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Evaluation of Intranasal Midazolam As Preanaesthetic Medication For Brief Pediatric Surgical Procedures

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ABSTRACT

BACKGROUND: *pain and anxiety symptoms are almost always undertreated due to concerns regarding the safety of administering sedatives and opioids. Pre-operative anxiety has many harmful effects on child's physiology and mental well being. Sedative premedications are more effective in this regard. The premedicant should be acceptable, rapid and reliable in onset with minimal adverse effects. Midazolam is a short acting benzodiazepine with rapid onset of action. The intranasal route avoids the need for painful I.V injection and I.V access. It can be administered easily.*

AIMS AND OBJECTIVES: *To evaluate the efficacy and safety of intranasal midazolam, also to study about Degree of sedation, Ease of separation from parents, Response to Venepuncture, Response to Induction/Mask placement, Post anesthesia recovery characteristics and Side effects.*

MATERIALS AND METHODS: *A prospective comparative study was conducted in the Department of anesthesia , Sri Venkateswara Medical College, Tirupati from June 2016 to May 2017. A total of 90 children patients aged between 3 - 6 years, of either sex belonging to ASA Grade I & II posted for elective surgeries were selected randomly and prospective study was done by dividing them into 3 groups. Group NS: Children received 0.04 mI/kg of Normal Saline ,Group M1:Children received 0.2mg/kg of intranasal midazolam, Group M2: Children received 0.3mg/kg of intranasal midazolam. The statistical software, namely SPSS 16.0 and WINKS SDA 6 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.*

RESULTS: *In all the three groups, the age, gender, weight & ASA physical status were comparable. At 5 minutes, in midazolam groups, the level of sedation was better in M1 than M2. At 10 minutes, separation from parents was much easier in both midazolam groups. Children in midazolam groups showed a satisfactory response to venepuncture than the children in normal saline group. At 15 minutes, the majority of the children in midazolam groups showed a favourable response to mask placement than the Normal Saline group. All the children were followed up for 24 hours for nasopharyngeal irritation, nasal congestion and bad taste was observed only in 3 children in M1 group, in M2 group 8 children had developed side effects. None had any complications in the saline group.*

CONCLUSION: T*he present study concludes that administration of preservative free intranasal midazolam in the dose of 0.2 mg/kg as premedication in paediatric patients produces satisfactory sedation.*

KEYWORDS: *INTRANASAL, MIDAZOLAM, SEDATION*

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I. Introduction

Surgery and Anesthesia induce considerable emotional stress upon children.[1] The consequences of this stress remain in the child's psyche long after the hospital experience has passed.[2,3] Although it is difficult to determine which component of *a* child's hospitalization experience results in psychological problems, age, parental anxiety level, previous hospital experiences and type of surgery are factors that can influence a child's anxiety level and mental well being.[2]

Pre-operative anxiety stimulates the Sympathetic, Parasympathetic and Endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability. Children aged two to five years are especially vulnerable to this problem since their understanding is limited.4 Preoperative anxiety in unpremedicated children is two fold.[5, 6] Hence all paediatric patients need to be premedicated in order to decrease preoperative anxiety.

Pharmacological agents are often helpful to provide sedation and smooth induction. Even parental presence inside the operation theatre may not be fully effective. Sedative premedication are more effective in this regard.[7]

The premedicant should be pleasant, acceptable, rapid and reliable in onset with little adverse effects. Many drugs have been tried for premedication in children. There is no single premedicant with all the ideal characteristics. It is rapidly absorbed and short-acting, having an elimination half-life of about 2 hours.

Oral, rectal, intravenous, intramuscular and sublingual routes for premedication have been tried. However, each route has its disadvantages. Owing to its high mucosal vascularity, pre-anesthetic medication administered nasally has a rapid and reliable onset of action. Avoidance of painful injection, ease of administration has made it a convenient way to pre-medicate children. The introduction of midazolam has provided us with a drug that can be pleasantly administered. It produces much tranquillity and does not unduly prolong recovery.

This study was designed to evaluate the efficacy of intranasal midazolam in children as pre-medication with two different doses in comparison with a placebo.

II. Materials And Methods

This study was designed to evaluate the following effects after intranasal midazolam Degree of sedation , Ease of separation from parents, Response to Venepuncture, post anaesthesia recovery characteristics, side effects. This study was conducted in Sri Venkateswara Medical College, Tirupati in Department of Anesthesia from June 2016 to May 2017.

After ethical committee clearance, a total of 90 patients aged between 3 - 6 years of either sex belonging to ASA Grade I & II posted for elective surgeries were selected randomly and prospective comparative study was done by dividing them into 3 groups. All the parents of the children undergoing the study were provided adequate information regarding the study to obtain informed consent. These patients were randomly assigned into three groups. Drugs were divided into two aliquots & given in both the nostrils using a INSED ATOMISER intranasal midazolam 5 mg /ml , [0.5 mg / metered dose].With the children sitting on the parent's lap, premedicant was administered 15 minutes before induction.

Group NS: Children received 0.04 mI/kg of Normal Saline

Group M1: Children received 0.2mg/kg of intranasal midazolam

Group M2: Children received 0.3mg/kg of intranasal midazolam

Patients with a history of allergy to study drug, nasal pathology, cardio-respiratory disorders were excluded from the study.

METHOD OF PREMEDICATION

A Preoperative visit was made on the day prior to planned surgery. Parents were explained about the concerned technique & informed consent taken. On the morning of surgery, Children were shifted along with one of the parents to the Preoperative holding room. Baseline vitals were recorded using Multichannel monitor before administration of the drug. In uncoperative children, monitors were connected after administration of the drug. With the children sitting on the parent's lap, the Saline/ drug administered by the anesthesiologist given equally in both nostrils.

Five minutes after administration of the drug / Saline the degree of sedation (Table no.1), Heart rate, Respiratory rate, Oxygen saturation, Blood Pressure were recorded.

At 10 minutes, children were separated from the parents & shifted to the operation theatre. Reaction to separation from parents was assessed (Table. no.2). IV Canulation attemped & response to Venepuncture recorded (Table no. 3) and appropriate monitors were connected. At 15 minutes, general anaesthesia was induced using N20, oxygen, Sevoflurane & response to mask placement assessed & recorded (Table no.4) .

Postoperative recovery score was assessed at 10, 20, 30 minutes on a ten point scale using the following parameters- color, airway, respiration, level of consciousness and movement of all the 4 limbs. (Table no.5)

Children were discharged from the PACU to the ward when they were awake, moving all the four limbs, with normal airway, adequate respiration, effective cough, Sp02 > 98% on room air with the PACU score of 10.

Post Operatively all the children were followed up for 24 hours for side effects & complication if any were noted.

METHOD OF STATISTICAL ANALYSIS:

The observed data was subjected to statistical analysis using Chi-Square test & Student t test. (independent)

STATISTICAL SOFTWARE:
The statistical software,namely SPSS 16.0 and WINKS SDA 6 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.

Table 1 – Grades of Sedation at 5 minutes

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

Table 2 – Parental separation score at 10 minutes

Behaviour of the child during separation from parents	Criteria	Score
Excellent	Patient unafraid, Cooperative or asleep	1
Good	Slight fear/crying, quite with reassurance	2
Fair	Moderate fear and crying not quiet with reassurance	3
Poor	Crying, need for restraint	4

III. Results

Distribution of Age In The Groups

TABLE -3

Group	N	Mean Age	Std. Deviation	Min	Max	"t" Value	"p" Value
M1	30	5.33	0.959	3	6		
M2	30	5.21	0.963	3	6		
NS	30	4.93	0.982	3	6		
Total	90	5.13	0.98	3	6	2.553	0.116

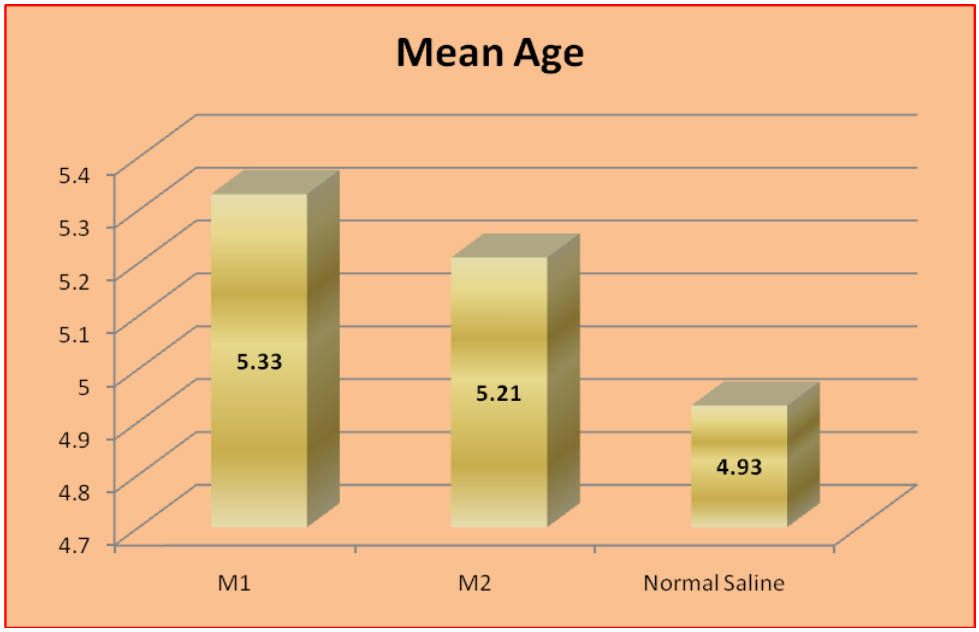

Fig 1 Mean Age Distribution of the study group

TABLE-3 and Fig 1 showing the age wise distribution in Group M1 , Group M2 & Group NS. It was observed that in all the groups, minimum age was 3 & maximum age was 6 years.

Distribution of weight in the groups

TABLE-4

	Group	N	Mean	Std. Deviation	Min	Max	"t" Value	"p" Value
Wt (in Kgs)	**M1**	30	15.17	3.715	8	25	0.16	0.691
	M2	30	15.52	3.862	8	28		
	Normal Saline	30	14.77	4.023	7	20		

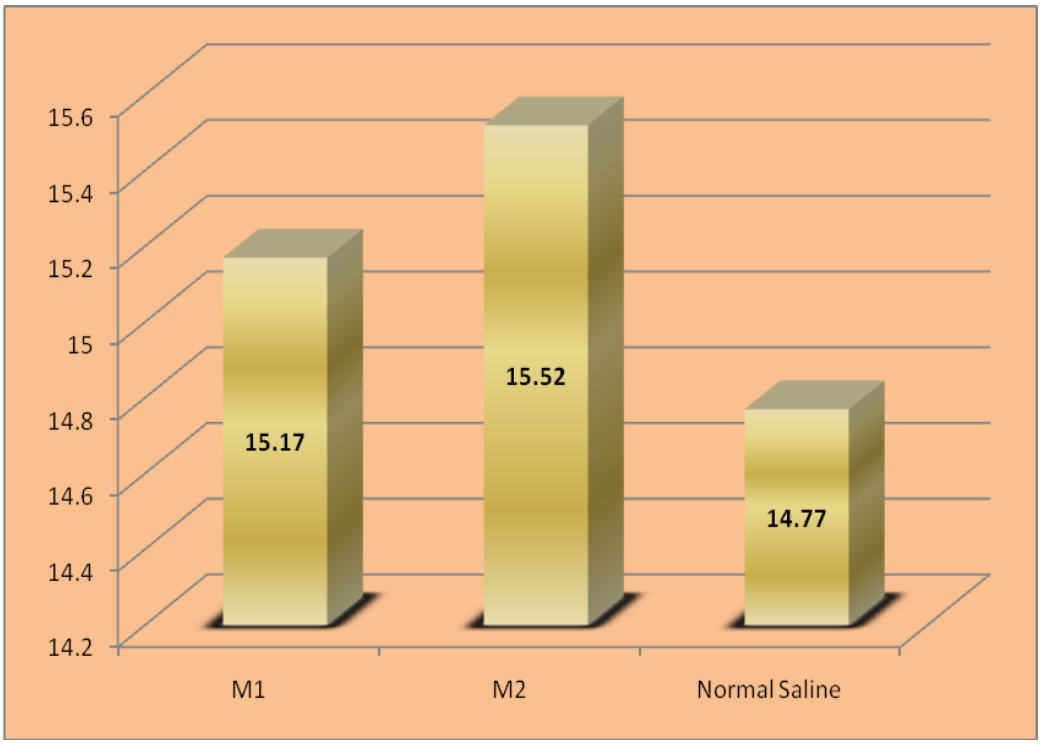

Fig : 2 Mean weight Distribution in the groups

TABLE 4 and Fig.2 showing the mean weight in the groups. Group M1 the minimum wt was 8 & and maximum was *25* kgs. Group M2 the minimum wt was 8 & and maximum was *28* kgs.

TABLE 5
SEDATION LEVEL AT 5 MIN AFTER PREMEDICATION

Sedation (before surgery)	Group		
	M1	M2	NS
Agitated	5	7	15
	16.70%	23.10%	50.05
Alert	12	10	12
	40.00%	33.30%	40.00%
Calm	10	8	3
	33.30%	26.60%	10.00%
Drowsy	2	2	0
	6.70%	6.70%	0%
Asleep	1	1	0
	3.33%	3.33%	0%
Total	30	30	30
	100%	100%	100%

	Chi- Square Value	df	p' Value
M1 – NS	11.7692	4	0.019
M2 – NS	8.3045	4	0.045
M1 – M2	0.6692	4	0.9551

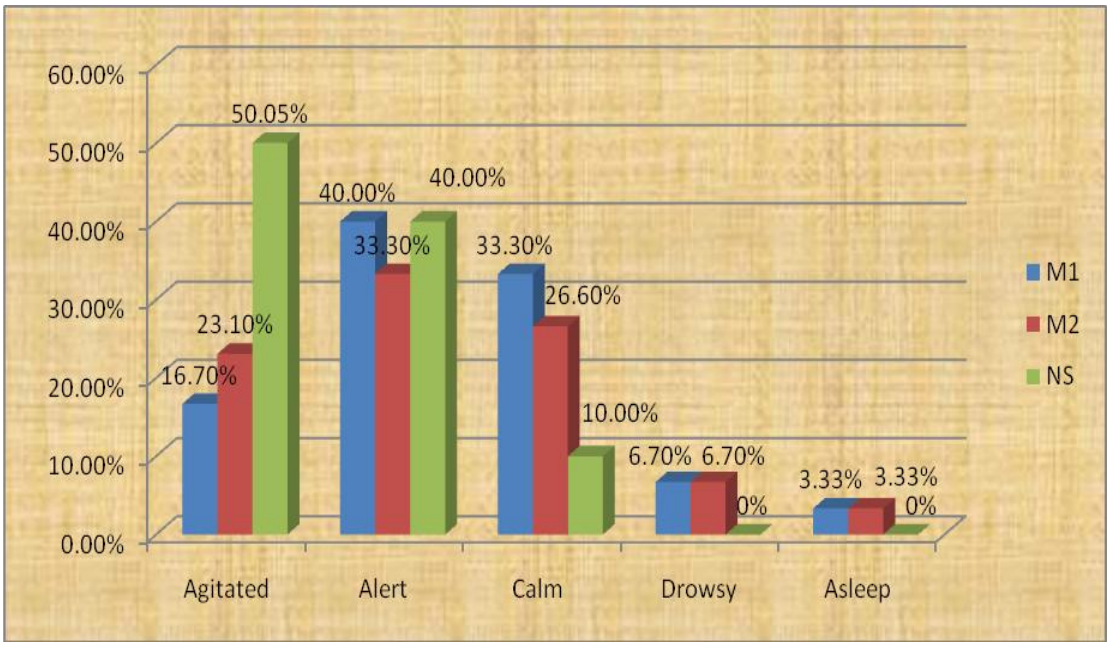

FIG- 3 SEDATION LEVEL AT 5 MIN AFTER PREMEDICATION

TABLE- 5 & FIG-3 shows the sedation level at *5* minutes was better in both midazolam groups than Saline group. When Comparing the Sedation Score in M1 group, majority *25* (83.3%) of the children were adequately sedated (ie. alert, calm, drowsy, asleep) in M2 group, majority *21* (70%) of the children were adequately sedated whereas in Normal Saline group, majority 15 *(50%)of* the children remain agitated.

TABLE-6
RESPONSE TO SEPARATION FROM PARENTS (AT 10 MINUTES)

Separation From Parents	**Group**			**Total**
	M1	**M2**	**NS**	
Excellent	12	10	0	22
	40.00%	33.30%	0%	24.4%
Good	15	12	4	31
	50.05%	40.00%	13.30%	33.3%
Fair	2	4	16	22
	6.70%	12.60%	53.30%	24.4%
Poor	1	4	10	15
	3.30%	12.60%	33.30%	16.6%
Total	30	30	30	90
	100%	100%	100%	100%

	Chi- Square Value	Df	p' Value
M1 – NS	36.621	3	<0.001
M2 – NS	23.7714	3	0.001
M1 – M2	2.9818	3	0.3943

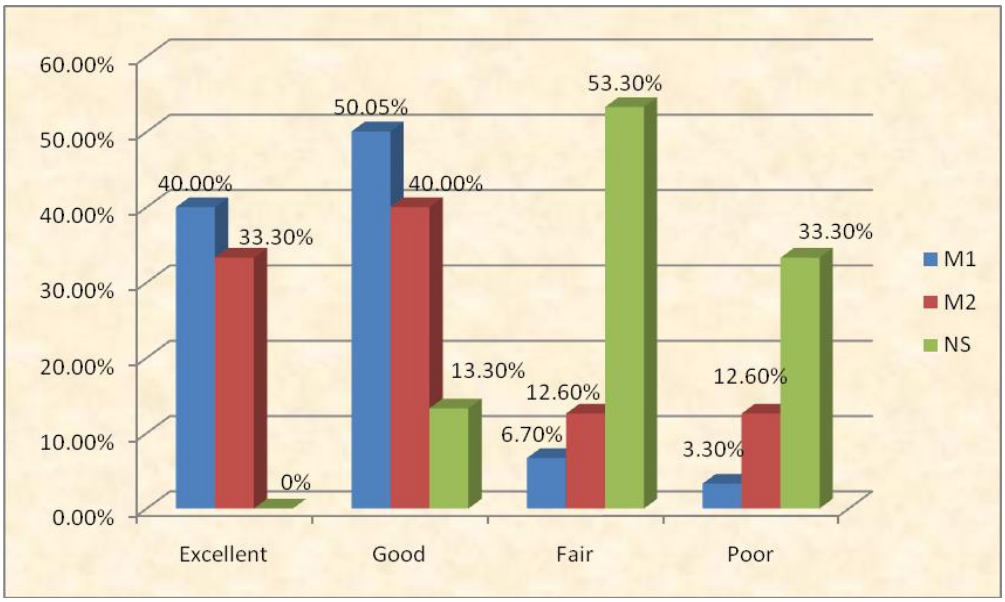

Fig 4 RESPONSE TO SEPARATION FROM PARENTS (AT 10 MINUTES)

Table: 6 fig:4 shows Separation from parents was much easier in Midazolam groups compared to Normal Saline group. In Midazolam groups, at the end of 10 minutes, it was found that in M1 27 (90%) & M2 22 (73.33%) Children were separated easily from Parents (grading being excellent & good) whereas in Normal Saline group, 26 (86 .6 %) children separation was not satisfactory (grading being *fair* & poor) needed further convincing and persuation.

Table: 7
Response To Venepuncture

Response To Venepuncture	Group			
	M1	M2	NS	Total
Satisfactory	21	15	7	43
	70%	50%	23.30%	47.78%
Unsatisfactory	9	15	23	47
	30%	50%	76.70%	52.22%
Total	100%	100%	100%	100%

	Chi- Square Value	Df	p' Value
M1 – NS	13.125	1	<0.001
M2 – NS	4.5933	1	0.0320
M1 – M2	2.500	1	0.1138

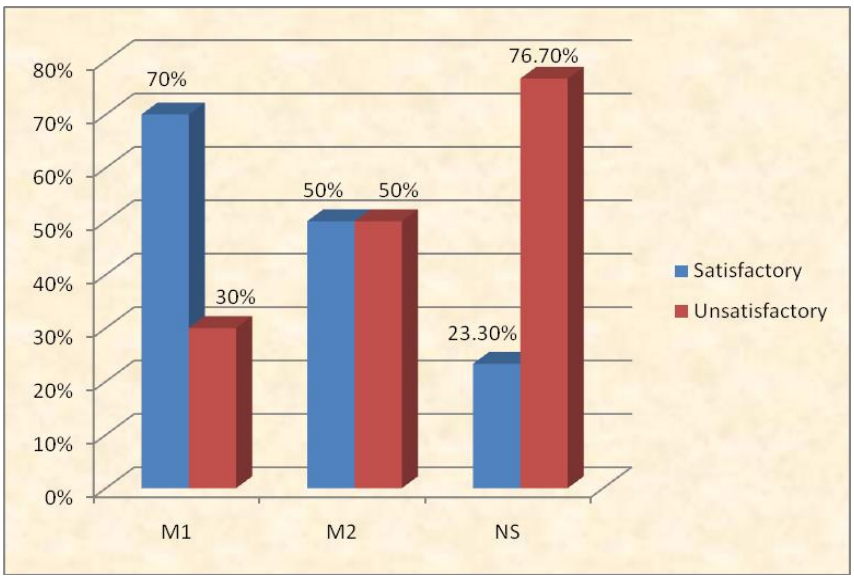

Fig: 5 Response To Venepuncture

Table : 7 and Fig: 5 shows that in M1 group, 21 (70%) children responded satisfactorily to Venepuncture, in M2 group15 (50 %) children responded satisfactorily to venepuncture. whereas in Normal Saline group, only 7 (23.3%) children responded satisfactorily. In M1 group, only 9 (30%) showed unsatisfactory response & in M2 group15 (50 %) children showed unsatisfactory response. In Normal Saline, in 23 (76.7%) children response was unsatisfactory.

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POST ANAESTHESIA RECOVERY SCORE AT 10 MINUTES

Group	Scores				
	6	7	8	9	10
M1	0	16	12	2	0
M2	0	12	10	4	0
NS	0	5	22	3	0

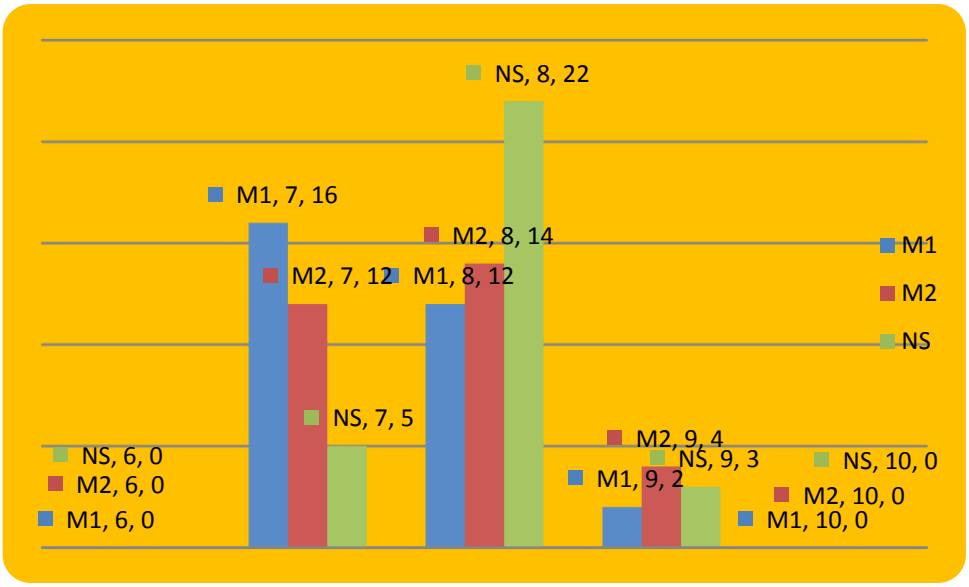

Fig -6 POST ANAESTHESIA RECOVERY SCORE AT 10 MINUTES

Table 8 & Fig -6 shows that at 10 minutes, minimum scores in both midazolam groups and NS was 7 and maximum score obtained was 9 in the three groups.

Table -9 SIDE EFFECTS

Group	Nasopharyngeal irritation		Nasal congestion		Bad taste	
	YES	NO	YES	NO	YES	NO
M 1	2	28	1	29	0	30
M2	4	26	1	29	3	27
NS	0	30	0	30	0	30

Table 9 shows the side effects observed in Midazolam groups and normal saline group. In M1 group only 3 had developed side effects, in M2 group 8 had developed side effects and in NS group none had side effects.

IV. Discussion

Conscious sedation is one of the most critical measures to help pediatric patients cooperate with the radiological imaging procedure. For this purpose, Midazolam is often used because its pharmacological properties are superior to other benzodiazepines (fast onset, better tissue compatibility, controllability of effect, short duration of action, short elimination half-life).

In the intranasal route, the desired effect can be achieved very fast, which is also confirmed in the present study. The bioavailability of intranasal Midazolam is very high and pharmacologically active metabolite is not formed in significant amount. The recovery is even faster, which has been proved again in the present study. No additional benefit was observed by increasing the dose to 0.3 mg/kg. This finding is again corroborating with earlier studies.

Sedation

In the present study, at the end of 5 minutes after premedication it was observed that in Groups M1 and M2 majority of children 25 (83.3%) and 21 (70%) respectively had satisfactory higher level of sedation (sedation level 2, 3, 4, *5)* and only 5 *(* 16.7%) in M1 and 9 (30%) in M2 were agitated whereas in NS group 15 (50%) were agitated, and the remaining 15 *(*50%) had lower level of sedation (sedation level 2 ,3 ,4 ,5*)* with p value being 0.019 between M1 and NS ; 0.045 between M2 and NS which are statistically significant.

Manjushree Roy et al. compared 2 doses of intranasal Midazolam with that of NS and concluded that majority of the children in Midazolam group had significant level sedation at 5 minutes with 0.2mg/kg and delayed onset of sedation at 10 minutes with 0.3mg/kg.8

From the present study, it is observed that intranasal Midazolam 0.2 mg/kg produces a significant level of sedation at 5 minutes after administration.

Results of the present study are consistent with the those studies done by Manjushree roy etal8 weber etal9 wilton etal10 with regard to satisfactory level of sedation at *5* minutes after intranasal Midazolam

Ease of parental separation

At 10 minutes after administration of the drug, the behaviour of the children to parental separation was studied. In midazolam groups, it was found that in M1 27 (90%) & M2 22 (73.33%) Children were separated easily from Parents (grading being excellent & good) and in M1 3 (10%), in M2 8 (26.6%) patients it was poor to fair. Whereas in the NS group only 4 (13 .3%) children were good and the rest 26 (86.6%) were poor to fair with p-value <0.001, which is very highly significant.

Children in the Midazolam group could be easily separated from the parents compared to the children in the saline group.

A study done by Karl et al11 Showed that Children in the intranasal group showed decreased anxiety. Wilton et al showed that was observed that parental separation was easy in both the doses of intranasal Midazolam at 10 minutes after administration of the premedication.[10]

Result of the present study is similar to that of the above- mentioned studies with respect to ease of Parental separation. Parental separation in Midazolam group was more comfortable due to the early onset of sedation.

Response to Venepuncture:

In M1 group 21 (70%) showed satisfactory response to venepuncture and the remaining 9 (30%) showed unsatisfactory response. In M2 group15 (50%) children responded satisfactorily to venepuncture and the remaining 15 (50%) children showed unsatisfactory response. In NS group 7 (23.3%) children showed a satisfactory response, the remaining 23(76.7%) showed an unsatisfactory response, with a p-value of 0.001, which is statistically, very highly significant between M1- NS groups. P-value of 0.032, which is statistically, significant between M2- NS groups.

Asif Pervez kazerni et al12 conducted a study on intranasal Midazolam, IM ketamine and NS and found intranasal Midazolam showed satisfactory response to venepuncture. The reason for satisfactory demeanour to venepuncture is higher mean plasma midazolam concentration.[13]

Hence it is concluded that Midazolam reduces the discomfort associated with venepunctue due to higher mean plasma concentration.

Ease of induction:

At 15minutes after premedication, the ease of induction in terms of mask acceptance was observed. In both midazolam groups, all the 60 (100%) children had a satisfactory response to mask placement whereas in NS group 15 *(*50%) were agitated, and the remaining 15 *(*50%) showed adequate response to masking placement. The p-value being < 0.001, which is statistically very highly significant.

The results of this study correlate with the reviews of Davis et al, Wilton et al10, Karl. et al[11] and Manjushree Roy et al[8].

Postanesthesia recovery characteristics

Children received in PACU, were administered oxygen through a face mask for an adequate period. NIBP, Spo2 and HR were monitored using Philips MP 20 Multichannel monitor. Post anesthesia recovery characteristics were assessed at 10 minutes interval of 30 minutes by the following parameters –

Colour, Airway, Level of consciousness, Movement of all four limbs and Respiration.

Children were considered fit for discharge from PACU, at a score of 10; that is When the children were conscious, colour pink, no obstruction in the airway, able to breathe deeply and cough freely, able to move 4 limbs freely, Spo2> 98% on room air. At 10 minutes, it was observed that the minimum score was 7, and the maximum score was 9 in all the groups.

At 20 minutes the minimum score was 8 in both midazolam groups and 9 in normal saline. At 30 minutes all the2 children in both the groups had a score of 10 and were fit for discharge to the wards. No significant changes were observed in NIBP, Heart rate during this period. All the children were followed up for a period of 24 hours.

Wilton et al. concluded that there was no difference in the recovery room score between those patients receiving normal saline and those receiving Midazolam. [10]

Manjushree Roy et al found that there was no evidence of delayed recovery in two doses of Midazolam. Postoperative recovery room score was comparable in normal saline and 2 doses of Midazolam.[8] This study concurs with that of Wilton et al, Manjushree Roy et al.

Side effects

Postoperatively all the children were followed up for 24 hours for side effects & complications. In the present study in the M1 group only 3 had developed side effects, in M2 group 8 had developed side effects. No side effects were observed in the saline group. The side effects observed in Midazolam group : nasal congestion, nasal irritation, bad taste.

Daniel P.Wermeling observed eyes watering, dizziness, bad taste, nasal congestion, nasopharyngeal irritation in the intranasal route.[14] Similar side effects observed in the present study.

V. Conclusion

On the basis of the present study it is concluded that administration of preservative free intranasal Midazolam in the dose of 0.2 mg/kg as premedication in pediatric patient produces satisfactory sedation.

Advantages are

1. Better sedation and rapid onset of action.
2. Ease of separation from parents
3. Decreased discomfort associated with IV cannulation
4. Better mask acceptance
5. Recovery time not prolonged
6. Minimal side effects

After considering all the parameters from this study it is concluded that intranasal midazolam 0.2 mg/kg as premedication provides effective sedation in paediatric patients of 3 -6 yrs without any untoward side effects. No nausea and vomiting were seen in the oral group.

Midazolam in the intranasal route produces nasal irritation because of the acidic PH. This drawback can he overcome by the use of the drug in the form of nasal spray or solution of Midazolam in cyclodextrin, which results in less acidic PH. However, more studies on a larger sample of paediatric population are needed for further evaluation.

References

[1]. Steward D.J preoperative evaluation and preparation for surgery. Ind: Pediatric 4 edition Churchill livingstone New York 2002.
[2]. Rosenberg H, Goldberg M, postoperative emotional responses. Complications in anesthesiology. 2nd edition. Lippincot.Raven publishers. Philadelphia 1996.
[3]. Dupuytren B. clinical lectures of surgery. Lancet 2:919, 1834.
[4]. Weksler N, Ovadia Muati G, et al. Nasal ketamine for pediatric premedication. Can J Anesth 1993 ; 40: 119 – 21
[5]. Savage GH. Insanity following the use of anesthetics in operations .BMJ 1887; 2:1199.
[6]. Eckenhoff JE. Relatioship of anesthesia to post operative personality Changes in children. Am J Dis child 1951; 86 : 587.
[7]. Rita L, Selemy FL et al. Ketamine hydrochloride for pediatric premedication: comparison to pentazocin. Anesth Analg 1974 *;* 53 : 375.
[8]. Manjushree Roy, Pradipta Bhakta et al. Evaluation of intranasal midazolam as preanaesthetic sedation in paediatric patients. Indian J Anaesth 2007; 51(2) :111-116.
[9]. Frank Weber MD, Hinnerk Wuif MD, Ghada el saeidi MD.Premedication with nasal S-Ketamine and midazolam provides good conditions for induction of anaesthesia in preschool children. Can J Anesth 2003 ; 50(5) : 470-475.
[10]. Niall C.T. Wilton et al. Preanaesthetic sedation of preschool children using intranasal Midazolam. Anesthesiology 1988; 69 : 972-75.
[11]. Helen W Karl, James L.Rosenberger, Marilyn G.Larach, et al.Transmucosal admirnistration of midazolam for premedication of paediatric patients. Anaesthesiology 1993 May: 78 : 885 - 891.
[12]. Asif Pervez Kazemi, Hamid Kamalipour, Mehrdad siddighi. Comparison of intranasal midazolam versus ketamine as premedication in 2-5 yrs old paediatric surgery patients. Pak J Med Sci 2005october- December; 2 1(4):460-64.
[13]. J.M.Malinovsky, Populaire, C. Cozien A et al. Premedication with midazolam in children. Effect of intranasal, rectal, oral routes on plasma midazolam concentrations . Anaesthesia 1995; 50 (4) : 351-354.
[14]. Daniel P. wermeling, Kenneth A, Thomas H et al. pharmacokinetics and pharmacodynamics of a new intranasal midazolam and formulation in healthy volunteers. Anaesth Anaig 2006; 103 : 344- 9.