SUMMARY

Most of the preschool children suffer from severe anxiety and apprehension before operation. This can largely affect the smooth conductance and emergence from anaesthesia. Above all this can lead to development of maladaptive behavioral responses in later part of life. Midazolam in current time has emerged as an ideal premedicant having all the desirable properties in this regard. It has been used by several routes for premedication. Each has its own advantage and disadvantage. The search for an ideal route and dose still exists. So the current study was planned to find out the efficacy of midazolam intranasally.

Forty five paediatric patients of 2-5 years of age belonging to ASA I & II, scheduled for minor elective surgery were selected for this study. Patients were divided in three equal groups to receive normal saline (Group I), 0.2 mgkg⁻¹ midazolam (Group II), or 0.3 mgkg⁻¹ midazolam (Group III) intranasally. Vital parameters and level of sedation (using a sedation scale) were assessed before administering the drug and at 5 min interval up to induction of anaesthesia. Standard anaesthesia technique was used intraoperatively. Recovery parameters were assessed in the recovery area using a recovery scale.

A statistically significant change in the level of sedation was found at 5 min in group II and at 10 min in group III compared to control group. Parental separation was significantly easier in midazolam groups. Mask acceptance rate was also found to be significantly higher in midazolam groups. There was no statistical difference in recovery parameters in any group. No major adverse effect was seen in any midazolam group. No major advantage was found with higher dose of midazolam.

Therefore we conclude that 0.2 mgkg⁻¹ intranasal midazolam is an effective method of producing anxiolysis and sedation in paediatric patients.

Keywords: Preanaesthetic sedation; Intranasal midazolam; Paediatric patients.

Introduction

Most of the children suffer from severe anxiety and apprehension when they are separated from their parents or family members for induction of anaesthesia.¹ The unfamiliar faces and the environment inside the operating room compound the sense of insecurity in the child.² Thus preoperative anxiety can largely affect the smoothness of induction, emergence from anaesthesia and also the psychological and emotional state of child in the remote future.³ Maladaptive behavioral response such as general anxiety, nighttime crying, enuresis, separation anxiety occur in up to 44% of children two weeks after operation. Twenty percent of these children will continue to demonstrate negative behavior even 6 months after surgery.³

Although the non-pharmacological means in the form of friendly visit by the anaesthesiologist to establish rapport with the child, briefing about the procedure whenever feasible, help to minimize child’s anxiety, pharmacological agents are often helpful to provide sedation and promote smooth induction. Even parental presence inside the operation theater may not be fully effective. Sedative premedication may be more effective in this regard.⁴

The ideal agent should have rapid onset, predictable duration and rapid recovery. Midazolam is a potent imidazo-benzodiazepine, which has rapid onset of action and has an elimination half-life of about two hours. It is water soluble in acidic medium but highly lipophilic at physiological pH. Like ideal benzodiazepine, midazolam has got all properties namely sedative, hypnotic and anxiolytic activities.⁵

Midazolam has been used for preoperative sedation by intramuscular (IM),⁶-⁸ rectal,⁹,¹⁰ oral¹¹ and sublingual routes,¹²,¹³ but each has its own advantages and disadvantages. The intramuscular route is painful and children dislike the needle most. The rectal administration is associated with unpredictable absorption and discomfort to the child. Oral
route, though now most popular, has got low bioavailability due to high first pass metabolism of midazolam. Oral bioavailability of midazolam is only 15-27% as reported in a study, so a larger dose (0.5-1 mg kg\(^{-1}\)) is required and the peak effect is also delayed. Bitter taste is also a limiting factor and cause for rejection as well as low compliance. In a recent report it has been mentioned that oral midazolam in larger dose prolongs recovery following brief sevoflurane anaesthesia. Sublingual route is more beneficial in this regard. But for desirable effect the drug must be held under the tongue for at least thirty seconds. This requires cooperation and that is difficult to achieve in the preschool children.

Use of intranasal midazolam as premedication has come into practice from early nineties. Intranasal midazolam in this regard has got some advantage. Owing to high mucosal vascularity, intranasal route offers rapid and virtually complete absorption with in one-two hours into systemic circulation. As midazolam has high hepatic clearance, avoidance of hepatic first pass metabolism offers greater systemic bioavailability. It has faster onset than oral or rectal route. Recovery from anaesthesia is also not affected even after minor surgeries.

Considering these aspects, the current study was planned to find out the effect of midazolam through nasal route as a premedicant in paediatric patients and also to find out the optimum dose for the desired effect without any undesirable side effect.

**Material and methods**

After obtaining the institutional ethical committee approval and informed parental consent, forty-five paediatric patients belonging to ASA (American Society of Anesthesiologists) physical status I and II, within the age group of 2-5 years, scheduled for elective minor operation, were included in the study. The patients were divided into three equal groups (n=15) to receive normal saline (NS) (Group I or control group), midazolam 0.2 mg kg\(^{-1}\) (Group II) and/or midazolam 0.3 mg kg\(^{-1}\) (Group III) intranasally. We have used the preservative free injectable preparation and the concentration of the drug was 5 mg/ml. This helped in limiting the drug volume, which has got major pharmacokinetic importance in intranasal route. Drugs were divided in two aliquots and given in both nostrils. Drugs were administered as drop by drop with the help of a dropper to avoid wastage of the drug through anterior and posterior nostrils. This took a little bit longer time. Any patient having nasal infection, nasal pathology, and allergy to any of the study drugs or taking any other sedative drugs were excluded from the study.

Heart rate (HR), respiratory rate (RR), oxygen saturation (SpO\(_2\)) and state of sedation were observed before administering the drug and then at five min interval. The ten min measurement was made immediately after the child was separated from their parents and so represents the response to separation. The fifteen min measurement was done just prior to induction of anaesthesia.

Using a five-point sedation scale the degree of sedation was assessed:

1. Agitated : Patient clinging to parents and/or crying.
2. Alert : Patient is aware but not clinging to parent, may whimper but not cry.
3. Calm : Sitting or lying comfortably with spontaneous eye opening.
4. Drowsy : Sitting or lying comfortably with eyes closed, but responding to minor stimulation.
5. Asleep : Eyes closed, arousable but does not respond to minor stimulation.

Patients were induced with oxygen (O\(_2\)), nitrous oxide (N\(_2\)O) and halothane by facemask. Intravenous line was started after induction and injection atropine was administered. The response to mask placement was assessed by another scale:

1. Agitated : Previous criteria and/or refuses mask.
2. Alert : Previous criteria and/or initially refuses mask, but accept after persuasion.
3. Calm : Previous criteria and accepts mask.
4. Drowsy : Previous criteria and accepts mask.
5. Asleep : Previous criteria and accepts mask.

Thus, if a patient was drowsy but refused mask induction, then the patient was recorded in score 1 and not 4.

Tracheal intubation was done after administration of standard non-depolarizing muscle relaxant. Anaesthesia was maintained by O\(_2\), N\(_2\)O and analgesia was provided by pethidine 1 mg kg\(^{-1}\). Ventilation was controlled by Jackson-Ree’s modification of Ayre’s T-piece. Residual neuromuscular paralysis was reversed at the end of operation by appropriate dose of neostigmine and atropine.

Postoperative sedation was assessed in the post anaesthesia recovery unit (PACU) at ten min interval for thirty min by using a ten point recovery scale which assessed patient’s colour, airway, respiration, level of consciousness and movement (each on a scale of 0-2) to give a maximum cumulative total of 10.
The study data were analyzed with the help of different statistical methods for different data analysis. The demographic profile, preoperative cardiovascular and respiratory status and recovery room score were analyzed using ANOVA (Analysis of variance) method. Sedation score was analyzed by using variants of ANOVA. Statistical significance was accepted if p value was less than 0.05.

**Results**

In our study forty-five paediatric patients were randomly divided in three equal groups. Demographic profile and vital parameters were comparable in three groups (Table 1 and 2).

**Table - 1 : Demographic profile.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>3.35±1.24</td>
<td>3.92±0.87</td>
<td>3.8±0.96</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex ( M: F)</td>
<td>2:1</td>
<td>2:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>12±2.03</td>
<td>12.93±2.28</td>
<td>13.6±2.91</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA status (I:II)</td>
<td>2.75:1</td>
<td>2.75:1</td>
<td>2:1</td>
</tr>
</tbody>
</table>

p - Not significant

**Table - 2 : Preoperative cardiovascular and respiratory parameters.**

<table>
<thead>
<tr>
<th>Vital Parameters</th>
<th>Group I (Mean±SD)</th>
<th>Group II (Mean±SD)</th>
<th>Group III (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (per min)</td>
<td>113±30.67</td>
<td>116.66±35.55</td>
<td>118.26±10.66</td>
</tr>
<tr>
<td>Respiratory rate (per min)</td>
<td>22.13±2.97</td>
<td>25.33±5.59</td>
<td>20.8±3</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>97.06±1.33</td>
<td>97.1±4</td>
<td>96.53±0.74</td>
</tr>
</tbody>
</table>

p - Not significant

When comparing the sedation score, majority of the patients in control group remained agitated throughout the study period with little variation in sedation scale (Fig. 1) which is as expected. Whereas significant changes in sedation occurred after 5 min in group II (Fig. 2) and 10 min in group III (Fig. 3). Separation from the parents was much easier in midazolam groups. 80% (24/30) of the children could be separated easily from their parents. The rest 6 patients could be separated after only persuasion in midazolam groups (Fig. 2 & 3). Whereas only 20% (3/15) patients could be separated only after persuasion in placebo group (Fig. 1). 66.6% patients (10/15) refused to accept mask in Group I (Fig. 1) while only 3.33% (1 patient in group II) refused mask in midazolam groups. Majority of the patients had accepted the mask in midazolam groups (80%) (Fig. 2 and 3). Only one patient in group II was found to be in grade 5 (asleep) of sedation scale (Fig. 2).
Heart rate, respiratory rate and \( \text{SpO}_2 \) did not alter much in any of the groups during the study period.

Postoperative recovery room score was comparable in all three groups (Table 3). There was no major side effect in any midazolam group.

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Group I (Mean±SD)</th>
<th>Group II (Mean±SD)</th>
<th>Group III (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min</td>
<td>7.13±0.35</td>
<td>7.2±0.41</td>
<td>7±0</td>
</tr>
<tr>
<td>20 min</td>
<td>9.13±0.74</td>
<td>8.93±0.79</td>
<td>8.86±0.99</td>
</tr>
<tr>
<td>30 min</td>
<td>10±0</td>
<td>10±0</td>
<td>10±0</td>
</tr>
</tbody>
</table>

\( p \) - Not significant

**Discussion**

In the present study, intranasal midazolam has been used in the doses of 0.2 mgkg\(^{-1}\) (Group II) and 0.3 mgkg\(^{-1}\) (Group III), because earlier report suggests that the dose less than 0.2 mgkg\(^{-1}\) was ineffective.\(^{19}\) Thus we tried to find out which dose gives the appropriate effect with out increasing any adverse effect. This study has demonstrated that both the doses of intranasal midazolam produced an effective anxiolytic and sedative response in paediatric patients, which is comparable with the other reported studies.\(^{19,20}\)

We selected children in the age group of 2-5 years, because this age group is most susceptible to the separation anxiety, since their understanding is limited.\(^{22}\)

A significant change of sedation was seen with both the midazolam groups by ten min. This is again comparable with the previous study.\(^{19}\) The change was maintained at fifteen min and at the time of induction of anaesthesia. Most of the patients in midazolam groups became either calm or drowsy (sedation scale score 3 or 4) which helps in easy separation of the child from their parents, and also in smooth induction. Only one patient in the group II became asleep (score 5) who responded to minor stimulation (Fig. 1). No other patient in midazolam group became excessively sleepy during study period. Clinically evident respiratory depression or apnoea during the study period did not occur in any group. This proved that midazolam used intranasally in this dose range is quite safe, which was again reported in other studies.\(^{19,20}\) A calming effect was seen after five min in group II and by ten min in both groups of midazolam. That means, intranasal midazolam 0.02 mgkg\(^{-1}\) had quicker onset than 0.03 mgkg\(^{-1}\). This again corroborated with the earlier study.\(^{19}\) The grade of sedation was otherwise equal in both the groups of midazolam. Higher dose of midazolam requires larger volume, resulting possibly in seepage of some volume in oral cavity through posterior nasal opening and expulsion of some dose by sneezing or dribbling from anterior nostril.\(^{19}\) This may explain the delayed effect in group III. Absence of any respiratory depression, apnoea or change in vital parameters makes this medication safe when given by intranasal route in the dose studied.

In control group 33.3% (5/15) of the patients became alert and accepted the mask only after persuasion during induction. Remaining 66.6% (10/15) patients however became agitated during mask induction. Some children were temporarily agitated by instillation of either normal saline or midazolam, but most of them settled down after some time. Midazolam in the intranasal administration has got the limitation because of its irritation. So the acceptance rate was low as also reported in literature.\(^{12}\) It may be possibly due to the irritation of parent drug midazolam or its acidic \( p \text{H} \).\(^{23}\) This drawback in intranasal route can be overcome by use of the same drug as nasal spray\(^{23}\) or a solution of midazolam in cyclodextrin, which results in greater concentration of drug as well as less acidic \( p \text{H} \). There is a report of high acceptance by this method.\(^{24}\) But this was not available at the time of our study. Nevertheless, adult patients reported this irritation as acceptable and not painful.\(^{25}\)

There are several reports of satisfactory acceptance of intranasal route.\(^{19,21,25,26}\) Though the initial acceptance in our study was limited by crying, but most of the children later accepted it after persuasion. Sometimes the children accepted when their mother administered it. In one study the compliance rate in sublingual route, which is currently the most acceptable route, has been reported to be only 67%.\(^{13}\) Similarly 62% acceptance rate of intranasal midazolam was reported in preschool children in another study.\(^{26}\) In our study, the acceptance rate was also quite good. But we didn’t measure the incidence rate.

There is some concern regarding the use of midazolam intranasally recently. Neurotoxicity has been reported in rabbit after use of midazolam in a study.\(^{27}\) The same group of authors have used intranasal midazolam few years after the previous study and mentioned intranasal midazolam as an excellent alternative for rapid premedication.\(^{28}\) This neurotoxicity is reported only after chronic administration of drug in intrathecal route.\(^{29}\) We used the drug intranasally and that too for one time premedication only. It has been reported that the pathological changes occurred after intranasal administration of drugs, which is reversible and the changes are more common after prolonged use.\(^{30}\) There is no major human study in this regard. In comparison there are various reports of safe use of midazolam in the intranasal route.
A study was done to evaluate the effect of midazolam on cilia beat frequency (CBF) in human nasal turbinates (HMT) in vitro. But nothing significant was found in CBF even after exposing the HMT with midazolam for ninety min in supraclinical concentration. Even intranasal midazolam has been used recently for termination of seizure in emergency setting safely and effectively.

There was no evidence of delayed recovery in any of the midazolam groups as seen in previous studies. So the agent can be used as an excellent premedicant in paediatric patients.

Midazolam administered by other route such as intramuscular and rectal routes takes longer time to achieve desired effect, acceptance of these routes in paediatric patients are not very well. Specially using rectal route at times may be embarrassing in the older children. Intramuscular route is painful, and children dislike the needle most. Oral and sublingual route have their inherent drawbacks. In oral route a significant amount of the drug undergoes first pass metabolism leading to formation of active metabolite 1-hydroxymedazolam which has got equipotent central nervous system (CNS) depressant effect and which is responsible for its low bioavailability. This can be the mechanism behind the delayed recovery seen in oral midazolam as reported in literature. In contrast to this, in the intranasal route desired effect can be achieved very fast, which is also confirmed in our study. The bioavailability of intranasal midazolam is very high and pharmacologically active metabolite is not formed in significant amount. The recovery is also faster, which was again proved in our study. No additional benefit was observed by increasing the dose to 0.3 mg kg\(^{-1}\). This finding is again corroborating with earlier studies.

We accept the fact that there are some major drawbacks in our study. First of all the sample size is very small to have a significant power of analysis. The fact is that our study was limited over a period of three months and the rate of paediatric operative procedure in our hospital is not very high. We have studied only the patients in 2-5 years of age group scheduled for minor elective surgeries. We selected the minor operation to study the effect of relatively shorter acting midazolam on recovery profile. The longer operations wouldn’t have the same effect on the recovery profile. So commenting on safety profile of the study drug would be difficult. According to the selection criteria we excluded all patients with any nasal pathology. The study was conducted in winter season. That was also a limiting factor for this relatively smaller sample size because of high incidence of nasal infection and allergy in that season. In most of the studies with larger sample size, they have selected much wider age group. But we selected this special section because they suffer the most from the anxiety and apprehension. In literature there is report of study even with lower sample size than ours where they have reported statistically significant results. In another study even the same sample size of 45 in three equally divided group used in 2-9 years age group patients. What should be the minimum sample size in a study to have a significant result is the most uncertain part in statistics. There is evidence that a sample size of 9 in ANOVA analysis was adequate to achieve a power of analysis of 80%. Another drawback was that the surgical procedure was not randomized. But our main intention was to evaluate the efficacy of midazolam as premedicant. Evaluation of recovery parameters was not our primary goal in this study. Still we recommend that another randomized study with a much larger sample size is needed to comment more specifically on this effect.

**Conclusion**

We conclude that intranasal midazolam in a dose of 0.2 mg kg\(^{-1}\) is an effective pre-medication for producing effective sedation and anxiolysis in paediatric patients without any untoward side effect. No added advantage was found in 0.3 mg kg\(^{-1}\) dose.

**References**


FAMILY BENEFIT SCHEME

The Indian Society of Anaesthesiologists through its family welfare programmes support the next kin of the deceased member of ISA to the tune of Rs. 10,00,000/- ?

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