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Comparison of Intranasal Midazolam with Oral Midazolam for Premedication in Children.

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ABSTRACT

Surgery and anaesthesia induce considerable emotional stress and psychological consequences in children. This stress may remain in the child's psyche long after the hospital experience has passed, and it was first described by Duputyren in 1834.Age, parental anxiety level, previous hospital experiences and type of surgery are factors that can influence a child's anxiety level and psychological well being. Preoperative anxiety stimulates sympathetic, parasympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability. These reactions reflect the child's-fear of separation from parents and home environment,fear of physical, harm, fear of unfamiliar routines,fear of surgical instruments and procedures
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INTRODUCTION

In paediatric anaesthesia, premedication needs to be in an acceptable form, to have a rapid onset with minimal hangover effect and without side effects. Midazolam, a sedative with all the desirable properties of a benzodiazepine was introduced into clinical practice in 1980s.

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.

This study was designed to compare intranasal Midazolam with oral Midazolam for premedication in children.

PREMEDICATION IN CHILDREN

Finding a suitable premedicant for children and the best route of administration is something that has been investigated for a long time.

An ideal paediatric premedication should-allay anxiety and fear, be easily available and affordable,produce the desired clinical effect, enable smooth separation from parents,abolish any preoperative pain facilitate smooth induction, reduce the dose of anaesthetic, maintain vital functions, maintain airway reflexes, offer rapid postoperative recovery, easily acceptable by parents, have minimal hangover effect, should produce amnesia of transfer and entry into the operating room

MIDAZOLAM PHARMACOLOGY

Midazolam is a short-acting, water soluble benzodiazepine and central nervous system depressant that was introduced into clinical practice in 1980s. It is two to three times as potent as diazepam.Midazolam has the following six principal pharmacological actions.-Anxiolysis, Sedation, Anticonvulsant, Skeletal muscle relaxation.

Anterograde amnesia,Hypnosis

The pharmacological effects of midazolam results from reversible interactions with the Gamma-Amino Butyric Acid (GABA) benzodiazepine receptor, the major inhibitory neurotransmitter in the central nervous system.

Midazolam is rapidly metabolized by hepatic and small intestine cytochrome p-450 (CYP3A4) enzymes to active and inactive metabolites .The principal metabolite of midazolam, 1–hydroxy midazolam has approximately half the activity of the parent compound. This active metabolite is rapidly conjugated to 1-hydroxy midazolam glucuronide and is subsequently cleared by the kidneys. The other pharmacologically active metabolites like 4 hydroxy midazolam are not present in detectable concentrations in the plasma.

Metabolism of midazolam is slowed in the presence of drugs such as Cimetidine, Erythromycin, Calcium channel blockers, antifungal drugs that inhibit cytochrome p-450 enzymes resulting in unexpected CNS depression.Hepatic clearance rate of midazolam is 5 times greater than that of lorazepam and 10 times greater than that of diazepam.

MATERIALS AND METHODS

Seventy paediatric patients belonging to ASA physical status I and II scheduled for elective minor surgical procedures were included in the study.Children belonged to the age group of 2 to 8 years of both

sexes.The children were randomly allocated into 2 groups with 20 patients in each group. (Group N and Group O). It was a comparative study.The study was approved by the Institutional Ethical Committee and parents provided written informed consent before premedication of their children.

Inclusion Criteria

- ASA I and II physical status
- Age group 2-8 yrs
- weight < 20 kg

EXCLUSION CRITERIA

- ASA III and IV
- Nasal Infection
- Nasal Pathology
- Nasal Allergy and URI

- Children with Seizure disorder
- History of adverse reactions to benzodiazepines
- patient taking other sedative drugs**.**

MATERIALS

- Nasal midazolam spray (Insed atomiser)
- Oral midazolam

PREPARATION OF THE PATIENT

Written informed consent from the parent obtained.All patients fasted as per NPO guidelines.Demographic data including age, weight and sex of the children were recorded.The children were given premedication 30 minutes before surgery orally or nasally. The reaction of the children to the premedication was noted

Group – N – received intranasal midazolam at a dose of 0.2mg/kg using Insed atomiser midazolam Nasal spray containing 100 micro litre / metered dose which delivers 0.5 mg/dose. The dose was calculated and divided equally into each nostril with the children in sitting position on their mothers' lap. Half of the dose was placed in each nostril .Placing half the medication in each nostril reduced the volume while doubling the available area for absorption. Then the patient was kept in slightly head-down position for 2 minutes for easy absorption.

Dosing guidelines of Nasal Spray

Age (years)	Approximate Wt	Dose (mg)	Metered Doses in each nostril
1-2	6-8	1.2 – 1.5	1-2
2-5	8-15	1.5 – 3.0	2-3
5-10	15-30	7.5 – 10	6-8

- Group – O – received oral midazolam at a dose of 0.5 mg/kg. The drug used was the injectable preparation which contains preservative free midazolam one ml (5mg/ml) in an ampoule. The drug was mixed with apple juice to mask the bitter taste before administration.
- After premedication, the children were observed carefully in the premedication room. Pulse oximeter was connected to the children and pulse rate and saturation were observed.
- The onset of sedation, levels of sedation and anxiolysis at 10, 20 and 30 minutes were noted. The reaction of the children at the time of separation from parents were noted and graded as per the co-

operation score.

- After bringing the child to the theatre, an intravenous cannulation was done and child's response to venepuncture was noted and scored.
- Standard Monitors such as ECG, Pulse Oximeter, Non-invasive BP, Precordial Stethescope were attached.
- Anaesthesia was induced and response of the child to mask application was noted and scored before surgery was started.
- The children were kept in the recovery position after the surgery was over and observed in the operating room for 30 minutes and shifted to the recovery room.

OBSERVATIONS

Time of Onset of Sedation. Sedation Score at various points of time (10 minutes intervals for 30 minutes). Anxiolysis score at various points of time (10 minutes intervals for 30 minutes). Co-operation score at the time of separation from parents.Co-operation score at the time of mask application. Co-operation score at the time of venepuncture. The presence or absence of the following side effects and complications from the time of instillation to 24 hours postoperatively, were noted.

- Nasal irritation
- Postoperative – nausea and vomiting
- Respiratory depression
- Laryngospasm/ Bronchospasm
- Other complications

SEDATION SCORE

Criteria	Grade	Score
Moving, physical or verbal display of apprehension	Alert /Active – agitated	1
Tearful, clinging to mother	Upset/ Worried	2
Calm, responding readily to Commands	Relaxed	3
Easily arousable	Drowsy	4

ANXIOLYSIS SCORE

Criteria	Grade	Score
Afraid and crying, restrained	Poor	1
Fearful, moderate apprehension	Fair	2
Slightly fearful	Good	3
No fear or apprehension	Excellent	4

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CO-OPERATION SCORE

Criteria	Grade	Score
Afraid and crying, restrained	Poor	1
Fearful, moderate apprehension	Fair	2
Slightly fearful	Good	3
No fear or apprehension	Excellent	4

OBSERVATION AND RESULT

The study was conducted in the operation theatre complex of Sree Balaji Medical College and hospital.

TYPES OF SURGERIES

SURGERY	GROUP N	GROUP O	TOTAL
Circumcision	12	12	24
Herniotomy	2	2	4
Tonsillectomy	4	3	7
Tongue Tie Release	2	3	5
TOTAL	**20**	**20**	**40**

ASA GRADE

All patients of both groups belonged to ASA Grade I and I

DEMOGRAPHIC PROFILE

The sample of 40 was taken for study. Test statistics used were Chi-Square test and 't' test.The level of statistics significance was set up at $p < 0.05\%$

TABLE 1 Comparison of Age distribution

Group	N	Mean (Years)	S.D.	Std Error Mean
Nasal	20	4.50	1.638	0.366
Oral	20	4.60	1.847	0.413

Chi – Square value is 1.740, p value = 0.654

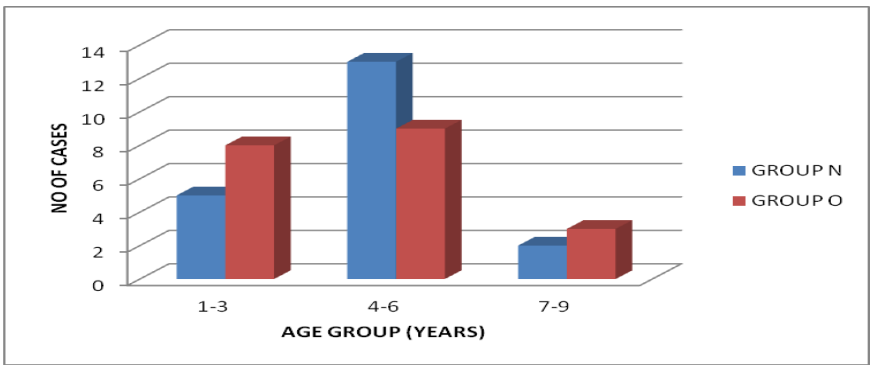

Figure : Bar Diagram Compares the age distribution of Nasal and Oral group

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The mean age in nasal midazolam group is 4.50 years and in oral midazolam group is 4.60 years. The data is statistically insignificant(p>0.05) and thus both groups are comparable in terms of age.

TABLE-2: Comparison of weight distribution

Group	N	Mean (Kgs)	S.D.	Std Error Mean
Nasal	20	12.30	4.219	0.943
Oral	20	14.15	3.453	0.772

Chi – Square value is 12.354, p value = 0.0654

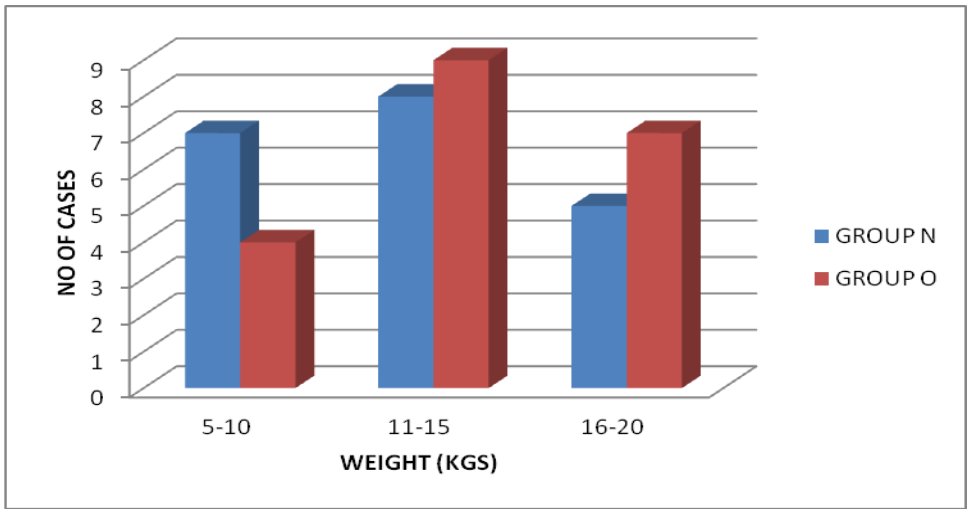

Figure : Histogram compares the weight distribution of Nasal and Oral group

The mean weight in Nasal group is 12.30 kg and in oral group is 14.60 kg. The data is statistically insignificant (p>0.05) and thus both groups are comparable in **TABLE – 3** : **Comparison of Gender Distribution**

GROUP	MALE	FEMALE	TOTAL
N	14	6	**20**
O	16	4	**20**
TOTAL	**30**	**10**	**40**

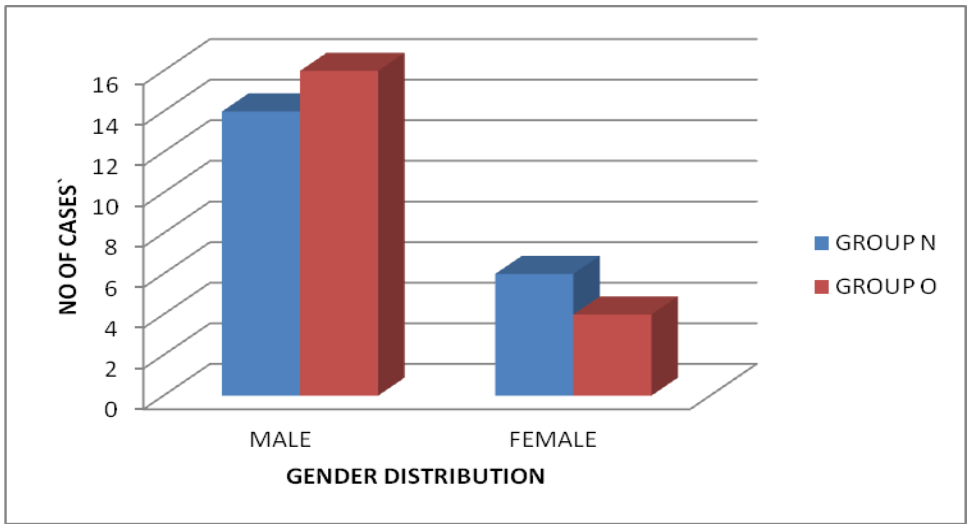

Figure : Bar Diagram shows Gender Distribution of Nasal and Oral group terms of weight.

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DISCUSSION

Wilton NCT[25], Karl HW[26] and many others have searched for the ideal paediatric premedicating agent and also for the best route of administration. A paediatric premedicant must have an acceptable, atraumatic route of administration in addition to other characteristics needed for such a drug.Midazolam has been extensively used in anaesthetic practice since 1982, and its pharmacodynamics and pharmacokinetics are well known. Midazolam is used frequently for premedication in children, preferably by non-parenteral routes.Nasal administration of various drugs such as ketamine and midazolam has been recommended previously for premedication in children. Oral midazolam remains the commonly used premedication in paediatric outpatients.Intranasal midazolam for premedication in preschool children was first described and advocated by Wilton and colleagues[25]. Midazolam has many desirable properties as a premedicant in children undergoing surgery. Midazolam exerts a reliable dose dependent anxiolytic effect without oversedation and provides minimal cardiovascular and respiratory effects. The anterograde amnesia produced by midazolam help reduce the psychological trauma of anaesthesia and surgery. Its elimination half life is 1.5 -2 hrs which is considerably shorter than that of diazepam. The elimination half life of intranasal midazolam is similar to that when the drug is given intravenously and no significant complications have been reported when it is given by the intranasal route.As midazolam has many of the properties of an ideal permedicant drug, this comparative study was undertaken to compare the efficacy of this drug when given by oral and intranasal routes.Most studies have used midazolam in a dosage of 0.1 to 0.3 mg/kg intranasally and several pharmacokinetic studies have examined plasma concentrations and effect at varying intranasal doses.Intranasal midazolam has generally been administered in the form of drops, which in the awake patient are difficult to keep in the nose and may be swallowed and subjected to first pass metabolism in the liver.

Twersky and colleagues used a Devilbiss 286 atomizer to deliver 0.2 mg/kg. Bjorkman, Rigemar and Idvall[27] used a spray bottle in adults and found the procedure acceptable. Midazolam has also been given to adults by nebulizer with good acceptability.It has been shown that the fine aerosol would allow greater contact with the absorbing surface and that application would be less unpleasant than drops. Bio-availability with nasal spray has been shown to be high (83%) with virtually complete absorption.N. Griffifth et al., [2]compared two methods of administering midazolam intranasally in 44 day-care children and used midazolam 0.2 mg/kg as drops or midazolam 0.1 mg/kg from an intranasal spray device.

Behaviour was recorded on a four point scale and co-efficients were obtained representing the change in behaviour score. There was no significant difference in the method of administration (coefficient 0.13, p=0.39). midazolam by either method was equally effective but acceptability of the premedication was poor in nasal drops group.

Intranasal midazolam in the form of a spray was used in this study. Each metered dose of 100 microliter of atomiser delivered 0.5 mg of midazolam.Oral midazolam used in this study was the preservative free injectable preparation (5 mg/ml) in an ampoule. The drug was mixed with the apple juice to mask the bitter taste and to increase the acceptability.Sunny Alex et al.[16] 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.[7]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 upto 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 this study and none of them experienced respiratory depression, nausea, vomiting or any adverse effect.Asif Pervez et al.[9]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.[29] 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.[3]conducted a double blind, placebo controlled, crossover study in which nasal

administration of midazolam spray 0.2 mg/kg was compared with placebo.Mittal Pankaj et al.,[30] showed that intranasal Midazolan at 0.2mg/kg provides safe and effective non-invasive method of sedation.Sunny Alex et al.[16]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, mean time for onset of sedation, time for satisfactory sedation, level of sedation at 10 minutes, 20 minutes, and 30 minutes, level of anxiety at 10 minutes, 20 minutes, 30 minutes in both the groups were compared. In addition, co-operation at the time of separation from parents, co-operation at the time of venepuncture and co-operation at the time of mask application were scored and compared.A four point scale for sedation score, five point scale for anxiolysis score and a four point scale for co-operation score were used to compare the groups in this study.In our study, the mean time for onset of sedation in nasal midazolam group was found to be 7.35 minutes and in oral group it was 14 minutes. Thus the onset time in oral group was almost twice that of nasal group.Sunny Alex et al., 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 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.,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., [26] 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 drus is adjacent to the 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 pK_a of midazolam 6.15 which is close to local pH. Both ionized and nonionized forms are absorbed from nasal mucosa.Kogan et al.,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.

Asif Pervez et al., conducted the study on paediatric surgical patients in 2-5 yr age group. Our study was conducted on patients between 2-8 yrs.In the study conducted by Sunny Alex et al.,sedation scores were slightly better in the nasal group upto 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 0.023 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 statictically significant. Sedation score at 30 minutes was better in the nasal group with a P value of 0.002 which is statistically significant.In our study, anxiolysis scores were better with the nasal group with p value of 0.013 at ten minutes and a P value of 0.021 at thirty minutes which are statistically significant. But this contradicts the study of Sunny Alex et al., who found the anxiolysis score to be similar in the two groups (nasal and oral) throughout the study period with a p value of >0.05 which was not significant statistically.In our study, co-operation scores at the time of parental separation are comparable in both groups with a P value of 0.132 which is statistically not significant. This result can be correlated with the study of Sunny Alex et al., who had similar results.Co-operation scores at the time of venepuncture are found to be similar in both groups with a P value of 0.121 which is not statistically significant. This also correlates with the study of Sunny Alex et al., who had the same results.The co-operation for mask application is comparable in both groups with a P value of > 0.05 which is not statistically significant.In both groups no patient had coughing, gagging, vomiting, laryngospasm or respiratory depression.

SUMMARY

We compared the efficacy of midazolam as a paediatric premedication when used in two different routes.Midazolam was used as premedication in intranasal and oral routes in children undergoing minor surgical procedures and the efficacy of the drug in producing preoperative sedation, anxiolysis and co-

operation during separation from the parents, venepuncture and face mask application was compared using separate scoring systems.The following observations were made during the study.There are no significant differences between the two groups in demographic data.The time of onset of sedation is 7.35 minutes with intranasal midazolam and 14 minutes with oral midazolam.We observed that 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, 20 minutes and30 minutes which are statistically significant.The anxiolysis is better with nasal midazolam group with statistical significance.There is no significant difference in the co-operation score for venepuncture, separation from the parents and mask application between the two groups.No patient was oversedated 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 **0.2 mg/kg** has more rapid onset of action with satisfactory sedation and anxiolysis than oral midazolam. The rapid onset of action of nasal midazolam makes it an ideal route for premedication in children.

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