"Preanaesthetic sedation with intranasal midazolam atomizer versus oral midazolam in paediatric patients" – a randomized comparative study

Sangamesh R Nainegali[1,*], Chhaya P Joshi[2], Arati C Koregol[3], Ramachandra DS[4]

[1]Assistant Professor, [2]Associate Professor, SN Medical College, Bagalkot, [4]Professor & Head, Dept. of Anaesthesiology, Maheshwari Medical College, Isnapur, [3]Professor, Dept. of Periodontology, PMNM Dental College, Bagalkot

***Corresponding Author:**
Email: ndrsangamesh@gmail.com

Abstract

Background: Separation from the parents and unfamiliar operation theatre environment adds severe anxiety and apprehension to children. Therefore, an effective preanaesthetic medication for use in children undergoing surgery is required. In spite of plethora of research activities, premedication in children remains a controversial subject as various premedication and delivery systems have developed using different routes of administration.

Aims and objectives: To compare the safety, efficacy, ease of administration, acceptability, degree of sedation, anxiolysis and parental separation of midazolam by oral and intranasal spray for preanaesthetic sedation.

Materials and Methods: Sixty six ASA-I and ASA-II paediatric patients of age group one to ten years, scheduled for elective surgical procedures were divided into Nasal(N) group and Oral(O) who were randomised to receive either intranasal midazolam atomizer spray (0.4mg/kg) or oral midazolam syrup (0.5mg/kg). The demographic details, vital parameters, sedation score, anxiolytic score, separation score and drug acceptability were noted before administering the drug and at 10,20,30 minutes interval till parenteral separation was done.

Results: There was statistically significant increase in mean pulse rate at 10 minutes interval in group-N ($P < 0.05$). Though statistically significant increase in systolic blood pressure(SBP) was noted at all 3 intervals($P<0.05$)in group O, statistically significant increase in diastolic blood pressure(DBP) was noted in group O only at 10 minutes of interval (P-value<0.05). Drug acceptability was good in group-O which was statistically significant(P- value <0.001). Sedation and anxiolysis were good in group-N compared to group-O but statistically significant scores were noted at 20 minutes interval ($P<0.001$, $P<0.01$ respectively). Parental separation in group-N was better compared to group-O which was not statistically significant.

Conclusion: Both the oral and nasal routes were equally safe. The transnasal route achieved faster sedation, anxiolytic and separation scores, virtually complete absorption as compared to oral syrup. Hence it may be preferred as a good alternative to oral midazolam. The oral route was better accepted by children.

Keywords: Intranasal midazolam, Oral, Premedication, Sedation, Atomiser.

Access this article online	
Quick Response Code:	**Website:** www.innovativepublication.com
	DOI: 10.5958/2394-4994.2016.00053.6

Introduction

Most of the children suffer from severe anxiety and apprehension when they are separated from their parents or family members. Most of the time, the anaesthetist struggles with the child to start the intravenous line or induce inhalationally.[1,2] The preoperative anxiety can largely affect the smoothness of induction and emergence from anaesthesia. The prevalence of preoperative anxiety is high and is reported to range from 40% to 60% among young children. 20% of these children will continue to demonstrate negative behaviour even 6 months after surgery.[2,3]

An effective preanaesthetic medication for use in children undergoing surgery is required which will allay apprehension regarding anaesthesia and surgery, lessen the trauma of separation and facilitate induction for general anaesthesia without prolonging the post anaesthetic recovery period.[1]

An ideal premedicant should be easily available in a ready preparation, easily acceptable by children, has rapid and reliable onset, has good anxiolytic and sedative effect and should be devoid of side effects.[4] Midazolam appears to be an excellent premedicant for pediatric patients as it satisfies most of the above characteristics. In addition, midazolam's short elimination half-life decreases its potential for accumulation after multiple doses; Midazolam is rapidly metabolized by hepatic microsomal enzymes to form inactive hydroxylated metabolites.[5]

It has been used through various routes, viz. oral, rectal, intramuscular, intranasal and intravenous routes, each route with their own merits and demerits. Of late, available transmucosal route of administering midazolam has a rapid and reliable onset of action due to the rich blood supply of the airway mucosa and bypassing first pass hepatic metabolism. Also, this route avoids the need for painful injection and trained personnel to administer the drug.[6,7]

Although various combinations of drugs and routes of administration have been used in children for preanaesthetic sedation, the oral route remains the least threatening method of drug administration.[8] Intranasal midazolam has been used for pediatric procedural and operative sedation for many years by conventional and aerosolized methods. However, with the recent availability of Nasal-Mucosal Atomization Device and proprietary oral midazolam formulations (syrup), these routes of administration have been revisited. The advantages of using atomized delivery include lesser drug being lost into oropharynx, better patient acceptability, and improved sedative effect.

Inspite of plethora of research activities, premedication in children remains a controversial subject as various premedication and delivery system have developed using different routes of administration. Most of the studies on intranasal midazolam atomizer spray with dose of 0.2, 0.3 and 0.5 mg/kg have been used with apparent difference in the observations. Hence ours is the first study which compared 0.4 mg/kg, to find out the optimum dose avoiding any undesirable side effects. Hence the present study was under taken to compare the safety, efficacy, acceptability, degree of sedation, anxiolysis and ease of administration of midazolam by intranasal spray and oral syrup for preanaesthetic sedation of pediatric patients in children in the age group of 1-10 yrs undergoing various surgical procedures in our hospital.

Materials and Methods

This study was conducted after obtaining written informed consent from the parent/guardian and after obtaining institutional ethical clearance. Sixty six ASA-I and ASA-II pediatric patients of age group one to ten years, scheduled for elective surgical procedures were enrolled for the study. ASA grade III and IV children with full stomach, with respiratory and cardiac diseases or having upper respiratory tract infection, with seizures, mentally retarded children, patients on drugs that interfere with midazolam, those with history of prematurity and chronic illness were excluded from the study

The selection of the patients was done randomly by allocating 66 Patients into 2 groups by computer generated randomized table

1. Group O (n = 33) received oral midazolam 0.5 mg/kg proprietary midazolam Oral formulation.
2. Group N (n=33) received intranasal midazolam 0.4 mg/kg dispensed through proprietary drug atomizer in upright position during inspiration.

Both the drugs were administered 30 minutes before induction of anaesthesia. The study was double blinded wherein the patients and the investigator were not aware to which group they belonged to. Patients were evaluated for fitness, parents were explained about the intended procedure and anaesthesia, nil oral protocols were explained on the day prior to the surgery.

Routine investigations like estimation of haemoglobin %, total blood cell count and differential white blood count, bleeding time and clotting time, urine analysis, chest x-ray were done. Clear liquids were avoided upto 4 hours before the procedure. Milk/solids were avoided for 6 hours prior to the procedure. Patients were accompanied with the parent /guardian to the preoperative room. The baseline recordings of pulse rate, oxygen saturation, blood pressure and activity of the child was noted.

Children were evaluated for safety by vital signs and adverse effects such as tachycardia, bradycardia, hypertension, hypotension, oxygen desaturation, vomiting. Degree of sedation and anxiolysis were scored at 10, 20 and 30 minutes interval from the time of drug administration. At 30 minutes, the child was separated from its parents and was taken to the operating room. The response to the child- parent separation was assessed and graded according to a 4 point scale at 30 minutes.

The sedation and anxiolysis scores and the level of safety, efficacy and acceptance were noted and tabulated systematically in a proforma for all the patients. The scoring system has been mentioned as an **appendix 1.**

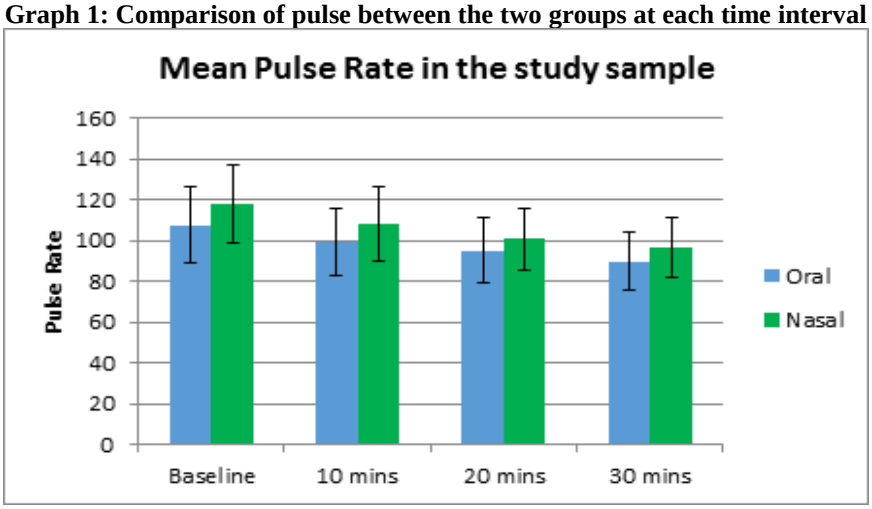
Statistical Analysis

The data were tabulated using Microsoft excel 2013 and analysed using SPSS. The data were tested for normality with the help of histograms, by comparison of means and medians and by performing skewness. Data were reported as mean and standard deviation(SD) for continuous variables and percentages for categorical variables. Variables were compared using paired T test for normally distributed data and the Mann-Whitney U and wilcoxon signed ranks test for non-normally distributed data. For all practical purposes P value less than 0.05 was considered as statistically significant.

Results

Demographic Data: The two groups were comparable in an age, sex and weight distribution. In Group O there were 46% male and 63% female children with age ranging from 1-10 years (mean 6.12±2.84) and weight ranging from 5-20kgs (mean 13.82±0.78). In Group N there were 54% male and 38% female children with age ranging from 1-10 years (mean 4.61±2.19) and weight ranging from 7-20kgs (mean 12.58±0.58).

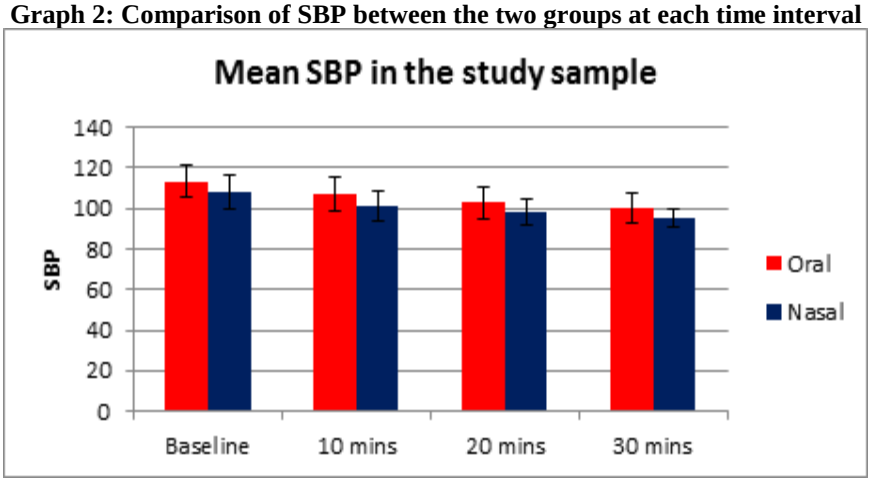
Graph 1: Comparison of pulse between the two groups at each time interval



At baseline, higher mean pulse(118.09) was recorded in nasal group compared to oral group(107.61) and the difference between them was found to be statistically significant (P<0.05).

At 10 mins, statistically significant higher mean pulse was recorded in nasal group compared to oral group (P<0.05) and though higher mean pulse rate was noted at20 and 30 min intervals in nasal group, it was not statistically significant (P>0.05)(mean values,oral-94.57 and nasal-101.70).

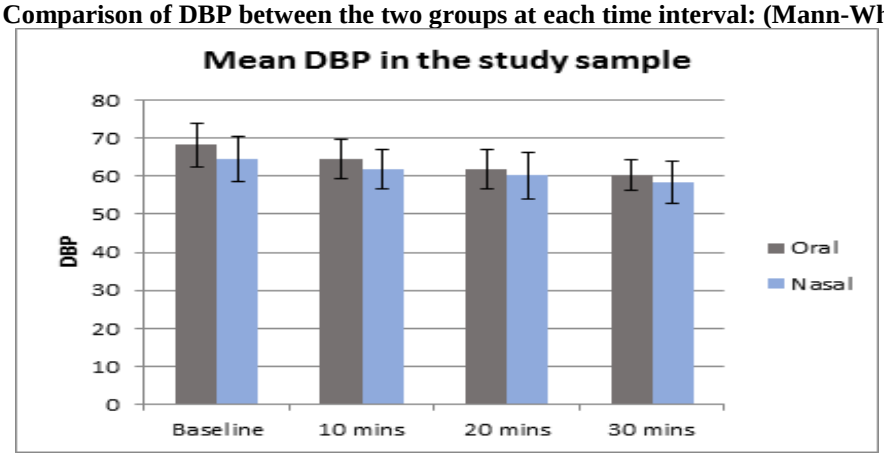
Graph 2: Comparison of SBP between the two groups at each time interval



At baseline, higher mean SBP was recorded in oral group compared to nasal group and the difference between them was found to be statistically significant (P<0.05).

In all 10 min, 20 min, 30 min higher mean SBP was recorded in oral group(103.38) compared to nasal group(98.41) and the difference between them was found to be statistically significant.

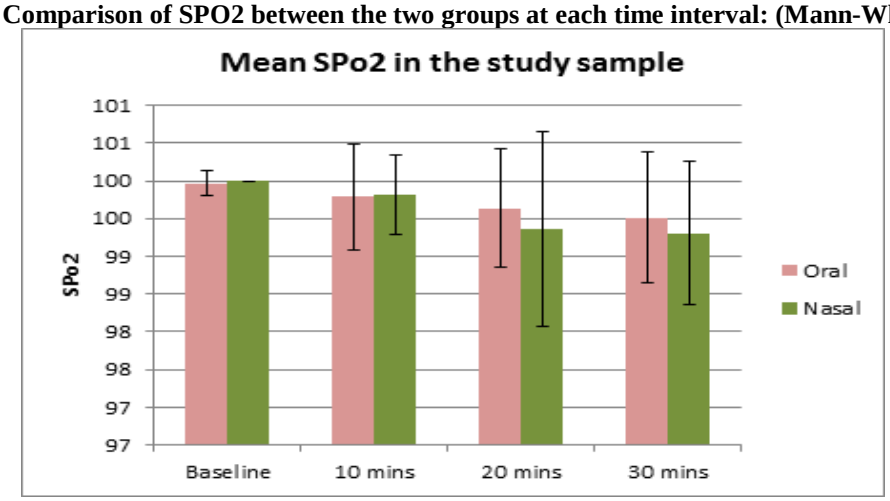
Graph 3: Comparison of DBP between the two groups at each time interval: (Mann-Whitney test)



At Baseline, higher mean DBP was recorded in oral group(68.24) compared to nasal group(64.55) and the difference between them was found to be statistically significant (P<0.05).

At 10 mins, 20 mins and 30min higher mean DBP was recorded in oral group (62.26) compared to nasal group(60.15) and the difference between them was found to be statistically significant at 10 min(P<0.05)and not significant at 20 mins and 30min(P>0.05).

Graph 4: Comparison of SPO2 between the two groups at each time interval: (Mann-Whitney test)



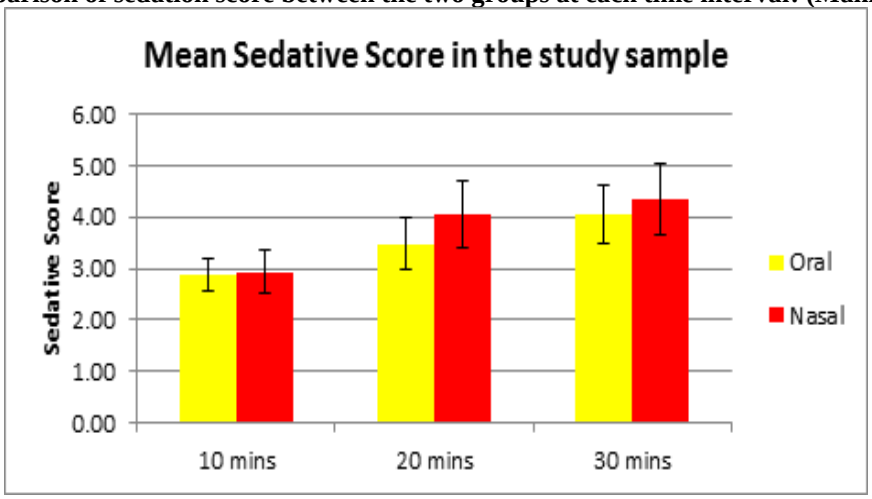
At Baseline, slightly higher mean SPO2 was recorded in nasal group(100) compared to oral group(99.97) but the difference between them was not statistically significant (P>0.05). At 10mins, 20min, 30min no statistically significant difference was noted(P>0.05).(mean values oral -99.65, nasal -99.49)

Table 1: Comparison of drug acceptability score between the two groups at each time interval: (Mann-Whitney test)

Group	Mean	Stddev	SE of Mean	Mean Difference	z	P-Value
Oral	1.09	0.29	0.05	-0.788	-6.355	<0.001*
Nasal	1.88	0.33	0.06			

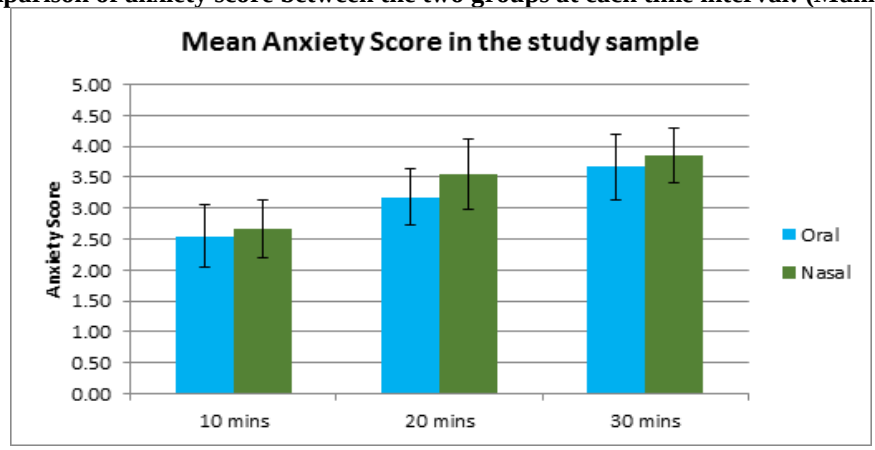
Higher mean drug acceptability score was recorded in oral group (1.09)compared to nasal group(1.88) and the difference between them was found to be statistically significant (P<0.001). Drug acceptability in percentage: 90.9% in oral, 12.1% in nasal.

Graph 5: Comparison of sedation score between the two groups at each time interval: (Mann-Whitney test)



Sedation scores achieved at 20mins in nasal group were high and statistically significant (P<0.001). Scores at 10 and 30 min though on higher side in nasal group, were not statistically significant when compared to oral group(mean values of nasal group at 10, 20, 30 min were 2.94, 4.06, 4.33 and mean values of oral group at 10, 20, 30 min were 2.88, 3.48,4.06 respectively).

Graph 6: Comparison of anxiety score between the two groups at each time interval: (Mann-Whitney test)



At all intervals anxiety scores were higher in nasal group but at 20 min, anxiety scores were found to be statistically significant in nasal group. (P<0.01).(mean values of nasal and oral at 10, 20, 30 min were 2.67,3.55,3.85 and 2.55,3.18,3.67 respectively)

Table 2: Comparison of parental separation score between the two groups at each time interval: (Mann-Whitney test)

Group	Mean	Stddev	SE of Mean	Mean Difference	z	P-Value
Oral	3.15	0.51	0.09	-0.242	-1.848	0.065
Nasal	3.39	0.61	0.11			

Higher mean parental separation score was found in nasal group compared to oral group but the difference between them was not statistically significant (P>0.05).

Discussion

Separation from the parents to a totally unknown operating room environment with unknown faces makes the operative experience traumatic for young children. Psychological stress because of forced separation from parents can cause nightmares and postoperative behavioral abnormalities. Preanesthetic medication may decrease the adverse psychological and physiological sequelae of induction of anesthesia in a distressed child.[9] Premedication not only comforts the anxious child, but also comforts the parents or the accompanying guardians.[10]

Despite efforts to disguise the bitter taste by mixing the parenteral formulation with the sweetening agents or juices, children occasionally spit or regurgitate the medication resulting in variation of bioavailability of the drug, when administered orally.[11]

Similar controversy existed in the literature regarding patient acceptance of intranasal midazolam (INM). Some authors have reported that the nasal route required less patient cooperation and was a simple, convenient, noninvasive, painless, and reliable alternative to oral drug administration.[12] Early approaches to the INM sedation used drops, but more recently use of an atomizer for intranasal administration has become more popular. The bioavailability with spray has been shown to be high (83%) with virtually complete absorption.[13] This high bioavailability led us to attempt this route of medication. Hence, in our study the atraumatic modes of administration of sedation were compared using the recent available INM atomizer spray and commercially available oral midazolam suspension.

The two groups were comparable in age, sex and weight distribution. In Group O there were 46% male and 63% female children with age ranging from 1-10 years (mean 6.12±2.84) and weight ranging from 5-20kgs. In Group N there were 54% male and 38% female children with age ranging from 1-10 years (mean 4.61±2.19) and weight ranging from 8-20kgs. Patients of either sex were randomly allotted to both the groups. These demographic data were in correlation with the data of Baldwa N[9] reports**.**

Children in nasal group did not show any adverse effects with INM atomizer spray at any point of observation which indicates safety of spray. Similar effects were observed in studies by Baldwa NM, et al(2012),[9] Lane RD(2008),[14] Mathai A. et al(2011),[15] and Klein EJ et al(2011).[16]

Children in oral group also did not show any adverse effects of the drug at any point of observation indicating safety of oral midazolam suspension. McMillan CO (1992),[4] Weldon C et al (1992), [8] Rosenberg M. et al (2000)[17] and Koppal R.et al (2011)[10] also reported no adverse effects of the drug. So from the present study it can be concluded that the use of INM atomizer spary and the oral midazolam suspension are safe to be used for premedication in pediatric patients.

The parameters: SBP and DBP were found to be higher in oral compared to nasal group at all-time intervals. This may be attributed to more potent action of INM atomizer spray leading to more intense sedation and anxiolytic effect as compared to oral syrup. The above observation of our study are in accordance with Kumar N.et al (2012),[18] and Al-Rakaf H.et al (2001)[19] research

There was no difference between SpO_2 readings in both the groups and saturation level did not drop below 97% of saturation at any time interval; this may be because of minimal respiratory depressant action of midazolam in oral and nasal route indicating safety of the drug. But few of the reports by Malinovsky JM.et al[20] and Fakuta O et al[21] observed minor respiratory depression in their study popula Twersky RS[22] used the atomizer DeVilbiss to deliver 0.2 mg/kg but did not mention acceptability.

In the present study we used the INM atomizer spray that is commercially available and delivers 0.5 mg per metered dose of midazolam and the children showed less drug acceptability of (87.9%) with INM spray, these present scores correlates to scores of Baldwa NM, et al(2012), Kumar N.et al(2012), Klein EJ (2011) and Griffith N. et al(1998)[9,18,16,23] who observed non acceptability of the drug in 76.6%, 60%, 74% and 87.5% respectively in their results. Ljungman[24] reported nasal discomfort in children (45%) and it was the principal reason for dropouts in their study. Mathai A. et al[15] also noted discomfort and stinging sensation in most of the children in their study.

But in contrast with our study Verma RK et al (2012),[13] reported 18 (60%) children accepted the drug in the nasal spray.

The reason for less drug acceptability by INM atomizer spray in our study can be attributed to midazolam, which is available in a hydrophilic vehicle with an acidic pH(3.5). Secretions from nasal irritation may also alter absorption. Transmucosal absorption depends upon the physical and chemical properties of the drugs. Absorption would be better if a more concentrated midazolam in a lipophilic vehicle with a neutral pH were to become available.[19]

In the present study we used the commercially available oral midazolam suspension in the dose of 0.5 mg per kg. Children showed good drug acceptability of (90.9%).These scores of our study mimic the results of Sheta SA (2009), Cote CJ.et al (2002), Pandit U. et al (2000)[25,26,27] who noted 100%, 95%, 95%, 100% scores respectively, which were similar to acceptance scores in the present study. Good acceptability in oral group in our study may be because of atraumatic method of administration and better taste.

Comparison of oral and nasal drug acceptability in the present study showed 90.9% in oral and 12.1% in nasal group. Higher mean drug acceptability score was recorded in oral group compared to nasal group and the difference between them was found to be statistically significant. Similar conclusion were observed in Koppal R.et al(2011)[10] and Alex S.et al(2008)[28] reports.

The increase in mean sedation score in nasal group was found to be statistically significant from 10 mins (2.94) to 20 mins (4.06) as well as from 10 mins to 30 mins (4.33) ($P<0.001$). At 30 mins 87.8% of children had satisfactory sedation. Our results were in concurrent with results of Koppal R.et al (2011)[10] with mean sedation score of 4.63 and 4.00 in Alex S.et al (2008)[28]. Baldwa NM, et al (2012) and Kumar N.et

al(2012)[9,18] noted 76% and 82%. A Study by Al-Rakaf H et al (2001)[19] reported satisfactory sedation in 96% children. In contrary to our study and other reports Verma RK.et al(2012)[13] noted 53.3% sedation.

The increase in mean sedation score in oral group was found to be statistically significant from 10 mins (2.88) to 20mins (3.48)as well as from 10 mins to 30 mins(4.06) (P<0.001). At 30 mins 87.8% of children had satisfactory sedation. Our scores were in accordance with reports of Rosenberg M. (2000) 92.6%, Weldon BC (1992) 96%, Cote CJ (2002)97% and Feld LH (1990) 89% of sedation.[17,8,26,1] Alex S.et al (2008)[28] reported similar mean of 3.86±0.5. But McMillan CO (1992)[4] noted lesser sedation score of 35% which was in contrary to our sedation scores.

According to our results higher mean sedation score in nasal group was noted compared to oral group but the difference between them was not statistically significant (P>0.05). Studies by Koppal R et al (2011)[10] and Alex S.et al (2008)[28] also reported higher mean sedation score in nasal group similar to the results of our study.

A faster onset of sedation in the nasal group was due to a rapid and nearly complete absorption of the drug, owing to the rich blood supply of the nasal mucosa and the nose brain pathway through the olfactory mucosa into the CSF. The effective delivering of the drug through the atomiser in the form of droplets which measure 30 –100 micron in size, helps in a larger dispersion of the drug over the mucosa and hence results in better absorption. As midazolam has a high hepatic clearance, and as the transnasal route avoids first pass hepatic metabolism, a greater systemic bioavailability can be achieved, unlike the oral route.[28]

The increase in mean anxiety score in nasal group was found to be statistically significant from 10 mins (2.67) to 20 mins (3.55) as well as from 10 mins to 30 mins (3.85) (P<0.001). Our scores were in accordance with Alex S.et al (2008)[28] mean score of 3.16±46. Davis PJ et al[29] also are of the opinion that nasal midazolam provides satisfactory anxiolysis without delaying the anaesthetic and hospital recovery times.

The increase in mean anxiety score in oral group was found to be statistically significant from 10 mins (2.67) to 20 mins (3.55) as well as from 10 mins to 30 mins (3.85) (P<0.001). The reports of Alex S.et al (2008)[31] also noted scores of 3.2±0.4 similar to our repots. McMillan CO (1992)[4] 90% had similar scores as our study.

So in our study slight higher mean anxiety score was recorded in nasal group compared to oral group, the difference between them was not significant. Our observations are in accordance with comparative studies of Alex S.et al (2008)[28] and Connors K and Terndrup TE (1994),[30] and found no significant difference between them.

Mean parental separation score 0.11 was found in nasal group. A total of 93.9% children had good parental separation in nasal group. Koppal R et al(2011), Baldwa NM et al (2012) 73.3%, Kumar N et al (2012) 85%[10,9,18]. A highest score of 100% was shown in Alex S.et al (2008)[28] study.

In the present study the mean parental separation score of 0.9 was found in oral group. A total of 93.9% children had good parental separation in oral group. The present scores were in accordance with results of Cote CJ (2002)96.4%, Pandit U.et al (2000) 95%, McMillan CO (1992)90%, Weldon BC (1992) 89% and Feld LH (1990) 79%.[26,27,4,8,1] A highest score of 100% was shown in Alex S.et al (2008)[28] study.

Higher mean parental separation score was found in nasal group compared to oral group but the difference between them was not statistically significant (P>0.05) our results are in accordance with the reports of Koppal R.et al (2011)[10] and Alex S.et al (2008).[28]

Limitations of the present study were, the age range could have been lesser upto 1-6yrs, as the age of the children increased the dose of intranasal drug administration increased leading repeated sprays which caused more discomfort and our facility did not include specifically equipped child area.

Conclusion

From our study we observed that commercially available INM atomizer spray and oral midazolam formulation for preanaesthetic medication were relatively safe and easy to administer. No serious complications were encountered with either method.

So we recommend the routine use of both the intra-nasal atomizers and oral midazolam as a safe pre-anaesthetic medication in paediatric patients who undergo surgical procedures. The INM atomized spray produced faster sedation, anxiolytic and separation scores as compared to oral syrup, leading to more cooperation of the children facilitating smooth induction. Hence INM atomizer spray can be preferred over oral midazolam syrup.

However, its use may be limited by nasal discomfort which can be attributed to acidic pH(3.34). A more concentrated INM spray with lipophilic vehicle and neutral pH would improve its acceptability. Further research to formulate such drugs with less nasal irritation may lead to a paradigm shift in the practice of premedicating the children.

References

1. Feld LH, Negus JB, White PF. Oral midazolam preanaesthetic medication in paediatric out patients. Anaesthesiology; 1990;73:831-34.
2. Bhakta P, Ghosh BR, Roy M, Mukherjee G. Evaluation of intranasal premedication for preanasthetic sedation in paediatric patients. Indian J Anaesth 2007;51(2):111-16.
3. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative Anxiety in Children; Predictors and Outcomes. Arch Pediatr Adolesc Med. 1996;150:1238-45.

4. McMillan CO, Spahr-Schopfer LA, Sikich N, Hartley E, Lerman J. Premedication of children with oral moidazolam. Can J Anaesth,1992;39(6):545-50.
5. White PF. Pharmacologic and Clinical Aspects of Preoperative Medication. Review Article. Anesth Analg 1986;65;963-74.
6. Wilton NCT, Leigh J, Rosen DR, Pandit UA. Preanaesthetic sedation of preschool children using intra nasal midazolam. Anaesthesiology 1988;69:972-75.
7. Karl HW, Rosenberges JL, Larach MG. Transmucosal administration of midazolam for premedication of paediatric patients. Anaesthesiology 1993;78:885-91.
8. Weldon BC, Watcha MF, White PF. Oral Midazolam in Children: Effect of Time and Adjunctive Therapy. Anesth Analg 1992;75: 51-55.
9. Baldwa NM, Padvi AV, Dave NM, Garasia MB. Atomised intranasal midazolam spray as premedication in pediatric patients: comparison between two doses of 0.2 and 0.3 mg/kg. J Anesth 2012;26:346–50.
10. Koppal R, Adarsh ES, Ambi U, AnilKumar G. Comparison of the midazolam transnasal Atomizer and oral midazolam for sedative premedication in paediatric cases. JCDR 2011;5(5):932-34.
11. Brosius KK, Bannister CF. Midazolam Premedication in Children: A Comparison of Two Oral Dosage Formulations on Sedation Score and Plasma Midazolam Levels. Anesth Analg 2003;96:392–95.
12. Primosch RE, Guelmann M. Comparison of Drops Versus Spray Administration of Intranasal Midazolam in Two- and Three-year-old Children for Dental Sedation. Pediatric Dentistry 2005;27(5):401-8.
13. Verma RK, Paswan A, Anisa De, Gupta S. Premedication with Midazolam Nasal pray: An Alternative to Oral Midazolam in Children. Anesth Pain. 2012;1(4):248- 51.
14. Lane RD, Schunk JE. Atomized intranasal Midazolam Use for Minor Procedures in the Pediatric Emergency Department. Pediatric Emergency Care 2008;24(5):300-3.
15. Mathai A, Nazareth M, Raju RS. Preanesthetic sedation of preschool children: Comparision of intranasal midazolam versus oral promethazine. Anaesthesia eassays and researches2011;5(1):67-71.
16. Klein EJ, Brown JC, Kobayashi A, Osincup D, Seidel K. A Randomized Clinical Trial Comparing Oral, Aerosolized Intranasal, and Aerosolized buccal Midazolam. Ann Emerg Med. 2011 Jun 18.
17. Rosenberg M, Norris L H. Oral Midazolam Syrup as a Safe Sedative for Pediatric Dentistry. Dental News 2000; Vol VII(III).
18. Kumar N, Sharma R, Sharma M, Verma I, Sharma M. Pre-medication in Paediatrics: Comparison of the Intranasal and Sublingual Routes by Using an Atomizer Spray. JCDR. 2012 February, Vol-6(1): 65-68.
19. Al-Rakaf H, Bello LL, Turkustani A, Adenubi JO. Intra-nasal midazolam in conscious sedation of young paediatric dental patients. International Journal of Paediatric Dentistry 2001;11:33-40.
20. Malinovsky JM, Populaire C, Cozian A. Effects of intranasal, rectal and oral routes on plasma midazolam concentrations. Anaesthesia 1995;50:351-54.
21. Fukuta O, Braham RL, Yanase H. Intranasal administration of midazolam: Pharmacokinetic and pharmacodynamic properties and sedative potential. J Dent child 1997;64:89-98.
22. Twersky RS, Hartung J, Berger BJ, McCain J, Beaton C. Midazolam enhances anterograde but not retrograde amnesia in paediatric patients. Anesthesiology 1993;78:51-55.
23. Griffith N, Howell S, Mason DG. Intranasal midazolam for premedication of children undergoing day-case anaesthesia: comparison of two delivery with assessment of intra-observer variability. British Journal of Anaesthesia 1998;81:865-69.
24. Ljungman G, Krueger A, Andreasson S. Midazolam spray reduces procedural anxiety in children. Pediatrics 2000;105:73-78. 1998;81:865-69.
25. Sheta SA, Al Sarheed M. OralMidazolam Premedication for Children Undergoing General Anaesthesia for Dental Care. International Journal of Pediatrics 2009;2:1-7.
26. Cote CJ, Cohen IT, Santhanam S, Rabb M, Rose J B, Weldon B C, et al. Comparison of Three Doses of a Commercially Prepared Oral Midazolam Syrup in Children. Anesth Analg 2002;94:37–43.
27. Pandit UA, Collier PJ, Malviya S, Lewis TV, Wagner D, Stewert MJ. Oral transmucosal midazolam premedication for preschool children. Can J Anaesth 2000;3:191-95.
28. Alex S, Coelho B, Ambareesha M. Comparision of Intranasal and Midazolam as Premedicant drug in Preschool Children. J Anaesth Clin Pharmacol 2008;24(3):333-36.
29. Davis PJ, Tome JA, McGowan FX, Cohen IT, Latta K, Felder H. Preanaesthetic medication with intranasal midazolam for brief pediatric surgical procedures. Anesthesiology 1995;82:2-5.
30. Connors K, Terndurp TE. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. Annals of emergency medicine 1994;24(6):1074-79.