



## COMPARISON OF INTRANASAL MIDAZOLAM WITH INTRAVENOUS DIAZEPAM FOR TREATING ACUTE SEIZURES IN CHILDREN: A PROSPECTIVE RANDOMIZED STUDY

**Neeraj Singh\***

Military hospital, Allahabad, Uttar Pradesh 211001, India \*Corresponding Author

**J Chhatwal**

Department of Pediatrics, Christian Medical College and Hospital, Ludhiana, Punjab 141008, India

### ABSTRACT

**Objective:** To study and compare the efficacy and safety of intranasal midazolam and intravenous diazepam for treatment of children with acute seizures.

**Subjects:** Children beyond neonatal period hospitalized with acute seizures. A total of hundred seizure episodes, 50 in either midazolam or diazepam group.

**Interventions:** Intranasal midazolam (0.2 mg/kg) and intravenous diazepam (0.3 mg/kg).

**Results:** In the midazolam group, the treatment was initiated within 30s in 78% of the patients as compared to 24% in the diazepam group. There was a significant difference between mean time taken from contact with physician to drug administration between the midazolam ( $29.02 \pm 32.64s$ ) and diazepam group ( $51.92 \pm 33.61s$ ) [ $p < 0.01$ ]. The mean time of contact with physician to cessation of seizure was almost comparable between the two groups ( $93.07 \pm 74.23s$  Vs  $95.74 \pm 79.79s$ ). No significant adverse events were noted in either group.

**Conclusions:** Treatment could be initiated quickly with intranasal midazolam and was efficacious for seizure control. As it is easy to administer, it can be safely recommended for use in domiciliary and home settings for control of acute seizures in children.

**KEYWORDS :** Intravenous diazepam, Intranasal midazolam, Seizures

### INTRODUCTION

Acute seizures can be a life-threatening event. The duration of seizure is one of the important determinants of patient outcome [1]. Hence, in addition to the immediate supportive treatment for airway and breathing, terminating the seizure at the earliest possible is a priority. The standard form of medication for this is intravenous administration of a rapidly acting anticonvulsant. Benzodiazepines are the most commonly used agents viz. Diazepam, Lorazepam, Midazolam. Diazepam is the most widely used drug for the acute management of all types of seizures in both adults and children [2]. There may be difficulties in establishing an intravenous access in a seizing patient, especially in children which may lead to delayed seizure control [3,4]. Acquiring intravenous access in a seizing pediatric patient is a skillful job. Transmucosal drug delivery offers an attractive alternate route for the administration of benzodiazepines, especially midazolam, in seizing patients [5, 6, 7]. Intranasal midazolam has been used as a sedative agent for minor surgical interventions and diagnostic procedures [13-16]. The safety and efficacy of midazolam has been shown by several clinical studies in children [8, 9, 10]. Midazolam becomes lipid soluble at physiological pH and crosses lipid membranes such as the nasal mucosa and the blood brain barrier [8]. The rapid plasma availability of transmucosal midazolam allows it to be administered intranasally. These make it an attractive option to use as an intranasal instillation in control of acute seizures in children. A prospective randomized trial was conducted to study the efficacy and safety of intranasal midazolam and to compare its efficacy with intravenous diazepam.

### METHODS

A prospective randomized study on a case control design was conducted among hospitalized children beyond neonatal period. The study was conducted after necessary approvals from institutional review board. A total of 100 seizure episodes were studied. A seizure episode was defined as focal or generalized convulsive activity which may be tonic, clonic or tonic-clonic in nature. The patients who had received anticonvulsants from the benzodiazepine group in the preceding 24 hrs or had documented hypoglycemia, hypocalcaemia as a cause of seizure were excluded.

After immediate resuscitative and supportive measures as per emergency protocol were instituted the patients were randomized into a study and control group by permuted block randomization method. In the study group, midazolam in a dose of 0.2 mg/kg was

administered via the intranasal route. The control group received IV diazepam 0.3 mg/kg.

The time of beginning of seizure episode, contact with the physician, drug administration, cessation of seizures and recurrence was noted. During the seizure activity and for 60 minutes after stopping of seizure, the children were monitored by continuous cardio- respiratory and pulse oximetry observation. Treatment was considered successful if the seizure stopped within 5 minutes. Seizures stopping 5-10 minutes after treatment were defined as successful but delayed control of seizures. Seizures that did not stop within 10 minutes were defined as treatment failure and rescue intravenous diazepam 0.3 mg/kg was given. Seizures that were controlled with midazolam or diazepam but recurred within 60 minutes were defined as recurrence of seizures.

The statistical analysis was performed using 't' test, chi square test and coefficient of correlation.

### RESULTS

Most of the children in both groups (58%) were brought within 5 min of onset of seizure. Status epilepticus was diagnosed in 18% of the children in the midazolam and 8% in the diazepam group at the time of presentation. In the study group, 78% of patients had initiation of treatment within 30s as compared to 24% in the control group. In 24% of the control group, the treatment was initiated only after 60s. There was a significant difference between mean time taken from contact with physician to drug administration between the study ( $29.02 \pm 32.64s$ ) and control groups ( $51.92 \pm 33.61s$ ) [ $p < 0.01$ ].

In 74.47% of control and 50% of the study group, cessation of seizure was noted within 40s from the initiation of the treatment. Mean time taken from administration of drug to cessation of seizure was higher in the midazolam group ( $63.45 \pm 62.61s$ ) as compared to the diazepam group ( $46.15 \pm 61.37s$ ) although, was statistically not significant ( $p > 0.10$ ).

The mean time of contact with physician to cessation of seizure was almost comparable between the two groups ( $93.07 \pm 74.23s$  Vs  $95.74 \pm 79.79s$ ).

The midazolam group had a lower rate of success (84%) as compared to the diazepam group (92%) ( $p < 0.05$ ). In 16% of the

children in the midazolam group, there was treatment failure and in 8% there was recurrence after initial seizure control. These rates were higher as compared to the diazepam group, but the differences were statistically not significant.

The time of contact with physician to drug administration was found to be higher in the diazepam group in all age groups. The differences were significant in 1-5 years group ( $31.70 \pm 26.20$ s for midazolam vs.  $54.80 \pm 30.80$ s for diazepam;  $p < 0.01$ ) and the  $> 5$  years age group ( $19.55 \pm 17.38$ s for midazolam vs.  $61.13 \pm 54.04$ s for diazepam;  $p < 0.05$ ).

The time of onset of seizure to contact with the physician was more in the children who had failure of treatment in either group than in children having successful control of seizures. No significant change in heart rate, respiratory rate, oxygen saturation and blood pressure was seen in any patient after administration of treatment.

## DISCUSSION

Midazolam, a fast acting benzodiazepine, has been used frequently for seizure control through intravenous route. It has been found to be effective and safe for all age groups an alternative route, intranasal, has been used to provide sedation in children. It seems attractive to explore the possibility of examining the efficacy and safety of intranasal midazolam for seizure control in children. O'Regan et al (1996) found that intranasal midazolam given to epileptic children without clinical seizures (who were continuously monitored by electroencephalography) was absorbed rapidly through the nasal mucosa, and that it could suppress epileptic activity and improve the background electroencephalography [8].

In the present study, the initiation of treatment was significantly faster than in the group treated with diazepam administered intravenously as seen from the time of contact of physician to the time of drug administration. The midazolam could be administered within 30 seconds in 78% of patients as compared to 24% in the diazepam group. It took more than a minute in administering in 24% of the children in diazepam group. The time of contact with physician to drug administration was found to be higher in the diazepam group in all age groups. The differences were significant in 1-5 years group ( $31.70 \pm 26.20$ s for midazolam vs.  $54.80 \pm 30.80$ s for diazepam;  $p < 0.01$ ) and the  $> 5$  years age group ( $19.55 \pm 17.38$ s for midazolam vs.  $61.13 \pm 54.04$ s for diazepam;  $p < 0.05$ ). In a similar study, Lahat et al (2000) found that the mean time from arrival at hospital to starting treatment was significantly shorter in the midazolam group (3.5 min and 5.5 min) [5]. At physiological pH, midazolam becomes highly lipophilic, readily crosses the blood-brain barrier, and enters the central nervous system, with rapid clinical effects. [11,12]

Mean time taken from administration of drug to cessation of seizure was higher in the midazolam group ( $63.45 \pm 62.61$ s) as compared to the diazepam group ( $46.15 \pm 61.37$ s) although, was statistically not significant ( $p > 0.10$ ). The overall mean time from physician contact to the control of seizure was almost comparable between the two groups ( $93.07 \pm 74.23$ s Vs  $95.74 \pm 79.79$ s).

In the present study, the midazolam group had a lower rate of success (84%) as compared to the diazepam group (92%) ( $p < 0.05$ ). Similar success rates (88% vs 92%) have been reported by Lahat et al (2000) when they compared the success rates of intranasal midazolam with intravenous diazepam [5].

The present case control study showed that intranasal administration midazolam can be administered quickly in a seizing child as compared to IV diazepam with almost comparable success rate. As it is easy to administer it can be recommended for use in settings where skills for IV administration are lacking as in domiciliary or primary contact settings. With appropriate instructions parents' acceptability for this mode of medication may be better as compared to rectal diazepam.

**TABLE 1. COMPARISON OF TIME PERIODS RELATED TO SEIZURE EPISODE IN THE TWO GROUPS**

Time	Study Group		Control Group		t-value	p-value
	Mean	SD	Mean	SD		
1. Onset of seizure to contact with physician	19.75	31.81	13.76	23.89	1.06	$> 0.10$ ns
2. Physician contact to drug administration	29.02	32.64	51.92	33.61	3.46	$< 0.01$
3. Drug administration to cessation of seizure	63.45	62.61	46.15	61.37	1.32	$> 0.10$ ns
4. Physician contact to cessation of seizure	93.07	74.23	95.74	79.79	0.16	$> 0.10$ ns

## REFERENCES

1. Aildredge B K, Wall D B, Ferriero D M Effect of pre-hospital treatment on outcome of status epilepticus in children. *Pediatr Neurol* 1995;12:213-216.
2. Treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's Working Group in status of epilepticus. *JAMA* 1993;270:854-49.
3. Chamberlain J M, Altieri M A, Futterman G, Young G M et al A prospective randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. *Pediatr Emerg Care* 1997; 13:92-94.
4. Kendall J L, Reynolds M, Goldberg R Intranasal midazolam in patients with status epilepticus. *Ann Emerg Med* 1997;29:415-417.
5. Lahat E, Goldman M, Barr J et al. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ*.2000;321:83-6.
6. Kutlu NO, Yakinci C, Dogrul M et al. Intranasal midazolam for prolonged convulsive seizures. *Brain Dev.* 2000;22:359-61.
7. Fisgin T, Gurer Y, Tezic T et al Nasal midazolam effects on childhood acute seizures. *J Child Neurol* 2000;15:833-835.
8. Regan M E, Brown J K, Clarke M Nasal rather than rectal benzodiazepines in the management of acute childhood seizures? *Dev Med Child Neurol* 1996; 38: 1037-1045.
9. Harbord MG, Kyrkou NE, Kyrkou MR et al. Use of intra nasal midazolam to treat acute seizures in pediatric community settings. *J Paediatr Child Health.* 2004;40:556.
10. Lahat E, Goldman M, Barr J et al Intranasal midazolam for childhood seizures. *Lancet* 1998;352: 620.
11. Greenblatt DJ, Arendt RM, Abernethy DR, Giles HG, Sellers EM, Shader RI. In vitro quantitation of benzodiazepine lipophilicity: relation to in vivo distribution. *Br J Anaesthesiol* 1983;55:985-9.
12. Arendt RM, Greenblatt DJ, de Jong RH, Bonin JD, Abernethy DR, Ehrenberg BL, et al. In vitro correlates of benzodiazepine cerebrospinal fluid uptake pharmacodynamic action and peripheral distribution. *J Pharmacol Exp Ther* 1983;227:981-6.
13. Latson LA, Cheatham JP, Gumbiner CH, Kugler JD, Danford DA, Hafschire PJ, et al. Midazolam nose drops for outpatient echocardiography sedation in infants. *Am Heart J* 1991;121:2091-0.
14. Lacon A, Reddy VG. Nasal midazolam and ketamine for pediatric sedation during computerized tomography. *Acta Anaesthesiol Scand* 1994;38:2596-1.
15. Wilton NCT, Leight J, Rosen DR, Pandit U. Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology* 1988;69:972-5.
16. SaintMaurice C, Landais A, Delleur MM, Esteve K, MacGee K, Murat I. The use of midazolam in diagnostic and short surgical procedures in children. *Acta Anaesthesiol Scand* 1990;94(suppl 92):3941.