study. After thorough preoperative assessment, informed and written consent was taken from their parents. All patients were kept Nil by Mouth for six hours for solid and non-clear liquid and 2 hours for clear fluid. Patients were enrolled to one of the two study groups (Group-N and Group-O) by closed envelope method. 30 patients included in each groups. In Group N, child was given 0.2 mg/kg body weight of Midazolam after being placed on parents lap by intranasal spray device. The total dose was rounded to nearest 0.2 mg/kg as each puff of nasal spray delivers 0.5mg of Midazolam. In Group O, child was given 0.5 mg/kg body weight of Injectable Midazolam solution mixed with 3ml of 25% dextrose to counter the bitterness of commercially available injectable preparation, orally. In both the groups patients received the drug 30min prior to surgery. The children were monitored in the preoperative room for 30 min and state of sedation, and vital parameters were recorded at 5min interval. Sedation score was labelled as 1, 2, 3, 4 or 5 by observing the sedation status of child as agitated, alert, calm, drowsy or asleep respectively. A Sedation Scores 3,4,5 were considered satisfactory and Scores 1,2 as unsatisfactory.[6]

Complications such as nausea, vomiting, nasal irritation, hypoxia and hypertension were noted in both the groups and treated accordingly. After 20 min of drug administration the child was separated from the parent and ease of separation noted as excellent, good, fair and poor. Separation Score 1- Excellent (Happily separated.) and Score 2 Good – (Separated without crying, quiet with assurance) were considered as satisfactory or acceptable and Score 3 - Fair (Separated with crying, not quiet with assurance) and Score 4-Poor (crying, need for restraint) were considered as unsatisfactory or said to have a difficult separation.[7] The child was taken into O.T and acceptance to mask was assessed as Score 1-(Agitated and/or refuses mask) and Score 2-( Alert and/or initially refuses mask but accepts on persuasion) were considered unsatisfactory . Score 3- (Calm and accepts mask), Score 4- (Drowsy and accepts mask) and Score 5-(Asleep and accepts mask) were considered as satisfactory. The multipara monitor was attached and Vital parameters (pulse rate, blood pressure, SpO2) were recorded during intraoperative period. An appropriate sized intravenous cannula was secured meanwhile its response was also noted as score1- crying and score 2-calm. After securing IV line, Inj. Glycopyrollate 10mcg/kg and Inj. Paracetamol 5mg/kg both given IV. In all patients, surgery was carried out under general anaesthesia with endotracheal intubation. Induction of anaesthesia was carried out using 8% Sevoflurane till loss of eyelid reflex. Followed by Inj. Vecuronium Bromide 0.08mg/kg-0.1mg/kg iv was administered to facilitate endotracheal intubation. After completion of surgery residual neuromuscular blockade was antagonized with Inj. Neostigmine -50mcg/kg IV and Inj. Glycopyrrolate – 10mcg/kg IV and patient was extubated when clinical criteria for extubation were fulfilled. Then the patient was shifted to recovery room.

All children were monitored for 30 min post operatively in the recovery room for pulse rate, blood pressure, SpO2, sedation score and Aldrete recovery room scoring at 10 minute interval for 30 minutes which included respiration, activity, consciousness, temperature and circulation, each on a scale of 0-2, to give a maximum cumulative total of 10,(8). Recovery score of 8 or more considered satisfactory and time taken for it was noted.[9] Patients must score greater than 9 for safe discharge from the recovery room. All the patients were monitored post operatively for any of the complications like Nausea and Vomiting, Nasal irritation, Excessive sedation,Apnea, Respiratory depression. All the qualitative and quantitative data were analysed by using chi square test and unpaired t-test respectively. Results were expressed as Mean ± SD. 'P' values $> 0.05$ were taken not significant and 'P' values $< 0.05$ were taken as statistically significant and values $< 0.001$ were taken as highly significant.

**OBSERVATIONS**

Demographic data like age, weight, gender, ASA grade and duration of surgery were comparable between both the groups.[Table 1].

The mean baseline sedation score in Group-N was 1.96±0.80 and in Group-O it was 2.1 ±0.61, comparable in both the groups. In both the groups increase in sedation score was observed as the time elapsed. At 5minutes after premedication mean sedation score in Group-N and Group-O were 2.83 ± 0.64 and 2.26 ± 0.52 respectively, which was highly significant ($P<0.001$).

At 10 minutes the mean sedation score in Group-N and Group-O were 3.26 ± 0.52 and 2.9 ± 0.50 respectively , which was statistically significant($P<0.05$).Later on at 15,20,25 and 30 minutes the sedation score were comparable in both the groups.($P>0.05$)(Table 2)

Totally, 25/30 (83%) patients in Group N and 26/30 (84%) patients in Group O showed acceptable parental separation (Score 1, 2)(Table 3)and 23/30 (77%) patients in Group O while 25/30 (83%) patients in Group N showed satisfactory

acceptance to mask (Score 3,4,5) and 26/30 (84%) patients in Group O showed acceptable mask placement.(Table 4) Only 1 patient was agitated and refused to accept mask in Group N.There were no significant differences in baseline vital parameters. Changes that occurred in vital parameters after sedation, during intraoperative period and postoperative period were statistically nonsignificant (P > 0.05).

Recovery score at 10 min, 20 min, and 30 min was similar in both the groups and all children in both the groups attained score of 10 at 30 min postoperative period.Transient nasal irritation in the form of rubbing of the nose, watering, sneezing and lacrimation was observed in 03/30 (10%) patients of Group N. There was no redness or ulceration observed in postoperative period.

**Table 1: Demographic Data**

| | Group N | Group P | P value |
|---|---|---|---|
| **Age (Years) (Mean ± SD)** | 3.03 ± 0.92 | 3.36 ± 1.25 | P > 0.05 |
| **Weight (Kgs.) (Mean ± SD)** | 13.13 ± 2.71 | 13.9 ± 3.33 | P > 0.05 |
| **ASA Grade (I / II)** | 26/4 | 25/5 | P > 0.05 |
| **Gender (M/F)** | 16/14 | 17/13 | P > 0.05 |
| **Duration of surgery(min) (Mean ± SD)** | 48.36 ± 9.3 | 47.9 ± 9.01 | P > 0.05 |

**Table 2: Sedation Score**

| | Group N (Mean ± SD) | Group P (Mean ± SD) | P value |
|---|---|---|---|
| **0** | 1.96 ± 0.80 | 2.10 ± 0.61 | P > 0.05 |
| **5** | 2.83 ± 0.64 | 2.26 ± 0.52 | P < 0.001 |
| **10** | 3.26 ± 0.52 | 2.90 ± 0.50 | P < 0.05 |
| **15** | 3.50 ± 0.62 | 3.63 ± 0.55 | P > 0.05 |
| **20** | 3.96 ± 0.55 | 3.86 ± 0.64 | P > 0.05 |
| **25** | 4.03 ± 0.66 | 4.01 ± 0.72 | P > 0.05 |
| **30** | 4.00 ± 0.58 | 4.21 ± 0.71 | P > 0.05 |

**Table 3: Response to parental separation**

| | Group N | | Group O | |
|---|---|---|---|---|
| **Score** | **No. of Patients** | **%** | **No. of Patients** | **%** |
| **1** | 13 | 43.33 | 14 | 46.66 |
| **2** | 12 | 40 | 12 | 36.6 |
| **3** | 4 | 13 | 5 | 16.6 |
| **4** | 1 | 3 | 0 | 0 |

**Table 4: Response to mask placement**

| | Group N | | Group O | |
|---|---|---|---|---|
| **Score** | **No. of Patients** | **%** | **No. of Patients** | **%** |
| **1** | 1 | 3.33 | 0 | 0 |
| **2** | 4 | 13.33 | 5 | 16.66 |
| **3** | 9 | 30 | 11 | 36.66 |
| **4** | 13 | 43.33 | 10 | 33.33 |
| **5** | 3 | 10 | 4 | 13.33 |

## DISCUSSION

An ideal premedication should be easy to administer and fast and prompt in action, with minimal adverse effects. Many premedications have been tried through many routes, with variable success e.g., Midazolam, Fentanyl, Ketamine, Clonidine, etc. Midazolam has been extensively used in practise since 1982 and its pharmacology is well known. Midazolam has been most commonly used for premedication in children preferably by non parenteral route like IM, rectal, sublingual, oral and intranasal routes. Each has its own advantage and disadvantage. The oral route is most widely accepted for premedication in children. Intranasal Midazolam as premedication in preschool children was first described and advocated by Wilton and colleagues.[6] It has many advantages. Various studies by Niall CTW , Davis PJ , Dallman JA , Vivarelli R , Malinovsky JM suggested that intra nasal Midazolam is a safe and effective premed in children with rapid onset , satisfactory sedation and rapid recovery without any serious side effects. We have compared sedation of midazolam given via intranasal and oral route. Atomised or fine aerosol preparations are available now a day. Bjorkmanshowed that aerosol would allow greater contact with the absorbing surface and application would be less pleasant than drops. Bioavailability was shown to be as high as 83% with virtually complete absorption. We used commercially available atomised intranasal midazolam spray for group- N patients. Nasal administration of midazolam may be in the form of drops, nasal spray or nebulization.[3,4,6,10] Intranasal midazolam has been used in the doses of 0.2, and 0.3 mg/kg, but found no additional benefits

from higher dosage andrecommended the lower dose of midazolam 0.2 mg/kg.[1,6] Similarly in other studies, intranasal midazolam spray was used in the dose of 0.2 mg/kg[11] while a mucosal atomizer device was used to administer midazolam intranasally in the dose of 0.4 mg/kg.[4] Concentrated, atomized midazolam spray ensures accurate drug delivery, covers larger nasal mucosal area and increases bioavailability maximally.[3] Oral midazolam in the dose of 0.5 mg/kg is a safe and effective mode of premedication than that of 0.75 mg/kg and 1 mg/kg which gives no additional benefit, may cause more side effects.[7] In group- O we used injectable preparation 5mg/ml ampoule addition of 25% dextrose reduced the bitter taste and made it more palatable but still 2 patients showed reluctance to swallow the drug. Only 1 patient in Group- N had severe nasal irritation ,coughing and spillage of the drug we excluded the case from study. We used oral midazolam syrup in the dose of 0.5 mg/kgand intranasal midazolam atomized spray in the dose of 0.2 mg/kg ofbody weight. We selected children in age group of 2-7yrs because this age group is most susceptible to separation, anxiety, fear of surgery, since their understanding is limited. Sedation scores were slightly better and earlier in Group- N at 5min interval with P value <0.001 which was highly significant. After 15min the sedation score were comparable in both the groups (Pvalue>0.05) but number of patients who achieved sedation score 3,4,5 were more (32) in Group- N while only (28) in Group – O. In our study 84%patients separated satisfactorily in group- N and 85% patients in group- O. only 1 patient showed poor separation in group- N which was done after persuasion with help of mother. In our study mask placement was found satisfactory and comparable in both the groups and resulted in smooth and rapid induction of anesthesia using Sevoflurane. PradiptaBhakta et al found that 33% patients become alert and accepted mask after persuasion, remaining 66.6% patients become agitated during mask induction. Alex et al 100% acceptance and cooperation at the time of mask induction in both the groups. Our results are in consonance with their study. Three patients in group N had nasal irritation after drug administration. No significant hemodynamic difference between both the groups during pre operative, intra and post operative. None of the patients had any complication like nausea, vomiting, excessive sedation, apnea, respiratory depression and bradycardia. The post operative period was uneventful in all cases.

## CONCLUSION

Achievement of sedation was earlier and higher in intranasal group than oral group, but parentral separation and mask acceptance were satisfactory in both the groups. So, we concluded that intranasal Midazolam is a safe and effective alternative as a sedative premedication in pediatric patients.

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