ELSEVIER

Intranasal Midazolam vs Rectal Diazepam in Acute Childhood Seizures

Madhumita Bhattacharyya, MD, Veena Kalra, MD, and Sheffali Gulati, MD

One hundred eighty-eight seizure episodes in 46 children were randomly assigned to receive treatment with rectal diazepam and intranasal midazolam with doses of 0.3 mg/kg body weight and 0.2 mg/kg body weight, respectively. Efficacy of the drugs was assessed by drug administration time and seizure cessation time. Heart rate, blood pressure, respiratory rate, and oxygen saturation were measured before and after 5, 10, and 30 minutes following administration of the drugs in both groups. Mean time from arrival of doctor to drug administration was 68.3 ± 55.12 seconds in the diazepam group and 50.6 ± 14.1 seconds in the midazolam group ($P = 0.002$). Mean time from drug administration to cessation of seizure was significantly less in the midazolam group than the diazepam group ($P = 0.005$). Mean heart rate and blood pressure did not vary significantly between the two drug groups. However, mean respiratory rate and oxygen saturation differed significantly between the two drug groups at 5, 10, and 30 minutes after drug administration. Intranasal midazolam is preferable to rectal diazepam in the treatment of acute seizures in children. Its administration is easy, it has rapid onset of action, has no significant effect on respiration and oxygen saturation, and is socially acceptable.

Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. Pediatr Neurol 2006;34:355-359.

Introduction

Seizure, a common neurologic medical emergency, continues to be associated with significant morbidity and mortality in the pediatric age group and affects 4-7% of children [1]. Early domiciliary treatment of seizures in the community, school, or home with drugs that can be administered by parents, teachers, or nonmedical staff may be beneficial and can decrease morbidity and mortality [2]. In planning domiciliary therapy, the safety, ease of administration, choice of drug, route of therapy, and the practicability of familiarization by the user are important issues. Various drugs administered through different routes have been tried in the management of acute seizures.

Rectal diazepam has been used successfully for home and hospital treatment of acute seizures [3]. Its use may be socially embarrassing and undesirable. Moreover, some special arrangement is required to administer it, which is difficult to arrange in homes, schools, and daycare centers. An effective treatment that can be easily administered by a more convenient, socially acceptable route is therefore needed.

Midazolam, a benzodiazepine, has been described as an alternative rescue medication in the management of acute seizures [4,5]. Recent studies have demonstrated intranasal midazolam to be effective in the management of acute childhood seizures [6-9,10]. However, not many comparative studies have been undertaken, and the search for an easily administrable, effective drug to control acute seizure continues.

In the light of the above background, the present study was undertaken to compare the efficacy and side effects of intranasal midazolam and rectal diazepam in the treatment of acute childhood seizures.

Materials and Methods

This study was a randomized, controlled, single masked study. All types of seizures including febrile seizures and all types of epilepsy in children of either sex, ages 3 months to 12 years, who attended the Institute's outpatient department or emergency were included in the study. A written consent was obtained from the parents or guardians of children regarding their willingness to participate in the study. The study was approved by the Institute ethical committee.

From the Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

Communications should be addressed to:
Dr. Bhattacharyya; 20/4, N.S.C. Bose Road; Graham's Land;
Kolkata – 700040, India.
E-mail: madhumita57@yahoo.co.in
Received June 21, 2004; accepted September 14, 2005.

doi:10.1016/j.pediatrneurol.2005.09.006 • 0887-8994/06/$—see front matter

Table 1. Diagnoses of children under study

Serial Number	Diagnosis	No. of Children (%) (n = 46)
1	Epilepsy	18 (39.13%)
2	Degenerative brain disease	10 (21.73%)
3	Neurocysticercosis	7 (15.21%)
4	Other central nervous system diseases	6 (13.04%)
5	Febrile seizures	5 (10.86%)

Drugs used in this study were intranasal midazolam (0.2 mg/kg) and rectal diazepam (0.3 mg/kg). Equal numbers of sealed, unmarked, identical envelopes containing the name of the drug to be administered were randomized by shuffling. A box containing these envelopes was kept in the pediatric ward. When a patient was enrolled into the study, randomization to either group was performed by picking an envelope, and the indicated medication was administered. Blood sugar and serum calcium were assessed before enrollment and after seizure in each patient.

Midazolam was instilled into the anterior nares with the help of a nasal dropper, and diazepam was introduced into the rectum with an 8-F size infant feeding tube that was inserted 4 cm inside the anal opening. Children with hypoglycemic seizures, hypocalcemic seizures, and upper respiratory tract infection were excluded from the study.

The end of the seizure episode (clinically) was defined as the cessation of visible epileptic phenomena or return of purposeful response to external stimuli. If the seizure did not end within 10 minutes of drug administration, the treatment was deemed to be ineffective. Heart rate, respiratory rate, blood pressure, and oxygen saturation by pulse oximetry were measured before drug administration and monitored at 5 minutes, 10 minutes, and 30 minutes after drug administration. Recurrence of seizures within 60 minutes of drug administration was also evaluated. The children were monitored for side effects such as vomiting, excessive somnolence, respiratory depression, and apnea after drug administration. A stop-watch was used to measure all time accurately by investigators.

Sample Size

A previous clinical study by Scott et al. [11], in which "seizure episode" was the unit of randomization, demonstrated the efficacy for control of seizure episode in the midazolam group and the diazepam group to be approximately 75% and 59%, respectively. Again, "seizure cessation time" after administration of the drugs was 6 minutes and 8 minutes in these two groups, respectively. Thus, considering both factors, it was calculated that at least 90 seizure episodes were required to be enrolled in each group to produce a statistically significant difference at a power of 90% with a P value of <0.05 and odds ratio 0.333.

Statistical Analysis

Data were recorded on a predesigned proforma. Unit of analysis was episode of seizure. Covariates between two groups (midazolam and diazepam) were compared by chi-square test, Fisher's Exact Test, or Student t test. In case of more than one episode of seizure per child, repeated-measures analysis of variance using generalized estimation of equation was applied. Mann-Whitney U test and Wilcoxon signed rank sum test were also applied to determine the pairwise comparison for continuous data.

Table 2. The types of seizure episodes in study children

Serial Number	Type of Seizure	Number of Episodes (%) (n = 188)
1	Simple partial seizures	92 (48.9%)
2	Generalized tonic clonic seizures	70 (37%)
3	Myoclonic seizures	19 (10.1%)
4	Others, e.g., absence, atonic seizures	7 (3.8%)

Table 3A. Comparative baseline characteristics of the two groups of children

Characteristics	Mean	S.D.	P Value
Chronologic age (months) (n = 46)			
Diazepam	74.53	38.29	0.29
Midazolam	60.47	45.35	
Age of onset of first seizure (n = 46)			
Diazepam	53.72	41.31	0.48
Midazolam	47.56	43.76	
Developmental age (n = 46)			
Diazepam	66.7	43.07	0.22
Midazolam	48.06	48.42	

Results

Of 188 seizure episodes in 46 children under study, 96 episodes were treated with rectal diazepam and 92 with intranasal midazolam. The diagnoses of these 46 children and the type of seizures are summarized in Table 1 and Table 2, respectively. Comparative baseline characteristics of the two groups under study are presented in Table 3A and 3B.

After comparing the baseline characteristics between the two groups, which did not vary significantly, an analysis of the 188 seizure episodes (96 episodes with rectal diazepam and 92 episodes with intranasal midazolam) was undertaken. "Doctor to drug time" (i.e., time taken by the doctor to prepare and administer the drug) and "seizure cessation time" after administration of the drug were significantly shorter in the midazolam group

Table 3B. Comparison of some other baseline characteristics

	Diazepam	Midazolam	P Value
Sex (n = 46)			
Male	67.9%	55.6%	0.29
Female	32.1%	44.4%	
Category of seizure (n = 46)			
Controlled	62.11%	68.4%	
Provoked	20.7%	10.5%	0.64
Intractable	17.2%	21.1%	
Family history of seizures (n = 46)			
Yes	7.1%	27.8%	0.071
No	92.9%	72.2%	
History of birth asphyxia (n = 46)			
Yes	89.3%	94.4%	0.48
No	10.7%	5.6%	
Perinatal history (n = 46)			
Normal	92.9%	94.4%	0.66
Abnormal	7.1%	5.6%	

Table 4. Comparison of doctor to drug time and drug to seizure cessation time in rectal diazepam and intranasal midazolam group

	Rectal Diazepam (Seconds)		Intranasal Midazolam (Seconds)		
	Mean	S.D.	Mean	S.D.	*P* Value
Doctor to drug time	68.3	55.1	50.6	14.1	0.002
Drug to seizure cessation time	178.6	179.4	116.7	126.9	0.005

(Table 4). Changes in heart rate, respiratory rate, blood pressure, and oxygen saturation, as measured at 5-minute, 10-minute, and 30-minute intervals after administration of drugs in both groups, revealed that mean heart rate and blood pressure changes were not statistically different. Mean respiratory rate decreased by 1/minute at 5 minutes and 4/minute at 10 and 30 minutes after administration of rectal diazepam from predrug mean respiratory rate, whereas there was no decrease of mean respiratory rate at 5/minutes and a decline of only 1/minute at 10 minutes and 30 minutes after administration of intranasal midazolam. By repeated-measures of analysis of variance, it was found that changes in respiratory rate differed significantly between the rectal diazepam group and the intranasal midazolam group at 10 minutes and 30 minutes after drug administration, with $P = 0.027$ and $P = 0.039$, respectively.

Again, mean oxygen saturation (SaO_2) after 5, 10, and 30 minutes of intranasal midazolam administration did not vary, whereas mean oxygen saturation in the rectal diazepam group decreased at 5 minutes and 30 minutes after administration of the drug from predrug mean value. This difference was again statistically significant ($P < 0.05$). Hypoxia was observed in one child treated with rectal diazepam who required oxygen inhalation for 7 hours. No significant hypoxia was observed in the midazolam group.

Seizures ceased within 10 minutes of drug administration in 85 of 96 episodes (88.5%) treated with rectal diazepam, whereas seizures ended in 89 of 92 episodes (96.7%) treated with intranasal midazolam ($P = 0.060$). Seizures were not controlled in 11 episodes (11.45%) of the rectal diazepam group and in 3 episodes (3.26%) of the intranasal midazolam group.

Seizures recurred in 6 of 96 episodes (6.25%) within 60 minutes of administration of rectal diazepam, and in 3 of 92 episodes (3%) after administration of intranasal midazolam. The difference was not statistically significant.

Side effects such as vomiting and excessive drowsiness were observed in 10 of 96 episodes (10.4%) in the rectal diazepam group, whereas no such side effects were observed in the midazolam group. The difference was significant statistically ($p = 0.009$).

Discussion

Early termination of seizures is important to prevent many adverse consequences and reduce the risk of development of status epilepticus. In a hospital setup, intravenous diazepam is commonly used for control of acute seizures, but it requires prompt establishment of an intravenous line and has the disadvantage of being a respiratory depressant [12]. Rectal diazepam is another alternative route, but is not always reliable owing to its variable bioavailability and wide range of serum concentration [13,14]. There is also a risk of child abuse. Episodes of acute seizures have also been treated with buccal diazepam and sublingual lorazepam [15,16]. Administering the drugs orally or sublingually is frequently difficult and hazardous when children are convulsing. Moreover, absorption of diazepam and lorazepam solution is relatively slow [16]. Application of drugs to nasal mucosa allows rapid absorption of drug into systemic circulation. Midazolam, a water-soluble benzodiazepine, was found to end seizures within 1 to 2 minutes of intranasal administration [7-9,17,18]. As such, the present study was undertaken to evaluate and compare the efficacy of rectal diazepam with intranasal midazolam in terminating acute seizures in children.

Among 188 episodes randomized in the study, 96 episodes were treated with rectal diazepam with a dose of 0.3 mg/kg body weight and 92 episodes with intranasal midazolam with a dose of 0.2 mg/kg body weight. The doses of rectal diazepam used in previous studies are variable, ranging from 0.16 to 0.5 mg/kg [11,12,17]. In the present study, a midlevel dose of 0.3 mg/kg of rectal diazepam was used in order to avoid any cumulative side effects of diazepam in children, which was a possibility as a child always had a chance to receive diazepam more than one time, because the unit of randomization in this study was seizure episode. The preparations of diazepam reported to be used in earlier studies were intravenous preparations introduced rectally [12] or commercially available prepacked rectal diazepam [11,17]. A rectal tube for diazepam and a nasal dropper for midazolam were used in the present study as neither prepacked rectal diazepam nor midazolam drop or spray were available in our country during the period of study.

Doctor to Drug Time

In the current study, the drug administration time was observed to be shorter in the midazolam group than in the diazepam group ($P = 0.002$). Fisgin et al. [7,17] used an injector for the introduction of intranasal midazolam, through which the drug was introduced within 30 seconds. Lahat et al. [18] did not mention the time, but they dropped the drug immediately in the anterior nares even before the establishment of an intravenous line in children. Therefore, this easy and shorter administration time for

Table 5. Comparison of earlier studies with present study

Study Authors	Dose of Rectal Diazepam	Dose of Intranasal Midazolam	Drug to Seizure (Cessation Time mean)	
			Rectal Diazepam	Intranasal Midazolam
Lahat et al. [18]	Not used	0.2 mg/kg		180–500 s
Kutlu et al. [8]	Not used	0.2 mg/kg		139.6 ± 129.8 s
Fisgin et al. [7]	Not used	0.2 mg/kg		60–120 s
Fisgin et al. [17]	0.3 mg/kg	0.2 mg/kg	120–300	60–120 s
Present study	0.3 mg/kg	0.2 mg/kg	178.6 ± 179.5 s	116.7 ± 126.9 s

Abbreviation:
s = Seconds

intranasal midazolam plays an important role in the management of acute seizures.

Drug to Seizure Cessation Time

The present study demonstrated that the mean time for seizure cessation in the intranasal midazolam group was significantly shorter than that for rectal diazepam ($p = 0.005$) (Table 4). Intranasal midazolam was therefore believed to be more effective in controlling acute childhood seizures rapidly, with less seizures cessation time than in the rectal diazepam group; this is probably because of the water solubility of midazolam and the rapid absorption of the drug through the nasal mucosal vasculature. Bypassing the portal circulation, it reaches the systemic circulation more rapidly than rectal diazepam. These results compare favorably with earlier studies (Table 5).

Comparison of Vital Parameters in Both Drug Groups

In this study, the mean change of heart rate and mean systolic and diastolic blood pressure at 5, 10, and 30 minutes did not vary significantly between the rectal diazepam group and the intranasal midazolam group.

Mean respiratory rate decreased in the diazepam group, whereas it increased after intranasal midazolam administration from predrug values. This finding indicates that intranasal midazolam probably has no significant respiratory depressant effect in children with acute seizures. Fisgin et al. [7,17] also detected tachypnea in their study children after administration of intranasal midazolam. The mean increase in respiratory rate by 1/minute after intranasal midazolam administration in the present study had no clinical significance. A possible explanation for this may be nasal mucosal irritation by local application of drug.

This study also revealed a significant difference of oxygen saturation as measured by pulse oximeter between the diazepam and midazolam groups at 5, 10, and 30 minutes after drug administration ($P < 0.05$). O'Regan et al. [14] found a severe decrease in oxygen saturation that corrected spontaneously in 1 of 19 children with intractable seizures who received intranasal midazolam. No other studies found any significant fall in oxygen saturation after administration of intranasal midazolam. On the contrary, Dickmann [12] reported that of 16 children who received rectal diazepam, 7 required oxygen alone or oxygen with bag valve mask device to combat respiratory depression. The present study, which had a sample size larger than the previous studies, substantiates earlier reports that intranasal midazolam appears to have a good safety profile with regard to posttherapy oxygen saturation levels.

Antiepileptic Efficacy

Lahat et al. [9] and Kutlu et al. [8] reported that intranasal midazolam was effective in ending seizures within 10 minutes in 88.4% of study children. The only earlier study [17] that compared rectal diazepam with intranasal midazolam demonstrated that 20 of 23 (87%) children stopped convulsing within 10 minutes of intranasal midazolam administration and 13 of 22 (60%) children receiving rectal diazepam had their seizures controlled within 10 minutes ($P < 0.05$). The dose of intranasal midazolam and rectal diazepam was the same as used in the present study, i.e. 0.2 mg/kg and 0.3 mg/kg, respectively.

In this study, 85 of 96 episodes (88.5%) in the rectal diazepam group and 89 of 92 episodes (96.7%) in the intranasal midazolam group were controlled within 10 minutes of drug administration. Seizures remained uncontrolled in 11 (11.45%) episodes in the diazepam group and in 3 (3.26%) in the midazolam group. The difference, however, was not statistically significant. Although this study had no untreated group for comparison owing to ethical constraints, it appears that intranasal midazolam may be a good domiciliary strategy for use in epileptic subjects. Seizures recurred in six episodes (6.25%) in the diazepam group and in three episodes (3.26%) in the midazolam group within 60 minutes of drug administration. This study thus reveals that intranasal midazolam as well as rectal diazepam are equally effective in controlling acute seizure within 10 minutes of drug administration and that recurrence of seizures may occur in both groups.

Side effects such as vomiting and excessive drowsiness were evident in 10 episodes (10.4%) treated in the rectal

diazepam group only. These side effects were observed in those children who were treated with the drug multiple times for recurrent episodes of seizures. This result is believed to be due to the cumulative effect of the drug after repeated administration. No such side effects were detected in the intranasal midazolam group, even on repeated use. This outcome reflects that intranasal midazolam is a safe drug without any significant side effects and can be used in children to control acute seizures. It compares favorably with rectal diazepam, with less side effects and marginal therapeutic superiority ($p = 0.06$). Social acceptability of rectal diazepam is understandably less, especially among young females.

In conclusion, intranasal midazolam was found to be a reasonably safe route for terminating acute seizures in children. Its antiepileptic effect appeared comparable to conventional rectal diazepam. Further, with regard to quickness of response, safety, and ease of administration, intranasal midazolam was found to be superior.

Future studies with concurrent electroencephalographic documentation are recommended to authenticate the effect of intranasal midazolam as an alternative route in the management of acute seizures.

References

[1] **Kalra** V. Seizure disorders and epilepsy. In: Kalra V, editor. Practical paediatric neurology, 1st ed. New Delhi: Arya Publication, 2002:51-77.

[2] **Alldredge** BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. Pediatr Neurol 1995;12:213-6.

[3] **Remy** C, Jourdil N, Villemain D, Favel P, Genton P. Intrarectal diazepam in epileptic adults. Epilepsia 1992;33:353-8.

[4] **Lahat** E, Aladjem M, Eshel G, Bistritzer T, Katz Y. Midazolam in treatment of epileptic seizures. Pediatr Neurol 1992;8:215-6.

[5] **Rivera** R, Segnini M, Baltodano A, Perez V. Midazolam in the treatment of status epilepticus in children. Crit Care Med 1993;21:991-4.

[6] **Koren** G. Intranasal midazolam for febrile seizures. BMJ 2000; 321:64-5.

[7] **Fisgin** T, Gurer Y, Senbil N, et al. Nasal midazolam effects on childhood acute seizure. J Child Neurol 2000;15:833-5.

[8] **Kutlu** NO, Yakinci C, Dogrul M, Durmaz Y. Intranasal midazolam for prolonged convulsive seizures. Brain Devel 2000;22:300-61.

[9] **Lahat** E, Goldman M, Barr J, Bristritzer T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: Prospective randomised study. BMJ 2000;320:83-6.

[10] **Wallace** SJ. Nasal benzodiazepines for management of acute childhood seizures? Lancet 1997;349:222.

[11] **Scott** RC, Besag FMC, Neville BGR. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: A randomised trial. Lancet 1999;353:623-6.

[12] **Dickmann** RA. Rectal diazepam for prehospital pediatric status epilepticus. Ann Emerg Med 1994;23:216-24.

[13] **Scheepers** M, Scheepers B, Clarke M, Comish S, Ibitoye M. Is intranasal midazolam an effective rescue medication in adolescents and adults with severe epilepsy? Seizure 2000;9:417-21.

[14] **O'Regan** M, Brown J, Clark M. Nasal rather than rectal benzodiazepines in the management of acute childhood seizure? Dev Med Child Neurol 1996;38:1037-45.

[15] **Yager** JY, Sestria SS. Sublingual lorazepam in childhood serial seizures. Am J Dis Child 1988;142:931-2.

[16] **Dhillon** S, Osley J, Richens A. Bioavailability of rectally administered lorazepam. Br J Clin Pharmacol 1982;13:427-32.

[17] **Fisgin** T, Gurer Y, Tezic T, et al. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: Prospective randomised study. J Child Neurol 2002;17:123-6.

[18] **Lahat** E, Goldman M, Barr J, Eshel G, Berkovitch M. Intranasal midazolam for childhood seizures. Lancet 1998;352:224.