Research Article

Intranasal Midazolam Versus Intravenous Diazepam for the Treatment of Acute Seizures in Paediatric Patients

Pooja Garg, R S Sethi, Aradhna Kankane, OS Chaurasia, Anuj Shamsher Sethi
Department of Peadiatrics, Maharani Laxmibai Medical College, Jhansi

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ABSTRACT

The objective of this study was to measure the time needed to control seizure attacks using intranasal midazolam compared with intravenous diazepam and to evaluate the probable side effects. This study was conducted as a non blind randomized clinical trial among 50 patients coming to MLBMC, Jhansi. The patients were 2 months to 15 years old children coming to our emergency department suffering from an acute seizure episode. Intranasal midazolam was administered 0.2 mg/kg equally dropped in both nostrils for group A and intravenous diazepam was administered 0.3mg/kg via intravenous line for group B. Choice of drugs for patient was based on randomization. After both treatments, the time needed to control the seizure was registered by the practitioner. Pulse rate and oxygen saturation were recorded at patient's entrance and in minutes 5 and 10 after drug administration. The mean time from physician contact to cessation of seizures was significantly shorter in the midazolam group (3.9880(SD 1.38784) minutes), than the diazepam group (5.4840 (SD 2.33661)min). The mean time from drug administration to cessation of seizures was significantly sooner (3.1160 (SD 0.97112)min) in the diazepam group than the midazolam group (3.8720 (SD 1.57229) min). No significant side effects were observed in either group. Seizures were controlled more quickly with intravenous diazepam than with intranasal midazolam, although midazolam was as safe and effective as diazepam. The overall time to cessation of seizures after arrival at hospital was faster with intranasal midazolam than with intravenous diazepam due to its shorter time of adminstration.

KEY WORDS: diazepam, intranasal, intravenous, midazolam, seizures

INTRODUCTION:

A seizure is a transient symptom of abnormal, excessive or synchronous neuronal activity in the brain. Approximately 4-10% of children experience at least 1 seizure in the first 16 year of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the cases start in childhood[1]. It constitutes about 70% of paediatric neurological disorders. It is a life threatening event and longer duration is associated with higher mortality and morbidity. Focus of management is to stabilize the patient, quickly terminate the seizure activity, identify and treat life threatening conditions and to initiate follow up.

Till date, short acting anticonvulsants like benzodiazepines have mainly been used to control seizures. Benzodiazepines cross the blood brain barrier promptly and achieve peak CSF concentration within minutes of administration. Conventionally short acting benzodiazepines (Diazepam, Midazolam, IBZD) are given by parental routes (IV or IM) for acute management of seizures.[2]However, intravenous (IV) line is difficult to establish in a convulsing child and requires expertise. Intramuscular (IM) route cannot be relied upon as it has erratic absorption and delayed CNS effects[3]. Thus various alternative routes of administration are under evaluation. Currently emphasis is being laid not only to control an acute episode in hospital setting but also for management of seizures at home. Various alternative routes of administration are intranasal, rectal, sublingual and buccal. Buccal and sublingual routes are difficult because of frothing and clenching associated with seizures.[4] Rectal route is socially less acceptable especially in adolescent.[5] Therefore, intranasal (IN) route may be a preferred route as it is more convenient for drug administration. Midazolam is a watersoluble triazole- benzodiazepine. It has imidizole ring

Corresponding Author: Dr. Pooja Garg,
Department of Peadiatrics, Maharani Laxmibai Medical College, Jhansi
Phone No.: +91 8126157775
E-mail: dr_pooja_sn@yahoo.com

different from other benzodiazepines. At a pH less than 4 it is water soluble, but at physiological pH it is highly lipophilic which accounts for its rapid absorption, shorter duration of action and rapid clearance[2], thereby making it ideal for intranasal administration.

The vascular nasal mucosa facilitates rapid absorption, a fact known by cocaine addicts for years, and drugs administered this way have been utilized in a variety of treatment methods.[6] The ease of intranasal midazolam administration to treat episodes of seizure makes it a good candidate to replace the conventional treatment methods not only for use at home but also for health professionals.[7]

The nasal mucosa provides a large (180 cm^2), highly vascular absorptive surface adjacent to the brain. Together with the neighbouring olfactory mucosa, it offers a direct pathway for drug absorption into the bloodstream & CSF. Therefore, the nasal route is a good option for drugs that undergo extensive hepatic metabolism increasing their bioavailability and drugs with erratic absorption patterns. It is also advantageous when drugs with a short latency of action, such as benzodiazepines are required.[8]

When venous access is challenging or cannot be obtained, the most common alternatives have been rectal diazepam and intranasal midazolam, with some studies suggesting intramuscular midazolam as an additional option. The difficulty of administering BZDs rectally or intranasally and the erratic absorption provided by these routes jeopardize anticonvulsant efficacy. Thus far, no consensus has been established as to the best route for administration of BZDs in the event of failed intravenous access.

Hence this study was conducted to compare the therapeutic efficacy of intranasal midazolam (IN MDZ) with that of intravenous diazepam (IV DZP) in children admitted to the referral service of a pediatric emergency department with epileptic seizures.

MATERIALS AND METHODS:

A prospective randomized study was conducted on 50 subjects over a period of 15 months in the Department of Pediatrics, MLB Medical College, Jhansi. All patients between the age of 2 months to 15 years arriving in emergency in a convulsing state were the subjects of this study. Strict ethical considerations were followed after seeking permission of the ethical committee of the institution. Accordingly a written informed consent was taken from Parents/Guardians. 50 subjects were randomized into two groups by random allocation software. The groups and drug administration is as under:

GP-A: They were administered commercially available preparation of intranasal midazolam @0.2 mg / kg as nasal spray.

GP-B: They were administered commercially available preparation of diazepam @ 0.3 mg/kg through IV route by placing an IV cannula of appropriate size. After administering the pulse rate and oxygen saturation was recorded at 0, 5 and 10 minutes.

Outcome was measured in terms of time taken from physician contact to cessation of seizures and from drug administration to cessation of seizures. The results were presented as mean and standard-deviation and statistically analyzed by using "student's unpaired t test" p -value (<0.05) was regarded as statistically significant. All analysis was performed using intention to treat analysis.

RESULTS:

A total of 50 subjects were studied over a period of 15 months. The two groups were comparable in terms of age, sex and prior history of seizure. Mean time from physician contact to cessation of seizures was significantly shorter in GP-A (IN MDZ) as compared to GP-B (IV DZP) and the difference was statistically significant (p =0.008) (Table 2). Time from drug administration to cessation of seizures was lesser in GP-B (IV- DZP) as compared to GP-A IN MDZ and the difference was statistically significant (p= 0.046) (Table III). Effect of drugs on pulse rate and oxygen saturation as observed in intergroup comparisons drawn was statistically insignificant between the two groups (Table 4). No significant effect was observed on recurrence rate and number of uncontrolled seizures.

DISCUSSION:

Seizure is a life threatening event and frightening experience for both parents and caregivers. Longer duration of seizure is associated with higher mortality and morbidity. Hence to abort an acute attack is the immediate need of a convulsing child. Parenteral routes like intravenous and intramuscular require hospital setting and expertise whereas rectal route has its own social and personal

Table 1 : Baseline Characteristics of intervention & the type of seizure in each group

Characteristics	Group A		Group B	
	Intranasal Midazolam (n=25)		Intravenous Diazepam (n=25)	
Median age (years)	5.0736		6.7368	
Male/Female, (M%)	36		26	
Type of seizures	Controlled (%)	Not Controlled (%)	Controlled (%)	Not Controlled (%)
GTCS	14 (56%)	2 (8%)	15 (60%)	3 (12%)
Partial	5 (20%)	0 (0%)	4 (16%)	0 (0%)
Focal Seizure progressing to secondary generalization	4 (16 %)	0 (0%)	3 (12%)	0 (0%)
Etiology of Seizures	Contolled (%)	Not Controlled (%)	Controlled (%)	Not Controlled (%)
Febrile Seizures	2 (8%)	0 (0%)	6 (24%)	0 (0%)
Meningitis	6 (24%)	0 (0%)	2 (8%)	1 (4%)
Epilepsy	9 (36%)	0 (0%)	9 (36%)	0 (0%)
Encephalopathy	4 (16%)	2 (8%)	4 (16%)	2 (8%)
Cerebral palsy with mental retardation	2 (8%)	0 (0%)	2 (8%)	0 (0%)
Others	0 (0%)	0 (0%)	1 (4%)	0 (0%)
Time needed to control seizures (min)	T1 3.988	T2 3.8720	T1 5.448	T2 3.1160

*GTCS: Generalized Tonic Clonic Seizures

Table 2: Depicting time from physician contact to cessation of seizures

Time from physician contact to cessation of seizures (T1)	Gp. A (Intranasal Midazolam) Time (min)	Gp. B (Intravenous Diazepam) Time (min)	p-value
Mean time & (SD) (n=50)	3.9880 (1.38784)	5.4840 (2.33661)	0.008

Table 3: Time from drug administration to cessation of seizures

Time from drug administration to cessation of seizures (T2)	Gp. A (Intranasal Midazolam) Time (min)	Gp. B (Intravenous Diazepam) Time (min)	p-value
Mean time & (SD) (n=50)	3.8720 (1.57229)	3.1160 (0.97112)	0.046

adverse effects (more so in adolescents). Therefore intranasal administration of midazolam has been area of tremendous interest in recent years. The ability of rich vascular nasal mucosa to absorb drug readily and helping quick attainment of peak plasma and CSF concentrations within minutes of administration make it the prime route for fast and easy drug delivery. Majority of subjects in our study were of 1-6 years of age and fairly uniformly distributed amongst the two groups.

Table 4: Comparison of O2 saturation & pulse rate in two group of patients receiving midazolam & diazepam

Parameters	Time (min)	Gp. A (Intranasal Midazolam)	Gp. B (Intravenous Diazepam)	p-value
O2 Saturation (%) Mean (S.D.)	0 min	97.16 (1.46287)	96.28 (2.24574)	0.107
	5 min	94.0800 (3.13475)	93.1200 (3.63226)	0.322
	10 min	94.8400 (1.65025)	94.6000 (2.02073)	0.648
Pulse Rate (/min) Mean (S.D.)	0 min	123.84 (28.15978)	137.0400 (27.41727)	0.100
	5 min	113.0400 (26.59022)	122.7600 (23.65953)	0.178
	10 min	116.0 (26.83282)	126.88 (24.37950)	0.140

There are reports of similar study groups.[9, 10] Majority of seizures were generalized tonic-clonic seizures which is in concordance with 70% reported frequency of GTCS in childhood seizures. [11] Recurrence rate in the two groups was 12% and 16% respectively, 8 % of seizures in group A and 12 % in group B failed to get controlled. The results are comparable with studies available in literature where seizure control with midazolam ranged from 75%-100%.[2,12,13,14,15] In our study we observed that intranasal midazolam is a safe and effective anticonvulsant for acute management of seizures. As time required from physician contact to cessation of seizures was considerably shorter 3.9880 min in group-A (IN MDZ) as compared to 5.4840 min in group-B (IV DZP), (p-value- 0.008), Intranasal midazolam proves it superiority over intravenous diazepam due to its speed & ease of administration. And such situations where seconds matter saving time can have significant impact on clinical outcome of a critically ill convulsing child and helps emergency physician to look into other aspects of critical care management. Reducing the duration of seizure also decreases the associated mortality and morbidity. Mean time from drug administration to cessation of seizures was 3.8720 min in group A and 3.1160 min in group B. p-value came out to be 0.046 which shows superiority of intravenous diazepam over intranasal midazolam. The results obtained are in concordance with other studies.[12,16,17,18,19] No adverse cardio respiratory effect was noted. These observations were comparable to other studies.[3,12,13,14]

CONCLUSION:

Intranasal midazolam is safe and effective for treating seizures in the hospital. Compared with the current standard of care using intravenous diazepam intranasal midazolam is more easier to use and is more socially acceptable.

Together, these advantages make intranasal midazolam a viable alternative to intravenous diazepam as the preferred method for treatment of seizures in patients without or having difficult intravenous access. The rapid onset of action of intranasal midazolam is noteworthy, given that early treatment can reduce the morbidity and mortality of children having seizures. Treatment should preferably start before arrival to the hospital, but only by trained health-care personnel or families.

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