Original article

A prospective randomised study on intranasal midazolam *versus* rectal diazepam for acute seizures in children

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Abstract

Introduction: Seizures, a common problem in children need to be terminated promptly to avoid significant morbidity and mortality associated with prolonged seizures. A variety of drugs through different routes have been used for quick relief of seizures. We conducted a study to compare the efficacy of intranasal midazolam with rectal diazepam for treatment of acute seizures in children.

Methods

This was a prospective, randomised study undertaken in children presenting with acute seizure at a tertiary carehospital over a period of 17 months. A total of 93 children were enrolled in whom 100 seizure episodes were randomly treated with either intranasal midazolam or rectal diazepam. Seizure Cessation time and Drug administration time were the primary outcome measures studied.

Results: The mean Seizure Cessation time in intranasal midazolam group was significantly less as compared to rectal diazepam group.(163.08± 34.63 seconds Vs181.96 ± 41.36 seconds; p= 0.017). The Drug administration time was also significantly shorter in intranasal midazolam group as compared to rectal diazepam group (60.52 ± 15.26 secondsvs68.80 ± 23. 24 seconds;p= 0.038).

Conclusion: Intranasal midazolam was more effective than rectal diazepam in control of acute seizures. Also, the time required to administer intranasal midazolam was much less as compared to rectal diazepam.

Keywords: Seizures, efficacy, midazolam, intranasal.

NTRODUCTION

Seizures, a common medical emergency in children need prompt treatment. Prolonged seizure activitycan lead to significant morbidity and mortality which is directly proportional to the seizure duration. It is recommended that seizures lasting longer than 5 minutes should be immediately treated with an anticonvulsant (1). Prompt treatment of seizuresis important to reduce the risk of development of status epilepticus and prevent permanent brain damage. In a hospital , intravenous diazepam is commonly used for control of acute seizures, but it requires an intravenous access and has the drawback of being a respiratory depressant (2).The introduction of an intravenous line may be difficult, particularly in children with generalised tonic-clonic seizure. Oral diazepam and lorazepam, sublingual lorazepam, rectal solutions/ suppositories of diazepam have been used to treatacute seizures(3). The oral or sublingual route of administering medications is often difficult and hazardous when children are convulsing. Rectal diazepam has been reported it to be effective for home and hospital treatment of acute seizures but rectal route is not

always reliable owing to its variable bioavailability(4–6).

Recent studies have demonstrated midazolam by intranasal route to be effective in the quick termination of acute seizures (7,8). There is a need of medication that is quickly effective, safe and more importantly easy to administer by medical & non-medical personnel as well. Few studies have studied the efficacy of rectal diazepam versus intranasal midazolam in treatment of acutely convulsing child. In view of this, we conducted this study with the primary objective of comparing the efficacy of intranasal midazolam with rectal diazepam in treatment of acute seizures and also assessing their adverse events.

AIMS AND OBJECTIVE

1) Tocompare the efficacy of intranasal midazolam with rectal diazepam in treatment of
   Acute seizures.

2) To study adverse effects associated with intranasal midazolam and rectal diazepam.

METHODS

This was a prospective, randomised controlled, single masked ,interventional study conducted from May 2013 to October 2014, over a period of 17 months. It was approved by the Institutional Ethics Committee. It involved study of seizure episodes in children presenting with acute seizure. Children were enrolled frompediatric epilepsy clinic, outpatient department, wards and emergency pediatric services.

Children between 6 months to 12 years presenting with seizures due to any epilepsy or with febrile seizures were included after obtaining written consent from the parents. Children with hypoglycaemic, hypocalcemic seizures, status epilepticus andcritically ill patients were excluded from the study. Patients satisfying inclusion and exclusion criteria were enrolled. Patients were clinically stabilised, consent was obtained from parents and were randomised to receive either intranasal midazolam or rectal diazepam. One hundred chits were made, 50 each of intranasal lmidazolam and rectal diazepam. With every seizure episode, randomization was done by shuffling the chits and picking up one by the houseofficer not involved in the study. The medication mentioned on the chit was administered. Data was recorded in pre designed case record form .Midazolam was administered by atomizer devise by the physician. The devise was held between thumb and finger and with patient's head upright, nozzle was inserted into the nostril, and the pump was depressed to administer the medication at the dose of0.2 mg/kg .Diazepam was administered as a rectal suppository available in strength 2.5 mg and 5.0 mg and was given at the dose of 0.3 mg/kg.Vitals like pulse rate, respiratory rate, blood pressure and, oxygen saturation were recorded at 0 minute (prior to drug), and at 5, 10 and 30 minutes post medication.

In every seizure episode, the Drug administration time, Seizure Cessation time and the Overall seizure cessation time were recorded. Drug administration time was defined as time taken by physicianto prepare and deliver the drug to the patient. Seizure Cessation time was defined as interval between drug administration to the end of seizure episode. Cessation of seizure episode was taken as no visible motor phenomenon or presence of appropriate response to external stimuli. Overall seizure cessation time was defined as time between initiation of preparation of the drug to the end of seizure. Recurrence was defined as a repeat episode of convulsion within one hour of administration of the drug and need of alternate medication to control the seizure. If the child continued to have a seizure at 5 min, then alternative rescue medication was administered. The requirement of rescue

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medication, at this stage was classified as a treatment failure.

SAMPLE SIZE

The sample size was calculated by using n Master 1.0. In previous study by Bhattacharya et al. seizure cessation timein rectal diazepam group was 178.6 ±179.4 seconds and in intranasal midazolam it was 116.7 ± 126.9 seconds. The standard deviation of seizure cessation time in rectal Diazepam group was assumed to be 155 seconds and in intranasal midazolam group as 125 seconds and the mean difference between both the groups as 72 seconds. Keeping alpha error at 5% and power of the study 80 % using two sided statistics, a total 50 seizure episodes need to be studied per group. Hence the total sample size of the study was 100 seizure episodes.

STATISTICAL ANALYSIS:

Primary outcome measures analysed were drug administration time, Seizure Cessation Time and overall seizure cessation time **Secondary outcome measures** studied were recurrence of seizure, failure of treatment and presence of side effects. Descriptive statistics was used. Data was calculated by using Graph Pad In Stat 3.0. Baseline difference of both the groups in age distribution was evaluated by chi square test. Difference in time to seizure cessation between both the groups was assessed by student t test. Difference between both the groups in terms of ADRs was evaluated by Chi square test. P<0.05 was kept as significant in all the statistical analysis.

OBSERVATIONS & RESULTS

A total of 118 children were screened of which 93 were enrolled and 25 were excluded. One hundred seizure episodes were studied in the enrolled children, of which 50 were treated with intranasal midazolam and remaining 50 with rectal diazepam. The flow of participants in the study is shown in ***Fig.* 1.**

Data collected was comparable in both the groups with respect to demographic characteristics viz age, type of seizure and etiology of seizure. Inour study, mean ages were 5.51± 3.55 years and 4.68± 3.01 (p=0.849) in intranasal midazolam and rectal diazepam groups respectively. Majorityofthe children(44.08%)were between 1 to 5 years of age.Inbothtreatmentgroups,therewasa maleprepon derance.Outof100children55(59.14%) weremalesand38(40.86%) were females. Other relevant characteristics *viz* birth history, development history and family history in both the groups, were comparable(Table : 1).There was no statistically significant difference in duration of seizure prior to treatment in both the groups (p=0.963).

Themean **drug administration time** in children treated with intranasal midazolam was 60.52 ± 15.26secondswhereas that in children treated with diazepam was68.80 ± 23.24 seconds. The difference was statistically significant (p value = 0.038).This implied that the time required to administerintranasal midazolam was comparatively lesser than that required for administration of rectal diazepam.

The mean **seizure cessation time** in children treated with intranasal midazolam was 163.08± 34.63 seconds where asthatin children treated with diazepam was181.96± 41.36 seconds. The p value was 0.017 which was statistically significant implying intranasal midazolam was more effective than rectal diazepam in control of seizures.

Overall seizure cessation time was taken as time from initiation of preparation of the drug to cessation of seizure. The mean overall seizure cessation time was less in intranasal midazolam (223.6± 39.39 seconds) as compared to rectal diazepam (250.6 ± 46.79 seconds). It was statistically highly significant (p =0.0029)(Table

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2).

Recurrence of seizures was observed in 12 seizure episodes , 8 of which were treated with intranasal midazolam and remaining four with rectal diazepam, how ever the difference was statistically not significant (p=0.683). Prolonged seizure (>5 minutes)were observed in 4 seizure episodes all of which were treated with rectal diazepam. Adverse events in form of tachycardia and hypotension were seen in 4 children who recieved intranasal midazolam whereas only 1 child treated with diazepam had tachypnea and hypotension.. A total of 8 patients had drowsiness post medication, 4 from each group. Overall, there was no statistically significant difference (p = 1). withrespect to side effects between the two groups .

Figure 1 : Flow of participants in the study

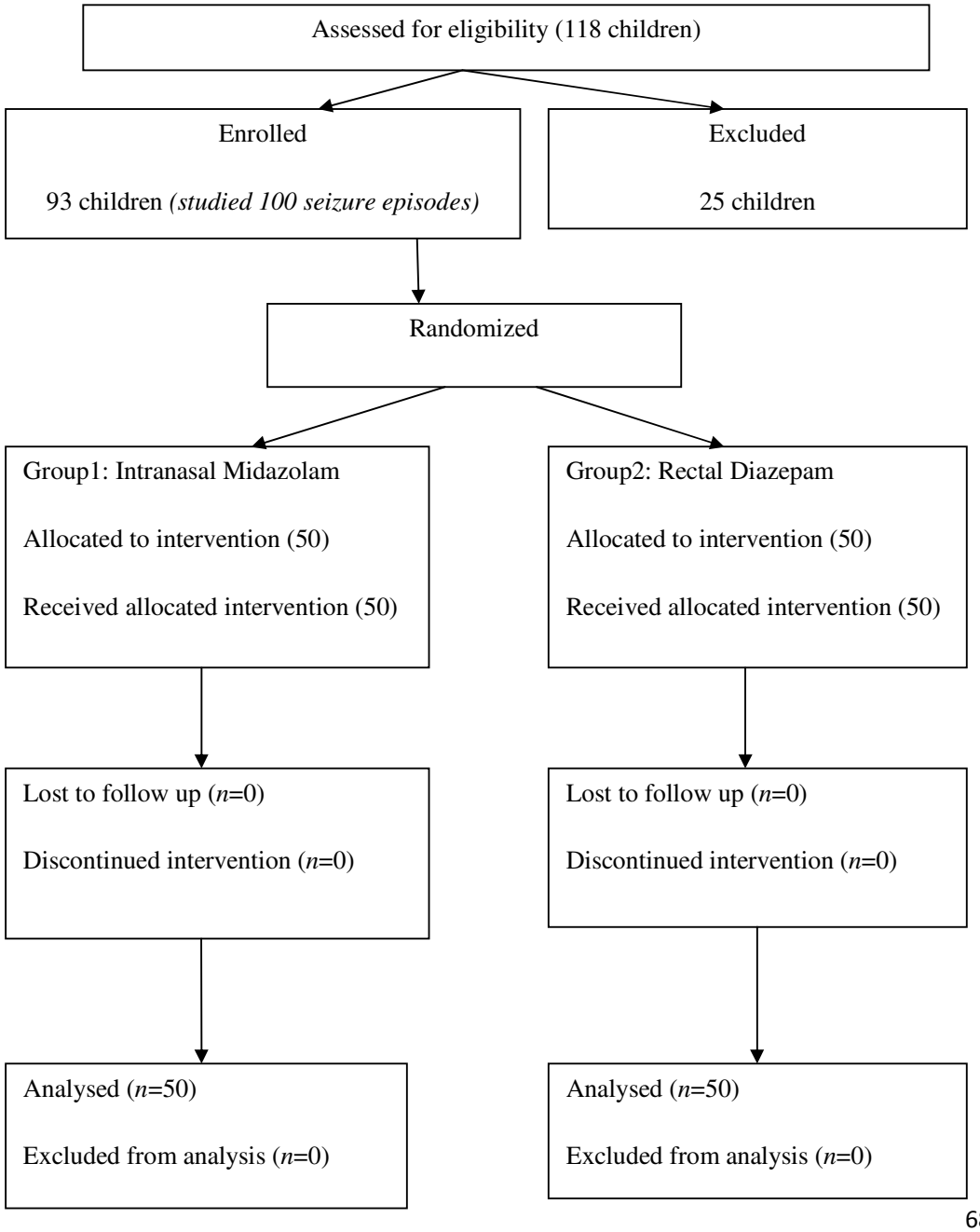

Table1:Baseline characteristics of two treatment groups

Baseline characteristics		Treatment group		
		Midazolam	**diazepam**	***p* value**
		n (%)	n (%)	
Sex	Males	27 (56.25)	28 (62.22)	
	Females	21 (43.75)	17 (37.78)	0.558
Type of seizure	Generalised	36 (72)	41 (82)	0.471
	Focal	12 (24)	7 (14)	
	Unclassified	2 (4)	2 (4)	
Aetiology of seizure	Febrile convulsion	27 (56.25)	22 (48.49)	0.305
	Idiopathic Epilepsy	19(39.58)	21 (46.67)	
	Neurocystisarcosis	3 (6.25)	1 (2.22)	
	Lennox Gasstaut	0 (0)	1 (2.22)	
Other parameters	Abnormal Birth history	1(2.08)	5 (11.11)	0.117
	Delayed Development	2 (4.17)	6 (13.33)	0.115
	Family history of seizure	5(10.42)	4 (8.89)	0.80

Table 2 : Comparison of primary outcome measures between two groups

	Intranasal Midazolam (Mean ± SD)	**Rectal Diazepam (Mean ± SD)**	***p* value**
Drug administration time(in seconds)	60.52 ± 15.26	68.8 ± 23.24	0.038
Seizure cessation time(in seconds)	163.08 ± 34.63	181.96 ± 41.36	0.017
Overall seizure cessation time(in seconds)	223.6 ± 39.39	250.57 ± 46.79	0.0029

DISCUSSION

Seizures constitute the commonest neurologic medical emergency in children. Prolonged seizure activity is not only frightening experience for families and care providers but can even cause permanent brain damage. Early treatment of acute seizure can prevent this and significantly reduce the risk of status epilepticus. In hospital settings, intravenous diazepam is used to control seizure however it requires an intravenous access, which at times is difficult in a convulsing child andis at disadvantage of causing respiratory depression. Researchers have tried alternate routes like intramuscular, buccal, rectal, and intranasal. Rectal diazepam has been used successfully for home and hospital treatment of acute seizures(4,5). But rectal route is not always reliable owing to its variable bioavailability(6) and moreover route of administration is not readily acceptable by many caregivers.

Midazolam , a water soluble benzodiazepine becomes fat soluble at physiological pH,(9)allowing it to cross the nasal mucosa into adjacent tissues including CSF, resulting in rapid

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onset of action.. Also, intranasal midazolam was believed to be more rapid in controlling acute seizures owing to its direct absorption of the drug through the nasal mucosal vasculature into the systemic circulation, by passing the portal circulation(7,10).

The present study was conducted with a purpose to compare the efficiency and safety of intranasal midazolam with rectal diazepam for control of acute seizures.

The two treatment groups were comparableas regards age, sex, duration of seizure, type of seizure and etiology of seizure. In our study, the commonest seizure type observed was generalized tonicclonic (77 %), followed by focal seizure (19%)and 4 (4 %) were unclassified. In present study, the **mean drug administration time** was much shorter inmidazolam group (60.52 ± 15.26 seconds)as compared to diazepam group(68.80 ± 23.24 seconds)with a significant statistical difference(p=0.038). These findings were similar to the study conducted by Bhattacharyya et al(6) wherein they noted the drug administration time was significantly shorter (p = 0.002) in intranasal midazolam group (50.6 +/- 28.2 seconds) compared to rectal diazepam (68.3 +/- 110.2 seconds) . Similar findings were noted in study by Eli Lahat et al(3) where in they compared intranasal midazolam with intravenous diazepam and found intranasal midazolam required less time (mean 3.5 +/- 3.6 minutes) compared to intravenous diazepam (mean 5.5 +/- 4.0 minutes). The intranasal routeowing to its shorter drug administration time, the ease of administration and painless therapy plays an important role in the quick management of acute seizures. In the present study, the **mean seizure cessation time** also was much shorter inmidazolam group (163.08 ± 34.63 seconds)as compared to diazepam group(181.96 ± 41.36 seconds) and the difference was statistically significantly (p = 0.017).These results compare favourably with earlier studies by various researchers. Bhattacharyyaetal(6) in their study found that time in terval to cessation fseizures was faster within tranasalmidazolam (mean =116.7 seconds)as compared to rectal diazepam (mean =178.6 seconds) which was statistically significant (p = 0.005)which was comparable to present study and they also demonstrated thatintranasal midazolam results in morerapidcontrolo fseizures. Another study in 2002 by Fisgin et al(11) regarding the anticonvulsant effect of midazolam also observed midazolam to be more effective than diazepam, and the difference was statistically significant (P < .05). Holsti et al (12) in their study, found no detectable difference in efficacy between IN-MMAD (intranasal midazolam via atomiser devise) and rectal diazepam as a rescue medication (p = 0.09). However, they mentioned that, there may be a trend toward faster seizure control in the intranasal midazolam (mean 3 minutes) group compared to rectal diazepam(mean 4.3 minutes) and also the ease of administration and overall satisfaction were higher in the IN-MMAD group than rectal diazepam . Instudydone by Lahat et al(3) in 2000 comparing intranasal midazolam with intravenous diazepam found statistically significant (p<0.001) data showing less time required for cessation of seizure after giving drug with intravenous diazepam (mean = 2.2 minutes) compared to intranasal midazolam (mean = 3.1 minutes).In our study, the mean **overall seizure cessationtime**in midazolam group was 223.6 ± 39.39 seconds whereas in diazepam treatment group it was 250.57 ± 46.79 seconds, the difference was statistically significant (p =0.0029). This shows that intranasal midazolam required less administration time and is also fast acting in relief of acute seizures. Similar results were demonstrated

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in previous studies. In study done by Lahat et al comparing intranasal midazolam with intravenous diazepam they found that significantly less time to cessation of seizure after arrival at hospital in intranasal midazolam group (6.1 ±3.6 minutes) compared to intravenous diazepam (8.0 ± 4.1minutes).(Table 3).Hence intranasal midazolam was considered to be more efficient in controlling acute seizure as compared to rectal diazepam. Moreover social acceptability of rectal diazepamis understandably less, especially among young females.

Table 3 : Comparison between present and previous studies.

		Mean ± S.D.		
		Intranasal midazolam	**Rectal diazepam**	*p* value
Drug Administration time	**Present study**	60.52 ± 15.26 seconds	68.80 ± 23.24 seconds	0.038
	Bhattacharya et al	50.6 ± 14.1 seconds	68.3 ± 55.1 seconds	0.002
	Holsti et al	3.0 minutes	4.3 minutes	O.09
	Eli Lahat et al	3.5 ± 1.8 minutes	5.5 ± 2.0 (IV diazepam)	<0.001
Seizure cessation time	**Present study**	163.08 ± 34.63 seconds	181.96 ± 41.36 seconds	0.017
	Bhattacharya et al	116.7 ± 126.9 seconds	178.6 ± 179.4 seconds	0.005
	Holsti et al	3 minutes	4.3 minutes	0.09
Overall seizure cessation time	**Present study**	223.6 ± 39.39 seconds	250.57 ± 46.79 seconds	0.0029
	Lahat et al	6.1 ±3.6 minutes	8.0 ± 4.1minutes	<0.001

In present study, 12 (12%) seizure episodes were followed by **recurrence of seizure** within 60 minutes, of which 8 were treated with intranasal midazolam and 4 with rectal diazepam, the difference was statistically not significant (p=0.683). This implies that the recurrence of seizures may occur in either group. These findings were comparable with study done by Bhattacharya et al(6)who noted that seizures recurred in six episodes (6.25%) in the diazepam group and in three episodes (3.26%) in the midazolam group. They concluded that recurrence of seizures may occur in both groups. In the present study, 4 cases in rectal diazepam treatment group required **alternative antiepileptic** for cessation of seizure episode however no cases in midazolam treatment group required use of alternative antiepileptics. Fisgin et al(11) conducted a study on, the effects and side effects of rectal diazepam *Vs* intranasal midazolam in the treatment of acute convulsions in children and found that 13 (60%) patients responded to diazepam in 10 minutes versus , 20 (87%) patients responded to midazolam in 10 minutes. They reported that the necessity of second drug for the seizures that did not stop with the first drug was significantly higher in the diazepam group than the midazolam group (P < .05).

In present study, children were observed for any change in their vital parametrs, desaturation and drowsiness.. In this study, there was no significant change in the mean heartrate, respiratory rate and mean systolic and diastolic blood pressure at 5, 10, and 30 minutes between

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the two treatment groups except 10 (10.75%) children had tachycardia and hypotension, 5 of these were treated withmidazolam and remaining 5 with diazepam. None of the children had any variation in respiration. Desaturation was not seen in any of the child in either treatment group. Drowsiness as a side effect was witnessed in 8 (8.6 %) children, 4 from each group. Of these 8 children, 6 (75%) had received multiple doses due to recurrence of seizures , implying drowsiness might be due to the collective effect of the drug after repeated administration. Our study did not findany serious adverse events with intranasal midazolam treatment. These findings were comparable to study done by Bhattacharya et al(6), who also found no significant change in heart rate and blood pressure between the rectal diazepam group and the intranasal midazolam group. But they observed that the respiratory rate and oxygen saturation decreased in the diazepam group as compared to intranasal midazolam administration from predrug values which was not noticed in our study. Fisgin et al(11) also detected tachypnea in children after administration of intranasal midazolam. O'Regan et al (10)found a severe decrease in oxygen saturation in 1 of 19 children with intractable seizures treated with intranasal midazolam.Whereas Dickmann reported in his study fall in oxygen saturation in 16 children who received rectal diazepam, who required either oxygen alone or oxygen with bag valve mask device to combat respiratory depression(13).

Our study results indicate that intranasal midazolam is more effective than rectal diazepam to control acute seizure without any significant side effects. The published literature also suggests that intranasal midazolam may stop seizures more quickly than rectal diazepam. Adverse effects appear to be minimal. Given the ease ofadministration and efficacy of midazolamin seizure cessation, intranasalmidazolammay be considered an alternative to rectal diazepam. Also considering ease of administration with intranasal route, drug can be administered by parents, teachers, or nonmedical staff in settings such as community, school, or home which may be beneficial and can decrease morbidity and mortality. Sample size of our study was small, so larger studies are needed in prehospital and hospital settings.

To conclude our study, we found intranasal midazolam to be fast acting than rectal diazepam in controlling seizures. Intranasal midazolam is easier and quicker to administer and a route easily acceptable by parents. Neither intranasal midazolam nor rectal diazepam was superior to each other as regards safety. Larger studies are required to establish intranasal midazolam as an alternative route to terminate acute seizures in any settings.

Acknowledgement:

The authors thank Dr Avinash N. Supe, Director (M E & M H) and Dean of Seth GS Medical College and KEM Hospital, Mumbai for granting permission to publish the study.

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