Comparison of medication acceptance of intranasal midazolam administered by parents versus doctors in children – A randomized trial

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Abstract:
BACKGROUND: The positive effects of midazolam as a premedication in pediatric patients are well documented. Although there are many studies regarding the route and dosage of administration, literature does not have any evidence on the outcome of medication acceptance based on the person administering the drug.

AIM: The aim of this study was to compare the medication acceptance and preoperative anxiolysis of intranasal midazolam administered by parents and anesthesiologists.

MATERIALS AND METHODS: This prospective randomized study was conducted in sixty children belonging to the American Society of Anesthesiologists Class 1 or 2 belonging to either sex, aged between 1 and 9 years, undergoing elective surgeries. Group P received intranasal midazolam administered by parents, whereas Group D received intranasal midazolam administered by doctors. Various scores were assessed.

RESULTS: Children were more sedated in Group P. Clinically, medication acceptance was better in Group P when compared with Group D, but a statistically significant difference in medication acceptance was seen only in patients who are >4 years of age. Parental separation, Ramsay Sedation Score, and mask acceptance were better in Group P than in Group D.

CONCLUSION: Intranasal midazolam when given by parents produces better preoperative anxiolysis and easier parental separation as compared with administration by a medical staff.

Keywords:
Children, intranasal route, medication acceptance, stranger

Introduction

Fear of the surgery, enforced separation from parents, exposure to an unknown environment, the different dress code in the operation theater, and being in the hands of doctors, who are relative strangers, makes the experience of surgery more distressing for children. If this anxiety is not addressed, it may lead to maladaptive behavior, nightmares, and temper tantrums. A total of 216,081 pediatric surgeries were projected during the year 2009 in the United States. If at least 50% of these children suffer from anxiety disorder due to distress of surgery, it may lead to a big social problem. It is always better to prevent a disease rather than treating a disease. Hence, to relieve the child from anxiety and to facilitate amicable separation of the child from parents, premedication is inevitable. A large number of studies are available in the literature on various drugs with sedative and anxiolytic

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properties as premedication drugs. Although there has not been an absolute consensus on what is the ideal drug for premedication is, in the pediatric age group, most authors agree that midazolam is a very good choice. Midazolam is the gold standard drug as a premedication with which other drugs are compared.\[3\]

Midazolam is a short-acting 1,4-benzodiazepine and is water soluble. The administration of midazolam via oral route has problems because of its bitter taste, the possibility of drug spitting, and poor oral bioavailability.\[4\] The bioavailability of midazolam through intranasal route is 55%–83% with rapid systemic absorption without first-pass effect.\[5\] Intranasal administration of drugs in a pediatric patient is more difficult for the anesthesiologist, and the instillation of the drug is an unpleasant experience for children.\[6\] However, if the child is suffering from esophageal motility diseases and diseases related to the absorption of the drugs, it is preferable to avoid the oral route. For example, if the patient has esophageal atresia and is on either feeding gastrostomy or feeding jejunostomy, the oral route is not preferred. In such cases, the intranasal route may be considered.

Violent movement of the child while administering the drug, spitting/sneezing after administration of the drug by a child, improper administration of the drug, and inadequate knowledge of the method of administration of the drug to the parent are some of the problems that are commonly encountered while administering a drug to children. Children generally may not accept the administration of the drug by a stranger. Children may not accept drug easily with the mother also, if they are administering it in a different route other than oral. Hence, in children, the effect of the drug depends also on the person administering the drug. The final effect of the drug depends on the amount of the drug that had reached the effector site. If a drug is administered properly on/into the targeted area, then only an adequate amount of the drug reaches the target organ leading to desired effect. Many advisories are issued by different hospitals in the Western world for pleasant administration of oral drugs.\[7\] Upon literature search, we could not find such an advisory on intranasal administration of the drug to children.

Thus, this study was designed to find whether there were effective medication acceptance and preoperative anxiolysis by comparing the intranasal administration of midazolam by parents and anesthesiologists.

**Materials and Methods**

This study was conducted in sixty patients in children of 1–9 years’ age, American Society of Anesthesiologists Class I and II children admitted to our hospital, scheduled to undergo elective surgery after institute

![Image](image-url)
Acceptance Scale were assessed by the anesthesiologist. PR was recorded at the time of drug administration and at 10 min interval after administering the drug till 30 min. The Ramsay Sedation Score was assessed at this point by the concerned anesthesiologist. After 30 min of drug administration, children were detached from the mother and the Parental Separation Anxiety Score was recorded by the anesthesiologist. After shifting the patient to the operation theater, monitors were attached and NIBP and PR were recorded. An anatomical face mask was applied for inhalational induction, and the Mask Acceptance Score was assessed along with the recording of PR and blood pressure. Once the intravenous (IV) cannula was inserted, NIBP and PR were recorded again, and the study was concluded at this point. Thereafter, the child was induced with general anesthesia by the concerned anesthesiologist. After induction, the patient was observed for any possible adverse events for the next 30 min. Scores used to assess in the study are appended in Annexure 1.

The group allocation was not blinded as it requires the introduction of placebo and administration of the drug and placebo. This requires the cooperation of the child twice for a subjectively unpleasant experience, and this was deemed unethical by the ethical committee of the institute. However, the persons assessing all the scores except Infant Global Acceptance Score and Modified Medication Acceptance Score were blinded to the group allocated. Blinding during assessment of the Infant Global Acceptance Score and Modified Medication Acceptance Score could not be carried out, as they need to be assessed during the administration of the drug.

Statistical analysis
Change in PR and blood pressure in both the groups over time was evaluated using the paired \( t \)-test and between the two groups with the progression of time was evaluated using the unpaired \( t \)-test. The Ramsay sedation scale, Mask Acceptance Scale, Parental Separation Anxiety Scale, Modified Medication Acceptance Scale, and Infant Global Acceptance Scale were analyzed using Mann–Whitney U-test. A sample size of minimum 29 in each group was considered using OpenEpi Software, Open epi version 3.01, Atlanta, GA 30322, United States, with a power of 80% and a confidence interval of 95% based on the study by Bhakta et al.

Results
Demographic characters such as age, gender distribution, and weight were statistically comparable [Table 1]. Mean blood pressure and PR were comparable between the groups. However, the increase in PR and mean blood pressure during the mask application was more in Group D than in Group P [Figure 2]. There was no statistical significance in the Modified Medication Acceptance Scale and Infant Global Acceptance Scale. Parental separation was easier in Group P than in Group D, as scores on the Parental Separation Anxiety Scale were significantly different between the groups (\( P = 0.02 \)). Five children in Group D were crying and clinging to the parent, but none in Group P. The Mask Acceptance Scale and Ramsay Sedation Score were better in Group P than Group D [Table 2]. The Infant Global Acceptance Score of children above the age of 4 years was statistically significant between the groups. No adverse events were observed during the study period.

Discussion
To alleviate the anxiety due to parental separation and to make the process of anesthesia smooth and atraumatic, it is better to give premedication to the child. The administration of premedication by a stranger may, however, make the child more anxious, thereby failing in its primary aim. Hence, it is always better that a known person administers the premedication. With this consideration, the parent is the best choice. Parents have the experience of giving medications to the child at home if the child suffers from any disease. Parents are most often advised to give oral medications rather than nasal medicines, and they may be unfamiliar with the administration of nasal medication. More errors are expected with an inexperienced person. There may be contraindications for oral premedication. If oral premedication is inadvisable, then we are left with IV, intramuscular (IM), rectal, and nasal routes. Both IV and IM routes suffer from the disadvantage of needle puncture, which may induce more agitation and defeat the aim of premedication. The rectal route is cumbersome and difficult to administer. Hence, if the oral route of premedication is contraindicated, it may be better to give premedication by nasal route. Nasal midazolam is a rapid, acceptable, and efficient method of premedication. The nasal administration may be a first for the parent but may not be so for anesthesiologists. So here, we compared the effectiveness and ease of administration of nasal premedication by a known inexperienced person (i.e., parent) to a trained unknown person (i.e., anesthesiologist) to the child.

Wilton et al. conducted a study using intranasal midazolam at two different doses of 0.2 mg/kg and 0.3 mg/kg in preschool children in the age group of

| Table 1: Demographic parameters |
|---------------------------------|
| Data                     | Group P | Group D | \( P \) |
|---------------------------|---------|---------|-------|
| Age in years (mean ± SD)  | 5.1 ± 1.9 | 4.7 ± 2.3 | 0.56  |
| Sex (male/female)         | 21/9    | 22/8    | 0.50  |
| Weight in kg (mean ± SD)  | 16.1 ± 5.6 | 14.3 ± 4.4 | 0.09  |
| SD = Standard deviation   |         |         |       |

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18 months to 5 years and discovered that anxiolysis and parental separation were easier with the intranasal route at both the doses.\[14\] They also concluded that a higher dose of midazolam has not provided an additional benefit over 0.2 mg/kg dose because using higher volume may cause excessive sneezing and coughing leading to the expulsion of the drug. Verma et al. conducted a study by comparing the oral route of midazolam at a dosage of 0.5 mg/kg and intranasal midazolam at a dosage of 0.2 mg/kg.\[5\] The authors observed that the sedation score was more satisfactory with intranasal midazolam than oral midazolam at 10 and 20 min after the administration of the drug. The authors used intranasal spray which is commercially available and delivers at the rate of 0.5 mg/spray. The same speed and dose of administration were used in our study.

Patients in both the groups were comparable to age and sex. The baseline PR and noninvasive mean blood pressure were also comparable in both the groups. There was a mild increase in NIBP and the PR in both the groups after the administration of intranasal midazolam. With the progression of time, both the PR and NIBP returned to the baseline value. There was no statistically significant change in the PR and noninvasive mean blood pressure in the groups until the child was shifted to the operation theater. However, PR during mask acceptance was comparatively well with Group P with the $P = 0.05$. Better PR in Group P might be attributed to significant sedation achieved in Group P preoperatively. This may be due to children having a good acceptance of the drug when delivered by parents, and they may have listened more to parents and controlled their behavior appropriately.

Comparing the medication acceptance in both the groups using the Modified Medication Acceptance Scale and Infant Global Acceptance Scale, we did not notice any statistically significant difference between Groups P and D. Karl et al. conducted a study using the sublingual route and intranasal route of drug administration.\[15\] The authors found that 71% of the children who received intranasal midazolam cried during medication administration, whereas in the sublingual group, only 18% cried after sublingual application of the drug. The authors theorized that the irritating nature of the nasal spray led to this and could have led to more drug spillage also. However, age was an important factor in medication acceptance. In our study, children aged 4 years and above accepted medication easily from their parents and were more compliant, which shows that the compliance of the children betters as the age increases. As there was no statistical significance in medication acceptance and Infant Global Acceptance Score after the completion of the study, we decided to do a subgroup analysis. We have done a subgroup analysis by taking a cutoff age of 4 years. This age was chosen, as it is customary to enroll children in school at 4 years, which is when their social interaction with the wider world begins. When they begin their socialization, it is more likely that they will develop a fear of drug

### Table 2: Different scores

| Name                          | Group P median IQ (25-75) | Group D median IQ (25-75) | $P$  |
|-------------------------------|---------------------------|---------------------------|------|
| Infant Global Acceptance Score| 3 (2.75-3)                | 3 (3-4)                   | 0.19 |
| Parental Separation Anxiety Score| 2 (1-2)                  | 2 (2-3)                   | 0.02*|
| Mask Acceptance Score         | 2 (1-2.25)                | 2 (2-3)                   | 0.04*|
| Ramsay Sedation Score         | 2 (1.75-3)                | 3 (2-3)                   | 0.02*|
| Modified Medication Acceptance Score| 4.5 (4-5)           | 4 (2.75-5)                | 0.18 |
| Infant Global Acceptance Score <4 years age | 3 (2-4.5) | 3 (2-3) | 0.82 |
| Infant Global Acceptance Score >4 years age | 3 (3-4)        | 4 (3-5) | 0.04*|

*Statistically significant
administration by unknown persons. In this subgroup analysis, we found that the Infant Global Acceptance Score was statistically significant in children more than 4 years. In this subgroup, it was found that the child was more easily accepting of the drug administered by the parent rather than an unknown person such as a trained anesthesiologist. As we had done subgroup analysis after the completion of the study, the sample size in each subgroup was not adequate, and we are unable to comment further on this finding.

When the children were observed for sedation following intranasal drug administration, there was a significant difference in the sedation score between Groups P and D. The sedation level in Group P was better than in Group D. In our study, we used the same route and dose of the drug in both the groups, but still patients were more sedated in Group P which can be explained by the amount of drug reaching the nasal mucosa. In Group P, the head position might have been held relatively constant during drug administration, whereas in Group D, the children were more agitated and moved their head more, leading to more spillage of the drug, hence receiving a lower amount of the drug. This might have led to less sedation in children in Group D.

Following that, the child was separated from the parents to the operating room and separation of the child from parents was assessed by the Parental Separation Anxiety Scale. Parental separation was better in Group P, which is statistically significant. The probable reason for this may be that children had significant sedation in Group P before separation from the parents because of better cooperation of the children for the administration of the drug in Group P.

After parental separation, the children were shifted to the operation room, and mask acceptance of the children was assessed using a standardized Mask Acceptance Scale. The Mask Acceptance Score was better in Group P in our study which could be attributed to the better preoperative sedation in Group P as the children were more comfortable with the administration of nasal medication by their parents.

In our study, the Modified Medication Acceptance Score and Infant Global Acceptance Score were statistically not significant. However, the parameters such as Ramsay Sedation Score, Parental Separation Anxiety Score, and Mask Acceptance Score, which indicate the final action of the drug, were statistically significant in favor of parental administration. This indicates that even though the child seems to accept the medication equally either by the parent or by a trained anesthesiologist, the effect of the drug was better in Group P. This indicates that less drug was wasted or more amount of the drug was properly administered to get the desired effect in Group P as the child was more cooperative to the parent.

Limitations of this study were as follows:
1. Blood midazolam levels were not measured
2. The amount of drug expelled after each administration was not recorded
3. Subgroup analysis after completion of the study was done, where the sample size in each subgroup was not adequate. We should have anticipated this problem and included sufficient numbers for subgroup analysis.

**Conclusion**

As the final effect was better in Group P, we conclude that drug administration by the inexperienced parent may be more effective than the administration of the drug by an experienced doctor.

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**Conflicts of interest**

There are no conflicts of interest.

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Annexure

Annexure 1: Scores used in the study

Infant Global Acceptance Scale:
- 5. = Acceptance with pleasure, seemed to enjoy
- 4. = Acceptance with no problems, no difficulty at all with administration
- 3. = Acceptance with slight resentment, resists mildly
- 2. = Acceptance with strong resentment, resists strongly
- 1. = Acceptance with much difficulty, refused to take drug

Parental Separation Anxiety Scale:
- 1. Easy separation
- 2. Whimpers
- 3. Cries and not easily reassured but not clinging to parents
- 4. Crying and clinging to parents

Mask Acceptance Scale:
- 1. Excellent (unafraid, cooperative, accepts mask readily)
- 2. Good (Slight fear of mask, easily reassured)
- 3. Fair (Not clamed with reassurance)
- 4. Poor (Terrified; crying or combative)

Modified Medication Acceptance Scale:
| Item and observed behavior with examples | Points |
|-----------------------------------------|--------|
| Cry                                     |        |
| Not crying, not screaming               | 2      |
| Crying or screaming but can be comforted| 1      |
| Crying or screaming, cannot be comforted| 0      |

Facial expression
- Happy or positive face: 2
- No facial distress: 1
- Abnormal facial expressions, signs of distress
  - E.g.: facial grimacing, scrunching up face, squinting eyes, looks of anger, distress or fear: 0
- Normal movement, level of agitation
  - Normal movement, calm: 2
  - Restless, mild agitation
    - E.g.: mild head turning, mild avoidance movement of arms or hands, mild restless movement of feet: 1
    - Thrashing about, hysteric
      - E.g.: Head turning, avoidance movement of arms or hands (pushing away, covering mouth/nose with hands), kicking: 0
- Reaction to placement of drug into mouth/nose
  - Allows drug to be introduced into the mouth/nose: 2
  - Resists placement of drug into the mouth/nose: 1
  - Refusal of placement of drug into the mouth/nose: 0
- Swallowing/inhalation of drug
  - Swallows/inhalates drug without loss: 2
  - Spits out/coughs (partial loss of dose): 1
  - Throws up/actively sneezes (full loss of dose): 0

Ramsay Sedation Score:
- 1. Patient is anxious and agitated or restless, or both
- 2. Patient is cooperative, oriented and tranquil
- 3. Patient responds to commands only
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6. Patient exhibits no response.