Original Article

DOI: 10.17354/ijss/2015/306

Buccal Midazolam versus Intravenous Diazepam in Prolonged Seizures in Children

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Abstract

Background: Seizure episode is a common neurological emergency carrying high morbidity and mortality. It has been shown that prompt treatment of episodes of seizure at home results in need of fewer drugs at hospital and quicker control of the seizure/seizure episodes. Buccal midazolam can be recommended as an alternative to intravenous (I/V) diazepam (DZ) as first choice in situations of difficulty in getting I/V access.

Materials and Methods: Design: Prospective randomized controlled study. Setting: Conducted in the Department of Pediatrics, Government Medical College and Hospital, Amritsar, during the period from January 2009 to December 2009. Total 100 (59 boys, 41 girls) patients were enrolled in the study. In the study group (BMDZ), patients received buccal midazolam (0.3 mg/kg/dose) and in control group (IVDZ), patient received I/V DZ (0.2 mg/kg/dose).

Results: In BMDZ group, 48 (96%) cases of seizures were aborted by giving buccal midazolam and in IVDZ group also an equal number, i.e., 48 (96%) cases of seizures were aborted by giving DZ intravenously ($P > 0.05$). The mean time needed for cessation of seizures in BMDZ group was 96.0 ± 144.69 s (1.60 min) with the lowest time being 30 s and the highest being 790 s, and it was 83.40 ± 124.27 s (1.39 min) in IVDZ group with the lowest being 30 s and the highest being 685 s. The difference in time taken to control seizures between two groups was statistically insignificant ($P = 0.641$). No significant side effects were seen in either group.

Conclusions: It is concluded from the above study that buccal midazolam is equally effective and more convenient as compared to I/V DZ in prolonged seizures while both are comparable in safety.

Key words: Buccal, Diazepam, Efficacy, Intravenous, Midazolam, Prolonged, Seizures

INTRODUCTION

Seizure episode is a common neurological emergency. Because the duration of seizure activity impacts morbidity and mortality, effective methods for seizure control should be instituted as soon as possible, preferably at home.[1]

Seizures continuing beyond 5 min have the potential of progressing into full blown status epilepticus. The potential of neuronal damage and sequelae of status epilepticus are well-known,[2-5] and intervention has been suggested for continuous seizure activity lasting more than 5 min.[6]

The longer a seizure endures, the more likely the development of pharmacoresistance[7] and animal studies suggest a greater likelihood of neuronal damage.[8] As a result, an operational definition of a seizure or intermittent seizures without full recovery of consciousness lasting more than 5 min is used as a guide for intervention.[9]

The value of early treatment in seizures in reducing seizure-related morbidity has been established.[10,11] It has also been shown that prompt treatment of episodes of seizure at home results in need of fewer drugs at hospital and quicker control of the seizure/seizure episodes.[12] The persistence of seizures longer makes it difficult to stop. Stoppage of seizure was 80% when first-line antiepileptic drug was started <2 h and was 40% when treatment was started after 2 h.[13]

Access this article online

IJSS

www.ijss-sn.com

Month of Submission : 05-2015
Month of Peer Review : 06-2015
Month of Acceptance : 06-2015
Month of Publishing : 07-2015

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Traditionally, benzodiazepines, barbiturates, or other anticonvulsants have been given intravenously. The main problem in the management of a child actively showing seizure is the delay in reaching a hospital and gaining an intravenous (I/V) access. Rectal diazepam (DZ) offers an alternate method of delivery but has much lower peak concentration, a slower onset of action, less socially acceptable than other routes. Other drugs are associated with known side-effects.

In acute medicine, midazolam has become more popular than other benzodiazepines such as DZ because it is shorter lasting, early onset of action, is more potent, and causes less pain at the injection site. This benzodiazepine that contains an imidazole ring is highly water soluble and is rapidly absorbed from rectal, nasal and buccal mucosa, and is also highly lipophilic at central nervous system.[14-17] When given via buccal route, it is absorbed rapidly with minimal side effects, offers ease of administration, can be given at home by parents/guardians and is socially more acceptable with no delay in the initiation of the emergency treatment. No clinically important side effects were seen in any patient when it was used. Intranasal midazolam has been used at some centers, but it cannot be used in patients with nasal blockage, anatomical abnormalities of the nose, nasal secretions, nasal allergy, etc.

Benefits of Buccal Drug Delivery

To compare with existing available therapies, buccal drug delivery products offer comfort, convenience and control for those who use them - patients, their caregivers, physicians, emergency care workers, and other healthcare professionals are simple and easy to administer are non-invasive, and virtually pain free reduce irritation as they are preservative-free, avoid bio-hazardous waste or needle stick accident risks, demonstrate rapid onset of action and efficient absorption.

Keeping in view the benefits of using buccal midazolam, and use of I/V DZ as the first line treatment to abort seizures in our hospital, we have compared buccal midazolam with I/V DZ.

MATERIALS AND METHODS

The aim of the study was to compare the efficacy of buccal midazolam and I/V DZ in children aged 1 month and over with seizures lasting more than 5 min. This was a prospective randomized controlled study which was conducted in the Department of Pediatrics, Government Medical College and Hospital, Amritsar, Punjab, India during the period, from January 2009 to December 2009. Approval from the Ethics Committee was taken prior to the study. Informed written consent from the parent/guardian was obtained. Efficacy is defined as cessation of seizures within 10 min of administration of the drug and no recurrence in the subsequent 1 h.

Inclusion Criteria

1. Prolonged seizures of more than 5 min duration
2. In children aged 1 month and over.

Exclusion Criteria

1. Patients who have already received I/V benzodiazepine/midazolam in last 24 h.

About 120 patients were included in the study. Of 120 patients 14 did not fill the inclusion criteria, 6 patients did not agree to participate. Hence, total 100 (59 boys, 41 girls) patients were enrolled in the study.

The weight of all the patients was recorded prior to drug administration. In the study group (BMDZ) (Group 1), patients received buccal midazolam (0.3 mg/kg/dose) and in control group (IVDZ) (Group 2), patient received I/V DZ (0.2 mg/kg/dose).

Method used to Administer Buccal Midazolam (0.3 mg/kg/dose)

After opening the midazolam vial (1 mg/ml), a prescribed amount of midazolam was drawn into the syringe. The syringe was taken out of the vial, and the needle was dislodged. The child was placed in the recovery position, and mouth was opened gently by holding chin and applying downward pressure on the lower lip. Any excess saliva was wiped away (without parting the teeth). The nozzle of the syringe was placed between the lower gum and cheek on one side of the mouth (the buccal cavity). The dose was given slowly into the mouth; then the syringe was removed, and lips were closed together. The cheeks were then rubbed on the outside. Midazolam can be given on either side, or both divided approximately into half each side. Midazolam was not given too quickly to avoid choking or swallowing it. The child was maintained in the recovery position. Using a stopwatch, the time taken to control the seizures was noted.

In case, if seizures were not controlled within 10 min of using the drug (buccal midazolam or I/V DZ), then I/V DZ and/or other anticonvulsant drugs (I/V phenobarbitone or phenytoin – as per the protocol) were used to control seizures. Patients in whom seizures recurred within 1 h of cessation of seizures were called as non-responders and received I/V DZ and/or other anticonvulsant drugs (as per the protocol) to control seizures.

Patient's vitals (heart rate, respiratory rate, blood pressure, and hemoglobin oxygen saturation) were monitored continuously and recorded at 0 min, 5 min, 10 min, 15 min,

20 min, 40 min, and 60 min after the drug administration. Children with seizures received routine life support on admission to hospital. During seizure activity, high flow oxygen was provided through a mask. The control group (IVDZ) with the same indication was given I/V DZ at the dose of 0.2 mg/kg/dose @ 1 mg/min.

Statistical Analyses

The following methods of statistical analysis have been used in this study. Data were entered in Microsoft Excel and analyzed using SPSS (Statistical Package for Social Science, Ver. 10.0.5) package.

The results were averaged (mean + standard deviation) for continuous data and the number and percentage of dichotomous data. The proportions were compared using Chi-square (χ^2) test of significance. The proportion of cases belonging to a specific group of the parameter or having a particular problem was expressed in absolute number and percentage. The Student's *t*-test was used to determine whether there was a statistical difference between groups in the parameters measured if the data is normal. A non-parametric test (distribution-free) used to compare two independent groups of sampled data. The test $P < 0.05$ was accepted.

RESULTS

As shown in Table 1, the mean age of patients in BMDZ group was 33.22 ± 39.37 months. In IVDZ group, the mean age of patients was 42.93 ± 49.69 months. It was observed that majority of cases were in age group 1 month to 1 year (47%) and in age group 1-5 years (33%), which means a total of 80% children were having seizures before the age of 5 years, and 20% were having seizures in age group of 5 years and above. However, both groups were comparable with respect to the mean age of cases ($P > 0.281$).

The mean weight of patients in BMDZ group was 11.42 ± 8.16 kg while that in IVDZ group was 13.07±10.50 kg, and the weight in both groups was comparable ($P = 0.382$).

There were 29 males (58%) and 21 females (42%) in group 1 and group 2, 30 males (60%) and 20 females (40%) were present. On applying statistical test (Chi-square), it was observed that both the groups were comparable with respect to sex distribution ($P > 0.05$).

Nearly, 51 cases (24 in BMDZ group and 27 in IVDZ group) had seizures of 5-10 min duration while 49 cases (26 in BMDZ group and 23 in IVDZ group) had seizures of >10 min duration. Patients in BMDZ group presented with seizures of mean duration 13.00 ± 4.94 min while in IVDZ group; it was 12.58 ± 4.72 min, and the difference between them was statistically not significant ($P > 0.05$).

Table 1: Buccal midazolam versus I/V DZ

Route/drug	Buccal midazolam	I/V DZ
Age (mean) (months)	33.22±39.37	42.93±49.69
Weight (kg) (mean±standard deviation)	11.42±8.16	13.07±10.50
Mean duration of seizures (minutes)	13.00±4.94	12.58±4.72
Number of seizures aborted	48	48
Time to control seizures (mean±standard deviation) (seconds)	96.00±144.69	83.40±124.27

I/V DZ: Intravenous diazepam

About 79 (38 in BMDZ group and 41 in IVDZ group) patients had generalized tonic-clonic seizures, 13 (9 in BMDZ group and 4 in IVDZ group) cases had clonic seizures, 7 (2 in BMDZ group and 5 in IVDZ group) cases had partial seizures, and only 1 case had tonic seizures in BMDZ group. The difference between the distribution of cases according to the type of seizures among two groups was statistically not significant ($P = 0.229$).

In both the groups, the response of only the last seizure episode which occurred in the hospital was treated, and the response was observed. While comparing the history of a number of episodes in each group, the difference was found to be statistically insignificant ($P > 0.05$).

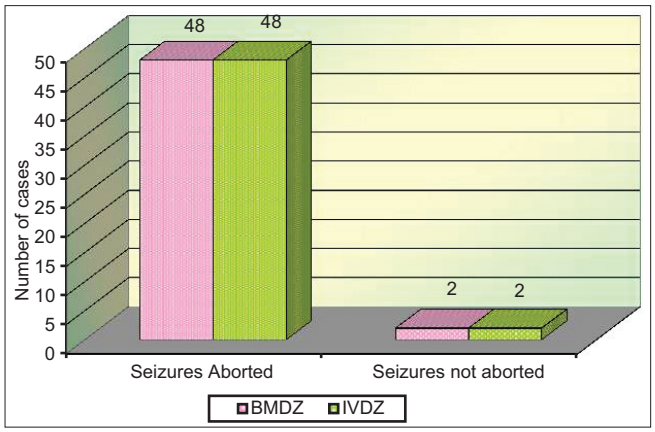
In BMDZ group, 48 (96%) cases of seizures were aborted by giving buccal midazolam and in IVDZ group also an equal number, i.e., 48 (96%) cases of seizures were aborted (Graph 1) by giving DZ intravenously ($P > 0.05$).

The mean time needed for cessation of seizures in BMDZ group (Graph 2) was 96.0 ± 144.69 s (1.60 min) with the lowest time being 30 s and the highest being 790 s, and it was 83.40 ± 124.27 s (1.39 min) in IVDZ group with the lowest being 30 s and the highest being 685 s. The difference in time taken to control seizures between two groups was statistically insignificant ($P = 0.641$).

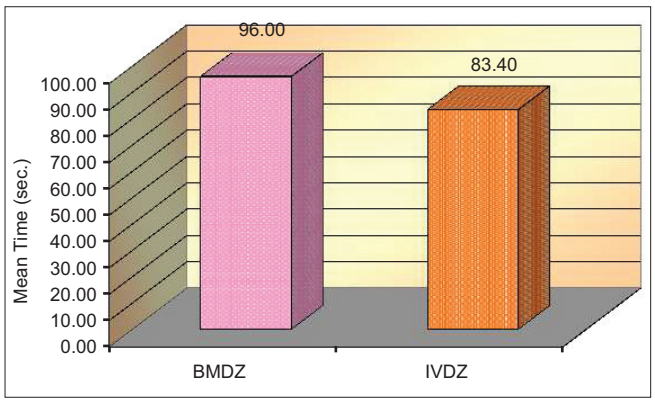
In the groups, two cases each required administration of I/V DZ to control seizures as seizures were not controlled within 10 min of the drug administration. In none of the cases in both groups seizures recurred in the subsequent 1 h. The distribution of cases, according to the diagnoses is shown in Table 2.

DISCUSSION

In this study, 48 (96%) seizures were aborted by buccal midazolam and 48 (96%) seizures were also aborted by I/V DZ. Talukdar *et al.*,[18] selected 60 cases in each group,



Graph 1: Distribution of cases according to seizures aborted



Graph 2: Comparison of mean time taken for cessation of seizures after administration of the drug in two groups

Table 2: Distribution of cases according to diagnosis

Diagnosis	BMDZ		IVDZ		Total	
	No.	%	No.	%	No.	%
Seizure disorder	15	30.00	11	22.00	26	26.00
Febrile seizure	10	20.00	8	16.00	18	18.00
Meningitis	10	20.00	14	28.00	24	24.00
Encephalitis	4	8.00	4	8.00	8	8.00
Neurocysticercosis	1	2.00	4	8.00	5	5.00
MRCP	8	16.00	7	14.00	15	15.00
Others	2	4.00	2	4.00	4	4.00
Total	50	100.0	50	100.0	100	100.00

MRCP: Mental retardation cerebral palsy, IVDZ: Intravenous diazepam

51 out of 60 (85%) seizures were aborted by buccal midazolam and 56 out of 60 (93.3%) by I/V DZ. In a study by Ashrafi *et al.*,[19] who studied 49 cases each on rectal DZ and buccal midazolam, 49% seizures were aborted by rectal DZ within 4 min of drug administration and 88% by buccal midazolam. Kutlu *et al.*[20] studied 19 patients, 84.2% seizures were aborted by buccal midazolam. In a randomized clinical trial by Tonekaboni *et al.*,[21] 92 patients with acute seizures, ranging from 6 months to 14 years, were randomly assigned to receive either buccal midazolam (32 cases) or I/V DZ (60 cases) at the emergency department of a children's hospital. In the midazolam group, 22 (68.8%) patients were relieved from seizures in 10 min. Meanwhile, DZ controlled the episodes of 42 (70%) patients within 10 min. The difference was, however, not statistically significant (P=0.9). In another study by Garnock *et al.*,[22] the time to response was longer with oromucosal midazolam than with I/V DZ, the latter took significantly longer to apply than the former, leading to a significantly shorter overall controlling time with oromucosal midazolam.

In our study, mean time taken by drug, from its administration to cessation of seizures in BMDZ group was 96.00 ± 144.69 s (1.60 min), and it was 83.40 ± 124.27 s (1.39 min) in DZ group. In the study by Talukdar *et al.*,[18] mean time for control of seizures after starting treatment in midazolam group was 1.69 min and 1.13 min in DZ, not counting the time to insert the I/V line. Both studies showed that buccal midazolam was as safe and effective as I/V DZ.

In the present study, it was observed that the mean time taken from receiving patient at hospital to starting treatment was shorter in midazolam group while it was longer in IVDZ group as already prepared solution of midazolam was used, and it did not require extra time for administration. It was also observed that the total time taken by IVDZ group from receiving patient to cessation of seizures was more, than total time taken by buccal midazolam since more than 2 min time was taken for establishment of I/V access in children with seizures. Tonekaboni *et al.*[21] also proved that buccal midazolam is as effective as and safer than I/V DZ in control of seizures.

Buccal midazolam was used in a dose of 0.3 mg/kg in the present study. It is similar to the dose used by Kutlu *et al.*[20] Scott *et al.*[23] used a fixed dose of 5-10 mg and McIntyre *et al.*[24] used 0.5 mg/kg. Talukdar *et al.*[18] used a lower dose of 0.2 mg/kg. Muchohi *et al.*[25] used midazolam at the currently recommended dose (0.3 mg/kg). It was found out that buccal midazolam was safe, there being no significant side effects especially cardio-respiratory that is most worrisome, similar to observations by other studies. Only two cases in each group required administration of I/V DZ to control seizures as it was not controlled within 10 min of drug administration. No serious adverse reaction was observed in both groups. Both Kutlu *et al.*[20] and Melendez *et al.*[26] reported no adverse cardio-respiratory effects in their series of patients. There was no recurrence of seizures in the subsequent 1 h in both the group. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs.

CONCLUSION

It is concluded from the above study that buccal midazolam is equally effective and more convenient as compared to I/V DZ in prolonged seizures while both are comparable in safety.

Given the ease of administration of buccal midazolam and the results of present study, we recommend the use of buccal midazolam for the hospital/home treatment of prolonged seizures especially when establishing an I/V line becomes difficult and also in the periphery where skilled personnel may not be easily available and transport of the child to a well-equipped center might take time.

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How to cite this article: Khandelwal R, Khandelwal LM, Singh K. Buccal Midazolam versus Intravenous Diazepam in Prolonged Seizures in Children. Int J Sci Stud 2015;3(4):58-62.

Source of Support: Nil, **Conflict of Interest:** None declared.