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RESEARCH ARTICLE
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STUDY ON COMPARATIVE EFFECTIVENESS OF ORAL MIDAZOLAM VERSUS INTRANASAL MIDAZOLAM AS SEDATIVE PREMEDICATION IN PEDIATRIC SURGERIES: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background: Surgery and anesthesia can cause considerable distress and psychologic consequences for both parents and children. Although it is difficult to determine which components of a child's hospitalization experience result in psychologic problems.

Aim: The aim of the study was to compare the effectiveness of Intranasal and oral midazolam used as a premedication in pediatric patients undergoing elective surgical procedures.

Methods: The study was conducted in "Govt. Medical college Srinagar" which is a tertiary care hospital during October 2020 to December 2022 in ASA 1 children who were scheduled for routine surgeries lasting for <75 minutes on 100 children who were randomly allocated into 2 groups with 50 in each. (Group A and Group B). Group A intranasal and Group B- oral group. Children belonged to age group of 4 to 10 years of both sexes. The parents provided written informed consent before premedication of their children.

Results: Midazolam was used as premedication in intranasal and oral routes in children undergoing surgical procedures and the efficacy of the drug in producing preoperative sedation, anxiolysis and co- operation during separation from the parents, was compared using separate scoring systems. The time of onset of sedation is 11 minutes with intranasal midazolam and 19 minutes with oral midazolam. Intranasal midazolam has more rapid onset of action compared to oral midazolam, which is statistically significant.

The sedation scores are better with intranasal midazolam than oral midazolam at 10 minutes, 15 minutes and 20 minutes which are statistically significant. No patient was over sedated or drowsy postoperatively. No complications were observed in both the groups.

Conclusion: In conclusion, Intranasal midazolam when used as a premedication in children, in a dose of 0.4 mg/kg has more rapid onset of action with good acceptance, satisfactory sedation, separation from parents and ease of induction than oral midazolam.

The rapid onset of action of nasal midazolam makes it an ideal route for premedication in children.

Keywords: Surgery and anesthesia, Intranasal midazolam, oral midazolam, distress, children

Introduction:

There are numerous sedative pharmacological agents currently administered to children as sedative pre-medicants to facilitate the induction of anesthesia. It is not uncommon to see an uncooperative, frightened, crying child in pediatric surgery preoperative holding area particularly if the child has not been sedated or premedicated. The child is afraid of strange hospital environment, its people and its equipment, of being separated from its parents and of the very word "operation", the meaning of which is not fully comprehensible to the child. Maladaptive behavioural problems such as enuresis, eating disorders, and general anxiety are some of the consequences of preoperative anxiety. [1,2,3] In fact, studies have indicated that up to 60% of all children undergoing surgery may present with negative behavioral changes at two weeks postoperatively.[3,4,5]

Surgery and anesthesia can cause considerable distress and psychologic consequences for both parents and children. Although it is difficult to determine which components of a child's hospitalization experience result in psychologic problems. Age, parental anxiety level, previous hospital experiences, and the type of surgery are factors that can influence a child's anxiety level and psychological well-being. [6,7,8]

Preoperative anxiety in children leading to postoperative negative changes like emergence delirium, sleep disturbances and long term behavioral problems needs better pre-anesthetic sedation. [3,4,5]

The preoperative interventions directed towards reduction of anxiety can be grouped into psychological and behavioral intervention and pharmacological strategy. [9] Although the non-pharmacological means in the form of friendly visit by the anesthesiologist 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. [10] The introduction of new drugs and alternative routes of administration like transmucosal route in last two decade by avoiding painful intramuscular injections, the most horrifying experience for a child, has facilitated a more rational approach to premedication for paediatric patients.

A variety of sedatives and various routes are being used for procedural sedation in children, each of them having their own pros and cons. [11]

The intranasal route for midazolam has been used since 1988 and has the advantage of rapid absorption directly into the systemic circulation with no first pass effect and a bio- availability of 55-83%. Intranasal midazolam is absorbed from an area rich in blood supply and avoids the disadvantage of passing through the portal circulation, thus increasing the bio-availability of the drug. Tolerance to midazolam is good, and the duration of action is shorter and more predictable than other benzodiazepines. Intranasal midazolam has all the advantages of intravenous administration without the disadvantages of pain and fear associated with intramuscular and intravenous injections.

Material and Methods

After obtaining the institutional ethical committee approval, the study was conducted on 100 children who were randomly allocated into 2 groups with 5 0 in each. (Group A and Group B). Group A intranasal and Group B- oral group. Children belonged to age group of 4 to 10 years of both sexes.

The study was conducted in "Govt. Medical college Srinagar" which is a tertiary care hospital during October 2020 to December 2022 in ASA 1 children who were scheduled for routine surgeries lasting for <75 minutes. The parents provided written informed consent before premedication of their children.

MATERIALS

- Nasal midazolam spray (Insed atomiser)
- Oral midazolam (syrup)

PREPARATION OF THE PATIENT

The recruited pediatric patients were visited a day before surgery for pre anesthetic review. Written and informed consent was obtained from parent or legal guardian of the child.

All the patients were fasted for 6 hrs for nonhuman milk or light meal. No child received any form of sedation before arrival in preoperative area. Baseline pulse rate, respiratory rate, oxygen saturation, blood pressure was recorded .Baseline sedation score was noted. Group A received intranasal midazolam spray 0.3 - 0.4 mg/kg with half the dose administered in each nostril with atomized CFC free nasal spray. Each spray delivered 0.1 ml. concentrated atomized midazolam nasal spray which ensures accurate drug delivery, covers large mucosal area and increases drug bioavailability maximally. While receiving the spray child was seated facing forward on the parent's lap while their arms were gently restrained by one parental hand and the other hand used to tilt the forehead back 15 degree. The spray was delivered by anesthesiologist or by other parent/ guardian.

Group B Oral midazolam syrup 0.5mg/kg was given (2mg/ml) by using measuring cap. Acceptance of drug was noted as:

Poor (refused to accept medication) score 1,

Moderate (accepted medication with difficulty) score 2,

Good (accepted medication without compliant) score 3.

Children who were crying before drug administration were excluded from the observation of response to drug administration .Response to drug administration was noted as yes or no, depending on whether the child started crying after administration of drug.

The child was observed in preoperative area for 20 min and vital parameters were recorded at 5 min interval sedation was evaluated using Ramsay sedation score:

Sedation score 1 and 2 were considered as unsatisfactory while sedation score 3,4,5 were considered as satisfactory. Complications such as nausea, vomiting, nasal irritation, hypoxia and hypotension were noted in both groups and treated accordingly.

20 min after drug administration the child was separated from the parent and ease of separation noted as excellent, good, fair and poor. Separation score 1(patient un-afraid, co-operative) and score 2(slight fair or crying, quite with assurance) were considered as satisfactory or acceptable and score 3(moderate fair, crying not quite with assurance) and score 4(crying, need for restraint) were considered as unsatisfactory and said to have difficult separation.

In operation theater, to set up an intravenous line, gaseous induction was done uniformly with oxygen and sevoflourane (4-8%) mask. Acceptance to mask or response to gaseous induction was noted using 3- point criteria .The quality of anesthetic induction was evaluated as excellent, good or poor and score was given 1,2,3. Score 1,2 were considered satisfactory and score 3 was considered unsatisfactory acceptance of mask. In all patients, surgery was carried out under general anesthesia with endotracheal intubation, vital parameters (pulse rate, blood pressure, spo2) were recorded during intraoperative period. After extubation, patient was shifted to recovery room.

In recovery room vital signs (respiratory rate, blood pressure, spo2) were monitored until the child was fully awake. Using a 10-point recovery room score (which include respiration activity, consciousness, temperature and circulation, each on a scale of 0-2, to give a maximum cumulative total of 10, recovery assessment was done at 10 min intervals for 30 min from the time of extubation. Recovery score of 8 or more considered satisfactory and time taken for it was noted.

In post-operative period, the children were followed up for 24hrs to observe nausea, vomiting, nasal irritation etc.

Statistical Methods:
The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and line diagrams. Student's independent t-test or Mann-Whitney U-test, whichever feasible, was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. A P-value of less than 0.05 was considered statistically significant.

Results:
A total of 100 patients were included as per our inclusion and exclusion criteria. For statistical purpose only these patients were categorized into two groups:
1. Group A included patients where intranasal midazolam was used and 50 patients were observed.
2. Group B included patients where oral midazolam was given and 50 patients were observed.
Patients were comparable with regard to demographic profile [Table1].

Table 1: Demographic profile of the study population

Demographics	Group I	Group II	P Value
Age (years)	6.58±1.875	6.22±1.741	0.322
Sex M/F	66/34	64/36	0.834
Weight (kgs)	21.68± 4.718	21.14 ± 4.543	0.561
ASA I	50	50	-

Mean Heart Rate in Group A at 0, 5, 10, 15 and 20 minutes was 88.52±6.29, 84.38±4.75, 86.32±6.29, 85.02±4.68, 83.40±5.42 respectively. Mean Heart Rate in Group B at 0, 5, 10, 15 and 20 minutes was 86.12±5.80, 85.40±5.13, 84.40±5.57, 84.96±5.31, 84.26±6.34 respectively. Difference in Mean Heart Rate at various time intervals in two groups was statistically insignificant [Table 2].

Table 2: Comparison based on heart rate (beats/min) in two groups atvarious intervals of time

Time Interval	Group A		Group B		P-value
	Mean	SD	Mean	SD	
0 Min	88.52	6.29	86.12	5.80	0.152
5 Min	84.38	4.75	85.40	5.13	0.305
10 Min	86.32	6.29	84.40	5.57	0.109
15 Min	85.02	4.68	84.96	5.31	0.952
20 Min	83.40	5.42	84.26	6.34	0.468

Difference in Mean Arterial Pressure at various time intervals in two groups was statistically insignificant (p>0.05) [Table 3].

Table 3: Comparison based on mean arterial pressure (mmHg) in two groups at various intervals of time

Time Interval	Group A		Group B		P-value
	Mean	SD	Mean	SD	
0 Min	**75.44**	**5.72**	**76.20**	**5.18**	**0.488**
5 Min	**74.40**	**3.02**	**74.34**	**4.10**	**0.934**
10 Min	**73.46**	**4.35**	**74.20**	**3.48**	**0.350**
15 Min	**74.30**	**3.34**	**73.70**	**3.11**	**0.355**
20 Min	**72.98**	**2.29**	**73.10**	**2.60**	**0.807**

Mean of Acceptance Score of Group A (Intranasal group) was 3.30±0.70 and that of Group B (Oral group) was 1.38±0.49. The difference in Acceptance Score in two groups was statistically significant with p<0.001 [Table 4].

Table 4: Comparison based on acceptance score in two groups

Group	N	Mean	SD	Range	P-value
Group A	50	3.30	0.707	3.10-3.52	
Group B	50	1.38	0.490	1.24-1.52	<0.001*

Mean of Sedation Score of Group A (Intranasal group) was 3.44±0.54 andthat of Group B (Oral group) was 1.64±0.59. The difference in Sedation Score in two groups was statistically significant with p<0.001 [Table 5].

Table 5: Comparison based on sedation score in two groups

Group	N	Mean	SD	95% CI	P-value
Group A	50	3.44	0.541	3.29-3.59	
Group B	50	1.64	0.598	1.47-1.81	<0.001*

Mean of Separation Score of Group A (Intranasal group) was 1.92±0.63 and that of Group B (Oral group) was 3.40±0.67. The difference in Separation Score in two groups was statistically significant with p<0.001 [Fig 1].

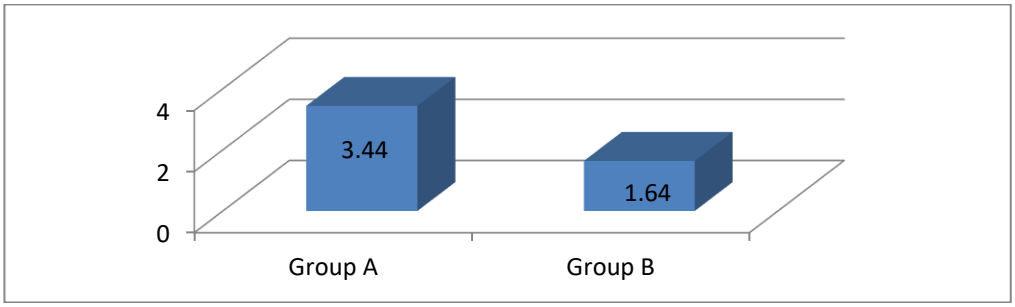

Fig 1

Mean of Ease of Induction in Group A (Intranasal group) was 1.58±0.53 and that of Group B (Oral group) was 3.32±0.62. The difference in Ease of Induction Score in two groups was statistically significant with p<0.001 [Fig 2].

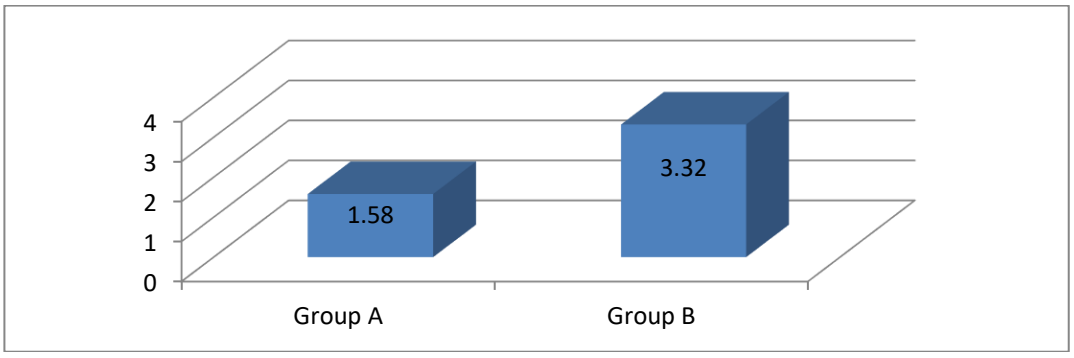

Fig 2

Discussion:

In children, preanesthetic medications frequently are administered as pharmacologic adjuncts to help alleviate the stress and fear of surgery as well as to ease child-parent separation and promote a smooth induction of anesthesia. For ambulatory surgery patients, pharmacologic adjuncts also should avoid prolonging anesthesia recovery and delaying hospital discharge time. Oral, rectal, and intramuscular routes of preanesthetic medication administration have been used; however, each

route has disadvantages. [12-15] Although nasal preanesthetic medications can cause irritation to the nasal mucosa and patient crying, its rapid and reliable onset of action, avoidance of painful injections, and ease of administration have made it a convenient way to premedicate children. Midazolam has been reported to produce partial anterograde amnesia, provide tranquil sedation, reduce separation anxiety, and facilitate induction of anesthesia. [16,17]
Intranasal midazolam in the form of a spray was used in our study. Each metered dose of 100 microliter of atomizer delivered 0.5mg of midazolam. Oral midazolam used in this study was midazolam syrup 0.5mg/kg body weight was given (2mg/ml) by using measuring cap.

Sunny Alex et al., [18] used intranasal midazolam at a dose of 0.3 mg/kg and oral midazolam in a dose of 0.5 mg/kg in their study.

Charles J.Cote et al., [19] studied 306 patients, using 3 different doses of oral midazolam syrup 0.25, 0.5, 1.0 mg/kg. Overall 97% of patients achieved satisfactory sedation (score>3) after treatment. The difference between the 0.25 and 0.1 mg/kg dosage was significant.($p<0.01$). There was no difference between the 0.5 and 1.0 mg/kg groups or between the 0.5 and 0.25 mg/kg groups. After study medication, 99% maintained satisfactory sedation scores and 97.5% achieved a satisfactory anxiolytic response (score>3). There was a positive association between dose and onset of anxiolysis($p=0.01$); a larger proportion of children achieved satisfactory anxiolysis within 10 minutes at the higher doses. >90% maintained satisfactory anxiolysis for up to 45 minutes. No child experienced respiratory complications before induction, two experienced nausea and three vomited before induction. The proportion of subjects experiencing an adverse event was slightly larger in the 1.0 mg/kg.
Hence it was decided to use oral midazolam in a dose of 0.5 mg/kg for all children in the oral group in our study and none of them experienced respiratory depression, nausea, vomiting or any adverse effect.

Asif Pervez et al., [20] compared the effect of intranasal midazolam with intranasal ketamine and used intranasal midazolam in a dose of 0.2 mg/kg.
In a study performed by Garcia-Velasco P et al., [21] intranasal midazolam was used in a dose of 0.25 mg/kg and it compared it with ketamine (5mg/kg) nasally and found that the nasal route of administration of the drug was well accepted in both groups and midazolam and Ketamine were equally effective as sedative premedication.

Gustaf L jungman et al., [22] conducted a double blind, placebo controlled, crossover study in which nasal administration of midazolam spray 0.2 mg/kg was compared with placebo.

Sunny Alex et al., [18] used a five point score for level of sedation, four point score for level of anxiety and a four point score for co-operation at the time of parental separation. Sedation score at 10, 20, 30, 40 minutes and at the time of separation from parents were evaluated and compared between the oral and nasal midazolam groups.
In our study, the mean time for onset of sedation in nasal midazolam group was found to be 11 minutes and in oral group it was 19 minutes. Thus the onset time in oral group was almost twice that of nasal group.
Sunny Alex et al., [18] found that the mean time for onset of sedation and satisfactory sedation were 8.63 minutes and 11.3 minutes respectively for the nasal midazolam group and 14.03 minutes and 18.3 minutes for the oral midazolam group with P value of 0.001 which was very highly significant.

Christy Lam et al., [23] compared the effectiveness of intramuscular and intranasal midazlolam as a premedication before intravenous conscious sedation. The patients ranged in age from 2-9 yrs (

mean age 5.13 yrs) and received a dose of 0.2 mg/kg of midazolam via intramuscular or intranasal administration. They studied 23 patients and reported that patients who were given intramuscular midazolam were more deeply sedated than those receiving intranasal midazolam.

Karl HW et al., [24] showed that the rich blood supply of the nasal mucosa allows rapid absorption of drugs directly into the systemic circulation. Absorption depends on the time that the drugs is adjacent tothe mucosal surface (Resident time), local pH (6-7), presence of secretions (respiratory tract infections), physicochemical properties of the drug and physicochemical properties of route of the administration of the drug.
The method and technique of administration also affect the drug absorption. The aqueous solubility of midazolam at acidic pH (3.5) allows this drug to maintain a high concentration in nasal mucosa (pH 6-7). The pKa of midazolam 6.15 which is close to local pH. Both ionized and no ionized forms are absorbed from nasal mucosa.

Kogan et al., [25] studied the effects of oral, rectal and nasal midazolam. The children accepted oral route significantly better compared to nasal or oral routes. The fastest onset of sedation was found after rectal route. The effect of oral midazolam was good in many children but less predictable.
In the study conducted by Sunny Alex et al., [18] sedation scores were slightly better in the nasal group up to 20 minutes after premedication with P value of 0.006 which was highly significant at 10 minutes, and P value of 0.028 which was significant at 20 minutes. At 30 minutes , 40 minutes and at the time of separation from parents sedation scores were comparable between two groups with p value of >0.05 which was statistically insignificant.
In our study, statistical analysis showed that sedation score at 10 minutes was better with the nasal group with a P value of <0.001 which is statistically highly significant.
Sedation score at 20 minutes after premedication was better with nasal midazolam with a P value of < 0.001 which is again statistically significant. Sedation score at 30 minutes was better in the nasal group with a P value of 0.003 which is statistically significant.
In our study, separation scores at the time of parental separation are better in nasal groups with a P value of 0.001 which is statistically significant.
The ease of induction for mask application is better in group A with a P value of< 0.001 which is statistically significant.
In both groups no patient had coughing, gagging, vomiting, laryngospasm or respiratory depression.

Conclusion:
In conclusion, Intranasal midazolam when used as a premedication in children, in a dose of 0.4 mg/kg has more rapid onset of action with good acceptance, satisfactory sedation, separation from parents and ease of induction than oral midazolam. The rapid onset of action of nasal midazolam makes it an ideal route for premedication in children.

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