

A Study on Intranasal Midazolam Versus rectal Diazepam in Acute Seizure

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Abstract: A seizure is a result of excessive nerve-cell discharges in the brain. 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. Intranasal midazolam suppresses epileptic activity and improves the background of electroencephalograms in children with epilepsy. Diazepam is most widely used drug for acute management in all types of seizures in both adults and children. Rectally administered benzodiazepine (diazepam) has been widely used to end seizures. In our study we compared the efficacy of intra nasal midazolam with rectal diazepam, by estimating the seizure control time.

Aims: To compare the safety and efficacy of intranasal midazolam with rectal diazepam for emergency room treatment of children aged 6 months and older with active seizures, without any IV access.

Materials And Methods: A prospective observational study which was carried out on patients admitted to the emergency unit at TDMC, Alappuzha. All types of seizures including febrile seizures in children of either sex, aged 6 months and above who attended the hospital outpatient department or emergency, in active seizures, without any iv access were included in the study. Drugs used in this study were intranasal midazolam (0.2mg/kg) and rectal diazepam (0.3 mg/kg). The whole duration of the study was 18 months.

Results: Out of the 25 patients in diazepam study group, 15 responded whereas 10 required a second drug for controlling seizures. Whereas in the midazolam group, 3 did not respond but 22 responded. This was statistically significant. The mean duration of seizures was almost same for both drugs, 10.9 min for diazepam and 10.08 min for midazolam. This was not statistically significant. The mean seizure control time was 7.27 mints for rectal diazepam and 4.24 mints for intranasal midazolam. This finding was statistically significant. Intranasal midazolam was found to control seizure faster than rectal diazepam.

Conclusion: Intranasal midazolam was efficacious than rectal diazepam in terms of shorter seizure control time as well as in terms of shorter drug delivery time. The safety profile of both drugs was almost similar.

Keywords: Intranasal Midazolam, Rectal diazepam, Seizure.

I. Introduction

A seizure is a result of excessive nerve-cell discharges in the brain. It is seen as a sudden abnormal function of the body, often with loss of consciousness, an excess of muscular activity, or sometimes a loss of it, or an abnormal sensation.

The excessive nerve-cell discharges or excitation may remain in a small area of the brain (a localized lesion or focus) giving rise to partial (focal) seizures, or start immediately in the whole brain or spread from the small area (focus) to the whole brain and spinal cord giving rise to generalized seizures⁴.

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 children¹.

Midazolam, the first water soluble benzodiazepine, is widely accepted as a parenteral anxiolytic and premedicant.² Intranasal midazolam suppresses epileptic activity and improves the background of electroencephalograms in children with epilepsy.¹¹ Intranasal midazolam administration has the advantages of being painless and allowing rapid absorption into systemic circulation, bypassing the portal circulation.¹³ After nasal use, the drug is available in the cerebral cortex in 2 to 5 minutes, and it increases beta activity seen on electroencephalograms.^{2,3}

The physical and pharmacokinetic properties of midazolam make it well suited for intranasal administration. It is soluble in water at an acidic pH, but becomes more lipophilic as pH rises which allows for the rapidity at which it crosses the blood-brain barrier.

Diazepam is most widely used drug for acute management in all types of seizures in both adults and children. However it has short duration of action and can be administered by intravenous (IV) and rectal route but cannot be given intramuscular (IM) as it is a lipophilic agent with erratic absorption and tends to accumulate if repeated doses are given with the possible rare complication of brainstem depression leading to bradypnoea or even respiratory arrest. In a convulsing child precious time is spent on securing the IV line and it is difficult to secure in a child with generalized tonic clonic seizures.³ Rectally administered benzodiazepine (diazepam) has been

widely used to end seizures, both inside and outside hospital, have variable absorption, may be socially unacceptable.

In case of intranasal midazolam, the maximum concentration was determined to be 104 ± 32 mg/L, and the mean absolute bioavailability of the intranasal route was 55%. The plasma clearance and volume of distribution was twice as high as the same dose administered intravenously.¹²

Rectal mucosa is also a very viable tissue, but unlike nasal mucosa, it does not offer the advantage of bypassing hepatic first-pass metabolism.^{13,14} Since its appearance more than 20 years ago, rectal diazepam has provided a safe, effective alternative to intravenous diazepam in urgent situations. Although well accepted, rectal diazepam gel does have a few disadvantages. After repeated doses, diazepam can accumulate and place the patient at risk for serious adverse drug reactions, such as respiratory depression.¹⁴ The pharmacokinetics of the rectal gel formulation has not been specifically studied in the pediatric population, but it is known that the rectal absorption of a diazepam solution is rapid.¹⁵ In our study we compared the efficacy of intra nasal midazolam with rectal diazepam, by estimating the seizure control time.

II. Aim

To compare the safety and efficacy of intranasal midazolam with rectal diazepam for emergency room treatment of children aged 6months and older with active seizures, without any IV access.

III. Materials And Methods

Study Design

A prospective observational study which was carried out on patients admitted to the emergency unit at TDMC, Alappuzha.

Study Setting

All types of seizures including febrile seizures in children of either sex ,aged 6 months and above who attended the hospital outpatient department or emergency ,in active seizures ,without any iv access were included in the study. Drugs used in this study were intranasal midazolam (0.2mg/kg) and rectal diazepam (0.3 mg/kg).The whole duration of the study was 18 months. Those children coming in active seizures during the first 9 months of study were given intranasal midazolam and those coming during the next 9 months were given rectal diazepam as per the hospital protocol. Blood sugar and serum calcium were assessed before enrollment and after seizure in each patient. A written consent was obtained from the parents or guardians of children regarding their willingness to participate in the study.

- 1) Assess airway, breathing and circulation.
- 2) Apply 100% oxygen to the seizing patient.
- 3) Calculate the dose of midazolam or rectal diazepam required.

INSTRUCTIONS	MIDAZOLAM	DIAZEPAM	
PREPARATION	APPLY OXYGEN.SUCTION	APPLY	
	NOSE IF SECRETIONS.	OXYGEN	
INDICATION	SEIZURE>5MIN	SEIZURE>5MIN	
DOSE	0.2mg/kg	0.3mg/kg	
MAXM DOSE	10 mg	20 mg	

Diazepam is introduced into the rectum with an 8F infant feeding tube that is inserted 4 cm into the anal opening.

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

Study Period

18 MONTHS

Sample Size

50 SUBJECTS

Inclusion Criteria

1) Children in the age group of 6 months and above coming with active seizures without IV access.

Exclusion Criteria

- 1) Child who received emergency treatment for present seizure from elsewhere.
- 2) Children with more than 1 previous treatment with diazepam
- 3) Clinically significant psychiatric disorder
- 4) Child with URI and profuse nasal discharge
- 5) Children with hypoglycemic or hypocalcaemia seizures.

Analysis

Data was collected and entered in MS Excel. Data analysis done using SPSS ver17.0. Quantitative variables described by mean and SD. Qualitative variables were described by percentage distribution. Group comparison of qualitative variables analysed using chi square test and quantitative variables by independent student t test. p value of .05 was taken as level of significance.

IV. Results

In this study of 50 children, majority belonged to the age group 1-5 yrs (48%), whereas 20% belonged to 6m -1year age group and 32 %to above 5 years age group. Out of 50 children, 31 were males (62%) and 19 were females (38%). Majority of the seizure type belonged to GTCS type-76%, about 22% were partial and the rest were absence type. Out of the 50 patients 47 were born full term and 3 were preterm.

In the diazepam group, 52% had tachycardia before drug administration and 36% had tachycardia after drug administration. In the midazolam group, 56% had tachycardia before drug administration and 48% after drug administration. This was not significant.

Tachypnoea was found in diazepam group in 3 patients before drug administration and 2 patients after drug administration. Also in the midazolam group, 3 patients had tachypnea and 1 patient had it after drug administration. In our study, 40% patients came with febrile seizures, 32% came with seizure disorder, 10% had cerebral palsy and about 6% had infections. 2% malformations. 4% had metabolic causes and syndromic causes. This study showed that 55% of patients studied had a past history of seizures, while 46% did not have any past history. Out of the 25 patients in diazepam study group, 15 responded whereas 10 required a second drug for controlling seizures. Whereas in the midazolam group, 3 did not respond but 22 responded. This was statistically significant.

The mean duration of seizures was almost same for both drugs, 10.9 min for diazepam and 10.08 min for midazolam. This was not statistically significant.

Table 1.

DRUG	N	Drug delivery time in minutes			T	p
		Mean	sd			
PER RECTAL DIAZEPAM	25	2.69	1.17	17	5.714	<0.001
INTRANASAL MIDAZOLAM	25	1.22	.54	4		

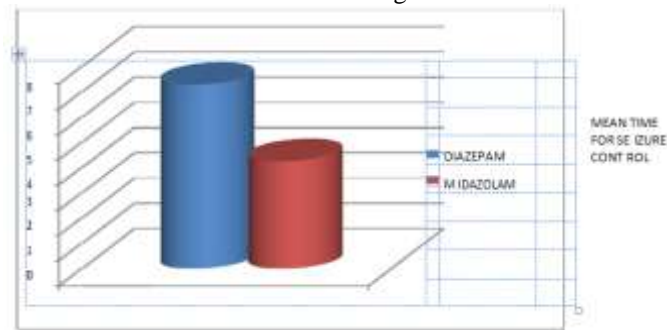


Table 2

DRUG	N	Seizure control time in minutes		T	p
		Mean	sd		
PER RECTAL DIAZEPAM	25	7.27	4.51	2.696	.010
INTRANASAL MIDAZOLAM	25	4.24	3.33		

Figure2

Time From Administration Of Drug To Control Of Seizure



The mean seizure control time was 7.27 mins for rectal diazepam and 4.24 min for intranasal midazolam, this finding was statistically significant. Intranasal midazolam was found to control seizures faster than rectal diazepam

V. Discussion

Administration of antiepileptics in children with acute repetitive seizures outside of the hospital setting is often difficult. At present, only rectal diazepam has been approved by the Food and Drug Administration (FDA) for use in these situations. This formulation, however, is expensive and difficult for many parents to administer, especially during seizures occurring outside the home. Many older children and adolescents object to this route as being intrusive and socially unacceptable.^{5,6,7}

In our study, which studied 50 children who came in with active seizures, intranasal midazolam was found to have better efficacy in controlling seizures than per rectal diazepam. Efficacy was assessed by comparing the time taken to control seizures from the time of administration of drug. The mean time for seizure control from the administration of drug was 7.27 mins for rectal diazepam and 4.24 mins for intranasal midazolam.

In this study a total of 50 children in age group of 6 months to 12 years were included which were further divided into two groups of 25 each. In group I, children were treated with per rectal diazepam (0.3 mg/kg) and in group II intranasal midazolam (0.2 mg/kg) for control of seizures was administered. Time interval for administration of drug and time from administration to control of seizures was noted and side effects like tachycardia, blood pressure changes, tachypnoea were compared.

Our study had majority of patients with febrile seizure as their diagnosis. This constituted about 40% of all patients who presented with seizures. Of the total, 32% came with seizure disorder, 10% had cerebral palsy and about 6% had infections. 2% had structural CNS malformations, 4% had metabolic causes and syndromic causes. These findings were compared with the studies of Bhattacharya et al and Shah et al. There was an almost equal predominance of febrile seizures and seizure disorder in our study. Various studies showed different results, probably because of the different etiologies compared. In the study population studied, in the diazepam group, 52% had tachycardia before drug administration and 36% had tachycardia after drug administration.

In the midazolam group, 56% had tachycardia before drug administration and 48% after drug administration. This was not significant statistically. In our study, tachypnoea was found in diazepam group - in 3 patients before drug administration and 2 patients after drug administration. Also in the midazolam group, 3 patients had tachypnoea before and 1 patient had it after drug administration. This was also not significant. In a study done by Bhattacharya et al, 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. 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 administration⁹Fisgin et al. also detected tachypnea in their study children after administration of intranasal midazolam.⁹As there was no significant variation in vitals both before and after the drug administration, drugs are thought to less likely produce serious side effects. Thevariation in vitals is not statistically significant also. The safety profiles of both drugs aresimilar.

The mean drug delivery time for per rectal diazepam was 2.69 mins (SD 1.17) and 1.22 mins (SD 0.54) for intranasal midazolam. This was statistically significant (<0.001). Intranasal midazolam had an easier drug delivery route (Table 1) and the duration of drug delivery was also short. This was comparable to the study done by Bhattacharya et al. In a study done by Bhattacharya et al, the drug administration time was observed to be shorter in the midazolam group than in the diazepam group (P = 0.002). Fisgin et al used an injector for the introduction of intranasal midazolam, through which the drug was introduced within 30 seconds. 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).⁹

Thakker and Shanbag conducted an additional study comparing intranasal midazolam to IV diazepam for acute seizures in children seen in a pediatric emergency department in Mumbai. Fifty children (1 month to 12 years of age) were randomized to receive either 0.2 mg/kg midazolam dripped into the nares or 0.3 mg/kg IV diazepam for a seizures lasting more than 10 minutes. The primary outcome measures were time from arrival to initiation of treatment and time from arrival to seizure cessation. As noted in earlier studies, time to treatment was significantly shorter in the midazolam group (mean 3.37 + 2.46 min versus 14.13 + 3.39 min in the diazepam group).According to Lahat et al ,in the comparison of intranasal midazolam with iv diazepam, the mean time from arrival at hospital to starting treatment was significantly shorter in the midazolam group (3.5 (SD 1.8) minutes, 95% confidence interval 3.3 to 3.7) than the diazepam group (5.5 (2.0), 5.3 to 5.7)⁸².

The mean seizure control time was 7.27 mins (SD 4.41 min) for rectal diazepam and 4.24 min (SD 3.33 min) for intranasal midazolam. This finding was statistically significant. Intranasal midazolam was found to control seizures (Table 2) faster than rectal diazepam, according to our study.

According to Fisgin et al, two drugs (rectal diazepam and nasal midazolam) with proven efficacy in the treatment of convulsions were compared. Thirteen patients (60%) in the first group and 20 (87%) patients in the second group responded in 10 minutes. Regarding the anticonvulsant effect, midazolam was found to be more effective than diazepam, and the difference was statistically significant. Regarding the anticonvulsant effect, midazolam was found to be more effective than diazepam, and the difference was statistically significant (P < .05).¹¹

In a study by Lahat et al, who did a comparison of intranasal midazolam and intravenous diazepam, overall, 23 of 26 seizures responded to initial treatment with intranasal midazolam and 24 of 26 responded to intravenous diazepam. Statistically significant differences were found between the time of treatment and control of seizures. Time from arrival at hospital to treatment was faster in the midazolam group. Seizures were controlled faster in the diazepam group, and the time from arrival at hospital to control of seizure was faster in the midazolam group.¹⁰

Bhattacharya et al in his study showed that, 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 the difference, however, was not statistically significant. Mean time from drug administration to cessation of seizure was significantly less in the midazolam group than the diazepam group (P = 0.005).¹¹

In our study, out of the 25 patients in diazepam study group, about 15 responded whereas 10 required a second drug for controlling seizures. Whereas in the midazolam group, 3 did not respond but 22 responded. This was statistically significant.

Fisgin et al found out that the necessity of a second drug for the seizures that did not stop with the first drug was higher in the diazepam group than the midazolam group, and the difference was statistically significant (P < .05).In the first group, the seizure of 13 (60%) patients terminated in 10 minutes; however, 9 (40%) patients did not respond.In the second group, 20 (87%) patients responded in 10minutes, but 3 (13%) patients did not respond⁸

VI. Conclusion

Intra nasal midazolam was efficacious than rectal diazepam in terms of shorter seizure control time as well as in terms of shorter drug delivery time. The safety profile of both drugs were almost similar. Thus from this study, intranasal midazolam can be used for emergency control of seizures outside a hospital setting especially. The probable hindrance to this could be the cost of the drug.

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