Original Article

Comparative Study of Intranasal Midazolam and Intravenous Diazepam Sedation for Procedures and Seizures

Pankaj Mittal, Ram Manohar and A.K. Rawat

Department of Pediatrics, S.S. Medical College and G.M. Hospital, Rewa (M.P.)

ABSTRACT

Objective. To evaluate the safety and efficacy of intranasal midazolam for seizures and various procedures.

Methods. Prospective randomized study. Total 125 children of all ages of either sex, for seizure episode (n-76) and various invasive and non-invasive procedures (n-49) received either intranasal midazolam (0.2 mg/Kg) or intravenous diazepam (0.3 mg/Kg)

Results. Mean time from arrival at hospital to starting treatment was significantly shorter in midazolam group compared to diazepam group [2.34±0.90; minute *vs* 4.61±1.08 minute p<0.001]. Mean time to control seizures after arrival in hospital was significantly shorter in midazolam group compared to diazepam group [5.25±0.86 minute *vs* 6.51±1.06 minute p< 0.001].

Conclusion. Midazolam by the intranasal route provides safe and equally effective non-invasive method of sedation for procedures and seizures. **[Indian J Pediatr 2006; 73 (11) : 975-978]** *E-mail - drakrawat01@rediffmail.com*

Key words : *Intravenous diazepam; Intranasal midazolam; Procedures, Seizures.*

The sedation modalities for procedures and seizures in children have advacned substantially in the past 15 years. Procedural sedation is a technique of administering a sedative or dissociative agent, with or without analgesic to induce a state that allow the patient to tolerate unpleasant procedures with maintained airway independently and continuously.[1] Benzodiazepines are commonly used drug for sedation and can be given by various routes like intravenous, intranasal, per-rectal and sublingual route. Disadvantage of these routes includes: training and painful administration (I.M. and I.V.), slow and variable absorption (oral and per-rectal), and delayed recovery (oral route). Drugs sprayed/instilled into the olfactory mucosa are rapidly absorbed by the (a) olfactory neurons (b) supporting cells and surrounding capillary bed into cerebrospinal fluid and reach the systemic circulation[2,3]. Midazolam has been used by the intranasal route for echocardiography in outpatient setting[4] and as an effective premedication in young children undergoing short surgical procedures. The present study was undertaken to assess the efficacy and safety of intranasal midazolam as a sedative in pediatric procedures and seizures.

Correspondence and Reprint requests : Dr. A.K. Rawat, D-2 , Doctor's Colony, Rewa (M.P.) 486001. Fax No. 07662- 251167; Phone No. 07662 -256785.

MATERIALS AND METHODS

Study design is prospective hospital based and randomized, conducted from July 2003 to August 2004 in pediatric department of S.S. Medical College and Associated Gandhi Memorial Hospital, Rewa (M.P.). Prior to procedure, written consent from parents was obtained and they were encouraged to stay with the child during the procedure. The inclusion criteria were children of all ages and both sexes brought during seizure episodes or required therapeutic and diagnostic procedures. Commercially available intravenous preparation of midazolam was administered in dose of 0.2 mg/Kg as drops, half in each nostril by one or two ml syringe from which needle had been removed. Diazepam was administered after inserting an appropriate size of IV cannula in the dose of 0.3 mg/Kg after dilution. Sedation level was noted before and ten minutes after giving drugs, by the scale described by Wilton NCT, Leigh Rozen and Pandit U.[5] Heart rate, respiratory rate and oxygen

saturation were noted before and ten minutes after giving drugs. Major negative behaviors during procedures were evaluated by a modified observation behaviour rating scale. Lignocaine (2%) after sensitivity testing was used as a local anaesthetic for invasive procedures. Duration from arrival of patient in hospital to starting treatment and cessation of seizure were recorded. All patients were monitored until score one or two of sedation. Resuscitation kit (Ambu bag, laryngoscope endotracheal tube, suction catheter, oxygen source and emergency drugs) were kept ready. The data generated was tabulated and statistically analyzed, using student 't' test for continuous data and Chi-square test for categorical data.

RESULTS

Total 125 children were enrolled for seizure episodes (n-76) and for various invasive and noninvasive procedures (n-49). The difference in mean age of children in procedures and seizures was found to be statistically insignificant (p>0.05) between midazolam and diazepam groups. Youngest patient in whom a procedure was performed was 11-day-old and who had seizures was 6-day-old. There was a male preponderance of patients in both procedures (65.3%) and seizures (63.2%). Mean weight of children requiring sedation for procedure and seizures for midazolam and diazepam group was comparable. Minimum weight was 2.5 Kg in procedures and 2 Kg. in seizures group of patients. Maximum weight of 30 Kg was recorded for both procedure and seizure. Twenty five percent of patients (19 out of 76) were afebrile during seizure episode. Maximum temperature recorded was 40.5°C. Mean temperature of febrile patients was comparable in two groups.

Difference in score of sedation before and after giving drug between IV-D and IN-M was found to be insignificant ($\chi 2 = 0.15$ and $\chi 2 = 5.63$; $p > 0.05$) (Table 1). There was no significant difference observed in cry, physical restraint and motor score between IN-M and IV-D during invasive procedures. ($\chi 2 = 0.01$, $\chi 2 = 0.01$, $\chi 2 = 0.79$ $p>0.05$). Similarly in the non-invasive procedure group no significant difference was observed between two drugs for cry, physical restraint and motor score. ($\chi 2 = 0.02$, $\chi 2 = 0.03$, $\chi 2 = 0.03$; $p>0.05$) (Table 2).

Although in the intranasal midazolam group, time to

Table 1. Score of Sedation Before and After Giving the Drugs in Procedures

Score of Sedation	IN-Midazolam (n-27)		IV-Diazepam (n-22)		
	Before Drug	After Drug	Before Drug	After Drug	
I (Agitated)	15 (55.55%)	0	11 (50.0%)	0	P>0.05
II (Alert)	12 (44.45%)	2 (7.41%)	11 (50%)	0	P>0.05
III (Calm)	0	4 (14.81%)	0	2 (9.1%)	P>0.05
IV (Drowsy)	0	21 (77.78%)	0	17 (77.27%)	P>0.05
V (Asleep)	0	0	0	3 (13.63%)	P>0.05

- Sedation Score before giving intranasal Midazolam and intravenous Diazepam $\chi^2 = 0.15$ p>0.05
- Sedation Score after giving intranasal Midazolam and intravenous Diazepam $\chi^2 = 5.63$ p>0.05

Table 2. Behaviour During Invasive and Non-invasive Procedures According to Drug Used

	Score	Invasive (n-25)		Non-Invasive (n-24)	
		Midazolam (n-14)	Diazepam (n-11)	Midazolam (n-13)	Diazepam (n-11)
Cry Score	I (Whimper)	10 (71.4%)	8 (72.7%)	12 (92.3%)	10 (90.9%)
	II (Cry)	4 (28.6%)	3 (27.3%)	1 (7.7%)	1 (9.1%)
	III (Scream)	0	0	0	0
		χ^2=0.01* P>0.05		χ^2=0.02* P>0.05	
Physical Restraint	I (Minimal)	9 (64.3%)	7 (63.6%)	11 (84.6%)	9 (81.8%)
	II (Moderate)	5 (35.7%)	4 (36.4%)	2 (15.4%)	2 (18.2%)
	III (Maximal)	0	0	0	0
		$\chi 2$ = 0.01* P>0.05		$\chi 2$ = 0.03* P>0.05	
Motor Score	I (Squirmish)	8 (57.1%)	5 (45.4%)	11 (84.6%)	9 (81.8%)
	II (Kicking)	5 (35.7%)	4 (36.4%)	2 (15.4%)	2 (18.2%)
	III (Flail)	1 (7.2%)	2 (18.2%)	0	0
		*$\chi 2$ = 0.79** *$\chi 2$ = 0.03**		P>0.05 P>0.05	

*P> 0.05 Insignificant

There is no significant difference observed in the behaivor score between IN-M and IV-D during invasive and non-invasive procedures

TABLE 3. Duration of time intervals (in minutes) for giving drugs, seizure control, and response to treatment in study groups (values are Mean±S.D. and 95% confidence interval)

	IN-Midazolam	IV-Diazepam
Time to giving drug after arrival in hospital	2.34±0.90 (4.26 to 4.96)	4.61±1.08 (2.06 to 2.62)
Time to cessation of seizures after giving drug	2.97±0.53 (1.77 to 2.07)	1.92±0.45 (2.81 to 3.13)
Time to cessation of seizures after arrival in hospital	5.25±0.86 (6.16 to 6.86)	6.51±1.06 (4.98 to 5.52)
P<0.001 Highly Significant for all groups		

cessation of seizures after giving drug was longer in comparison to intravenous diazepam (2.97±0.53 *vs* 1.92±0.45 minute) the time to cessation of seizures after arrival in hospital was significantly shorter with IN-M than IV-D (5.25±0.86 *vs* 6.51±0.5 minute); because administration of drug was sooner in the midazolam group than the diazepam group (2.34±0.90 *vs* 4.61±1.08 minute); ($p< 0.001$; Highly significant in all the groups). (Table 3). No significant difference was observed in heart rate, respiratory rate and oxygen saturation before and ten minutes after administration of both drugs for procedures and seizures.

DISCUSSION

Midazolam is a newer water soluble Benzodiazepine absorbed *via* the intranasal route, which provides an easy and painless method of sedation. Intravenous diazepam (IV-D) is the most frequently used method of sedation but administration is painful, takes time and requires more material and training. The objective of this study was to compare the efficacy and safety of intranasal midazolam (IN-M) with intravenous diazepam (IV-D) for various pediatric procedures and seizures.

Out of 125 children of all ages and either sex, attending outdoor or indoor pediatric emergency department, various procedures were performed in 49 children and 76 children required treatment for seizures. There was no statistically significant difference in the duration of non-invasive and invasive procedures between IN-M and IV-D groups. In the present study fever was not an inclusion or exclusion criteria for selection of patients. Lahet E *et al*[6] compared IN-M with IV-D for treating only febrile seizures in children.

The assessment of sedation was performed after 10 minute of drug instillation. This interval was also chosen by Wilton NCT *et al*[5] and Slover R *et al*[7]. In the present study in the midazolam group (n-27), 55.55% of children were agitated (Score-I) and 44.45% were alert before giving drug. Most of the children (n-21; 77.78%) became drowsy after giving IN-M (Score-IV). The findings of this study are consistent with that of Wilton NCT *et al*[5], who found most patients become either calm or drowsy (sedation scale III or IV). Slover R *et al*[7] also found that majority of patients (80%) were in the calm and/or drowsy category. There is no significant difference observed in the cry, physical restraint and motor score between IN-M and IV-D during invasive procedures. ($\chi 2 = 0.01$, $\chi 2 = 0.01$, $\chi 2 = 0.79$ $p>0.05$). Similarly in non-invasive procedures no significant differences were observed between the two drugs for cry, physical restraint and motor score. ($\chi 2 = 0.02$, $\chi 2 = 0.03$, $\chi 2 = 0.03$; $p>0.05$) (Table 2). M. Fishben *et al*[8] evaluated IN-M in children undergoing esophagogastrodudenoscopy and noted fewer incidence of crying and screaming and other major negative behavior during separation from parents after administration of the drug. Major negative behavior scores were the highest for the invasive procedures. The present study shows no difference in the efficacy of these drugs (IN-M and IV-D) during procedures.

In the use of IN-M control of seizures after arrival of patients in hospital was achieved sooner than with diazepam given intravenously. Mean time to control the seizure by intravenous diazepam, after arrival in hospital was maximum in the age group 0-1 year and minimum in the age group > 6 year. This difference is due to difficulty in establishing intravenous access in younger age groups as evident from the mean time to giving drug after arrival in hospital being more in younger than older age groups of children.

In the present study there were no significant differences observed in heart rate, respiratory rate and oxygen saturation before and after giving IN-M or IV-D in procedures and seizures.

Key Message: Midazolam by intranasal route provides a rapid, safe and effective non-invasive method of sedation for procedures and for treating seizures.

Acknowledgements

The authors sincerely acknowledge Dr. C.B. Shukla , Superintendent of G.M. Hospital and Dr. P.K. Baijal Dean, S.S. Medical College, Rewa for their kind permission and support to carry out this study in G.M. Hospital and S.S. Medical College, Rewa (M.P.)

REFERENCES

1. Krauss Baruch, Steven M Green. Sedation and analgesia for

procedures in children *New England J Med* 2000; 342 (13): 938-945.

2. Gopinath PG, Gopinath G, Kumar TCA. Target site of intranasally sprayed substances and their transport across the nasal mucosa: a new insight into the intranasal route of drug-delivery. *Curr Ther Res* 1978; 23 : 596-607.
3. Kida S, Pantazis A, Weller R.O. CSF Drains Directly from the Subarachnoid Space into Nasal Lymphatics in the Rat-Anatomy, Histology and Immunological Significance. *J Neuropathology and Applied Neurobiology* 1993; 19: 480-488.
4. Latson Larry A, Chaetham JP, Gumbiner CH, Kingler JD, Danford DA, Hofschire PJ. Midazolam Nose Drops for Outpatients Echocardiographic Sedation in Infants. *Am Heart J* 1991; 121: 209.
5. Wilton NCT, Leigh J, Rosen DR, Pandit U. Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology* 1988; 69: 972-975.
6. Lahet Eli, Micheal G, Joseph B, Tzvi B, Matithyahu B. Comparison of intranasal Midazolam with intravenous Diazepam for treating febrile seizures in children-prospective randomized study. *British Med J* 2000; 321: 83-86.
7. Slover R, Schlesinger T. Use of intranasal midazolam in preschool children. *Anaseth Analg* 1990; 70 : 51-54.
8. Fishbein Mark, Lugo Ralph A woodland Jennifer, Lininger Barbara and Linscheid Tom. Evaluation of intranasal midazolam in children undergoing esophagogastro-duodenoscopy. *J Pediatr Gastroenterol Nutr* 1997; 23(3): 261-266.