Original Article

Intramuscular Midazolam *vs* Intravenous Diazepam for Acute Seizures

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Abstract. ***Objective:*** To determine effectiveness of intramuscular midazolam to control acute seizures in children as compared to intravenous diazepam. ***Methods:*** 115 children in the age group of 1 month to 12 years who presented with acute convulsions were enrolled in the study. Patients who already had an intravenous access present were treated intravenous diazepam. Patients without an IV access at the time of convulsions were randomised into 2 groups and treated with either intramuscular midazolam or intravenous diazepam for control of seizures. Time interval from administration of drug to cessation of seizures was compared. Effectiveness of IM midazolam in various age groups, types of convulsions and etiology of convulsions was analyzed. Side effects of both drugs were evaluated. ***Results:*** The mean interval to cessation of convulsions with IM midazolam was 97.22 seconds whereas in diazepam group without prior IV access it was 250.35 seconds and in diazepam group with prior IV access it was 119.4 seconds. IM midazolam acted faster in all age groups and in patients with febrile convulsions, which was statistically significant. IM midazolam was equally effective in various types of convulsions be it GTC or focal convulsions. 7 patients (10.8%) had thrombophlebitis associated with IV diazepam administration whereas none of the patients in the midazolam group had any side effects, which was statistically significant. ***Conclusion:*** IM midazolam is an effective agent for controlling acute convulsions in children especially in children with febrile convulsions. It has relatively no side effects as compared to Intravenous diazepam and can be used as a first line agent for treatment of acute convulsions in patients with difficult intravenous access. **[Indian J Pediatr 2005; 72 (8) : 667-670]** *E-mail: irashah86@hotmail.com*

Key words : *Midazolam; Intramuscular; Convulsions; Seizures; Diazepam.*

Convulsions or seizures are one of the commonest neurological diseases seen in neonate and preschool children with an incidence of upto 60 per 1000. 85% of cases of status epilepticus occur in this age group.[1] Seizures can lead to unrelenting muscular activity, leading to anaerobic metabolism and tissue breakdown as well as increase the cerebral metabolic rate exceeding the oxygen and glucose supply to the brain leading to brain ischemia and neuronal death.[2] Thus it is important to control seizures rapidly to minimize the systemic as well as brain damage.

Benzodiazepines are the first line of anticonvulsants for treatment of acute seizures. Diazepam is one of the most frequently used benzodiazepines both intravenously as well as rectally. It cannot be used intramuscularly as it is a lipophilic agent with erratic intramuscular absorption. Thus in a convulsing child, precious time is spent on getting an intravenous access or for per rectal catheterization. Midazolam is a lipid soluble benzodiazepine with 3-4 times more potency as diazepam on a milligram-to-milligram basis and can be given IV, rectal or intramuscular. Midazolam in the dose of 0.1 mg/kg to 0.3 mg/kg is readily available for intramuscular dose due to its water-soluble nature. Bio-availability of midazolam is approximately 90% post intramuscular administration.[2]

The aim of the study was thus to compare efficacy of intramuscular midazolam to stop acute convulsions as compared to intravenous diazepam.

MATERIAL AND METHODS

This prospective trial was conducted over a period of 1 year in a tertiary general hospital after clearance from the Hospital Ethics Committee. Patients in the age group of 1 month to 12 years who were brought to the emergency department with acute convulsions, or those patients admitted in the pediatric ward and pediatric intensive care unit who developed acute seizures, were included in the study. Patients who had received other anticonvulsants for treatment of acute seizure were excluded from the study. Patients who already had an intravenous access present were treated with 0.2 mg/kg of intravenous diazepam for control of seizures and time interval from administration of diazepam to cessation of seizures was noted. Patients without an IV access at the time of convulsions were randomised into 2 groups. Patients in Group 1 were given 0.2 mg/kg of intramuscular midazolam for control of seizures and time interval from administration of midazolam to cessation of seizures was noted. In the Group 2, time interval was taken from starting an intravenous access, administration

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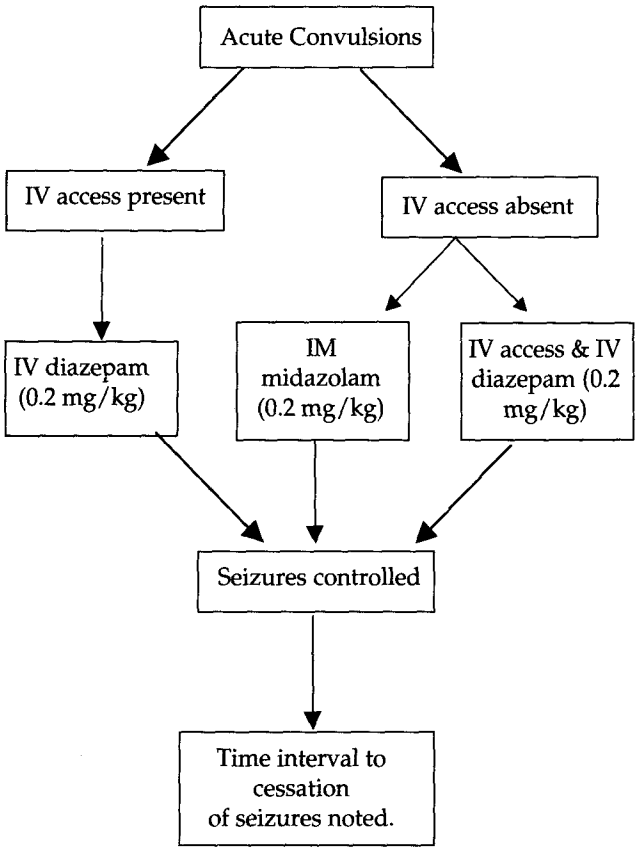

Fig. 1. Flow chart demonstrating the study design.

Note:

- Seizures not controlled after 5 minutes - Other anticonvulsants were used.
- Patients who were given other anticonvulsants as first line agents were excluded from the study.

of drug to cessation of seizures (Fig. 1). An unbiased junior resident doctor noted time interval from the moment of administration of the drug and cessation of seizures with a stopwatch. Patients were monitored for vital parameters including heart rate, respiratory rate, blood pressure and sensorium and side effects of the drug administered were noted every 10 minutes till one hour after control of seizure and then every 6 hourly for next 24 hours. Both diazepam and midazolam were kept in a pre-filled syringe in the emergency tray for immediate use. The efficacy of each drug was compared in different age groups with different etiologies of convulsions and in different types of convulsions.

In those patients in whom seizures persisted, even after 5 minutes after administration of the drug, other anticonvulsants were given as routinely done.

The data was analyzed by 't' table and compared using chi-square test for proportions.

RESULTS

115 patients with acute convulsions were included in the study of which 50 patients were given IM midazolam and 65 patients were given IV diazepam. Of the 65 patients given IV diazepam, 31 patients had no prior intravenous access and 34 patients had an intravenous access already present. Sixteen (13.9%) patients required other anticonvulsants for stopping their seizures of which 5 (31.25%) belonged to the midazolam group, 2 (12.5%) belonged to diazepam group without an IV access and 9 (56.25%) belonged to diazepam group with an IV access.

The mean time to cessation of seizures with intramuscular midazolam was 97.22 seconds with a range from 15 seconds to 240 seconds. In patients in diazepam group without an intravenous access, the mean time to cessation of seizures was 250.35 seconds with a range from 90 seconds to 300 seconds, which was statistically significant. (t_{72} = 7.280, <p 0.005). In patients in the diazepam group who already had an intravenous access present, the mean time to cessation of seizures was 119.44 seconds with a range from 1 second to 270 seconds, which was statistically insignificant (p = 0.17).

Patients were divided into various age groups and efficacy of intramuscular midazolam was determined (Table 1). Intramuscular midazolam was statistically faster for controlling seizures in all age groups as compared to IV diazepam when intravenous access was not present. There was no significant difference in time interval of cessation of seizures in patients with diazepam group with IV access and midazolam group.

The presentation of acute convulsions was varied with predominant convulsion types being generalized tonic clonic convulsion and focal convulsions. In both these types of convulsions, cessation of seizures was statistically faster with IM midazolam as compared to IV diazepam without IV access. (Table 2) with no significant difference in those who had an intravenous line already present.

Patients with febrile convulsions had statistically faster control of seizures with IM midazolam as compared to IV diazepam without IV access [p<0.001, (t_{18}=5.35)]. Also patients with infective parenchymal lesions such as pyogenic meningitis or TBM, epilepsy, neurocysticercosis, viral encephalitis and hypoxic convulsions had faster control of seizures with IM midazolam as compared to IV diazepam without IV access though statistical significance cannot be commented on as the patient groups were small. (Table 3).

7 (10.8%) patients in the diazepam group had thrombophlebitis, which was statistically significant (P= <0.05). No significant abnormality in the vital parameters was noticed in any of the groups and none of the patients had hypotension or respiratory depression due to the drugs.

DISCUSSION

Seizures if not effectively controlled may lead to status epilepticus, brain ischemia and neuronal damage. Diazepam and lorazepam have been proved to be equally

TABLE 1. Mean Time Interval to Cessation of Seizures with IM Midazolam and IV Diazepam in Different Age Groups

Age group	IM Midazolam Mean Sec + S.D (n)	IV Diazepam without IV access Mean Sec + S.D (n)	P value	IV Diazepam with IV access Mean Sec + S.D (n)	P value	Other ACT (n)	Total n (%)
1 month – 1 year	97.81 ± 53.8 (16)	281.25 ± 200.9 (8)	<0.001 (t22=3.848)	122.5 ± 94.1 (6)	0.45	6	36 (31.3%)
1 year – 5 years	104.74 ± 71.6 (19)	258 ± 126.6 (10)	<0.001 (t27=4.19)	132 ± 66.6 (5)	0.46	5	39 (33.9%)
5 years – 12 years	85.11 ± 36.5 (10)	215.5 ± 78.5 (11)	<0.001 (t_{19}=4.29)	115.7 ± 68.3 (14)	0.4	5	40 (34.8%)

ACT=Anticonvulsants

TABLE 2. Mean Time Interval to Cessation of Seizures with IM Midazolam and IV Diazepam in Different Types of Convulsions

Type of Convulsion	IM Midazolam Mean Sec ± S.D (n)	IV Diazepam without IV access Mean Sec ± S.D (n)	P value	IV Diazepam with IV access Mean Sec ± S.D (n)	P value	Other ACT	Total (%)
GTC	99.4 ± 65.5 (25)	257.83 ± 145.9 (23)	<0.001 (t_{46}=4.92)	125.1 ± 73.9 (9)	>0.20 (t_{32}=0.97)	6	63 (54.8%)
Focal Convulsion	88.33 ± 47.5 (18)	205 ± 72.0 (6)	<0.001 (t_{22}=4.57)	109.6 ± 77.4 (14)	>0.20 (t_{30}=0.96)	9	47 (40.9%)
Tonic Convulsion	150 ± 42.4 (2)	-	-	162.5 ± 60.1 (2)	-	-	4 (3.5%)
Clonic Convulsion	-	-	-	300 sec (1)	-	-	1 (0.8%)

GTC=Generalised Tonic Clonic convulsion; ACT=Anticonvulsants

TABLE 3. Mean Time Interval to Cessation of Different Etiological Seizures with IM Midazolam and IV Diazepam

Etiology	IM Midazolam Mean Sec + S.D (n)	IV Diazepam without IV access Mean Sec + S.D (n)	IV Diazepam with IV access Mean Sec + S.D (n)	Other ACT	Total (%)
Febrile Convulsion	67 + 43.4 (10)	195 + 62.0 (10)	180 (1)	-	21 (18.3%)
Meningitis (Pyogenic + TBM)	120 + 51.2 (7)	270 + 42.4 (2)	158 + 90.3 (5)	3	17 (14.8%)
Epilepsy	62.5 + 32.0 (4)	243.3 + 179.5 (6)	56.67 +5.8 (3)	4	17 (14.8%)
Neurocysticercosis	110 + 62.4 (3)	172.5 + 61.8 (4)	176.7 + 77.7 (3)	-	10 (8.7%)
IEM	55.83 ± 35.3 (6)	-	112.5 + 95.5 (2)	-	8 (7.0%)
Hypocalcemic	110 + 62.4 (3)	300 (1)	150 (1)	3	8 (6.9%)
Viral Encephalitis	165 + 106.1 (2)	270 ± 42.4 (2)	205 (1)	2	7 (6.1%)
Hypertensive Encephalopathy	45 (1)	- 60	(1)	1	3 (2.6%)
SOL	120 (1)	-	180 (1)	1	3 (2.6%)
Congenital Malformations	240 (1)	300 (1)	30 (1)	1	3 (2.6%)
Hemorrhage	50 (1)	-	60 (1)	-	2 (1.7%)
Others Including Hypoxic	136.4 (7)	330 (2)	81.2 (5)	2	16 (13.9%)

TBM=Tuberculosis meningitis, IEM= Inborn error of metabolism, SOL = Space occupying lesion

effective in treatment of acute seizures.[3] However, they have to be administered intravenously though diazepam can be given per rectally. Getting an IV access immediately may be difficult in children and rectal administration of diazepam is also not easy Also incidence of thrombophlebitis with diazepam is quite high.[4] Midazolam being water-soluble can be given intramuscularly[3] which may be a good option for office management of acute seizures.

In the present study, we found intramuscular midazolam was effective in controlling seizures which was similar to those reported in other studies.[5,6,7,8] The

mean time to control of seizures was 97.22 seconds which was comparable to 113 seconds reported by Galvin *et al.*[6]

It was also found that time interval to cessation of seizures was faster with intramuscular midazolam as compared to intravenous diazepam as time was consumed in putting an intravenous line in patients receiving diazepam as statistical significance was found only in patients without prior IV access. Thus midazolam results in more rapid control of seizures because of more rapid administration. Chamberlain *et al* demonstrated similar results as patients in the midazolam group received their medications sooner.[9]

In the present study, intramuscular midazolam is effective for controlling seizures in all age groups that was statistically significant which again signifies that it may be effective in all children irrespective of age.

IM midazolam was equally effective in generalized tonic clonic convulsions and focal convulsions and thus may be effective in different type of convulsion which is similar to those reported by Lahat *et al.*[5]

In the present study, it was found that IM midazolam is effective in treatment of acute convulsions due to febrile convulsions which was statistically significant as compared to IV diazepam which may make it an effective tool in the management of febrile convulsions in office practice where intravenous access may often be difficult.

There was no difference in the ratio of patients going into status epilepticus in the midazolam or diazepam group which is similar to that reported in other studies.[5,9]

None of the patients in either group developed hypotension or respiratory depression though a significant number of patients in the diazepam group developed thrombophlebitis. Propylene glycol in the ampoule of diazepam is considered to be the agent leading to thrombophlebitis.[4]

CONCLUSION

Thus it may be concluded, that intramuscular midazolam is safe and effective in control of acute seizures irrespective of the type of convulsions and age of the child. It may be used as a first line agent in management of acute convulsions in children in whom intravenous access is difficult especially in those with febrile convulsions.

Key Messages

- Intramuscular midazolam is safe & effective for control of acute convulsions in children.
- IM midazolam can be used as a first line agent for management of acute seizures in office practice especially in patients with febrile convulsions and in whom the IV access is not easy irrespective of age or type of convulsion.

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