Comparison of Buccal Midazolam with Rectal Diazepam in the treatment of prolonged seizures in children

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Abstract

Background : Seizure is common neurological disorder in children. It is one of the common causes of referral of child to hospital and often requires emergency intervention. Rectal diazepam is the established first line drug for this purpose, but seizure recurrence and respiratory depression are the two major side effects. Midazolam is a water-soluble benzodiazepine with anticonvulsive activity at physiologic PH, which facilitates its effects on brain tissue. Midazolam is also easy to use, and no adverse events were reported in relation to the route of administration.

Objectives : To compare the efficacy and safety of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in children.

Methodology : This prospective randomized study was conducted in the Department of pediatrics, Sir Salimullah Medical College (SSMC) and Mitford Hospital, from March 2018 to December 2018.Fifty (50) patients aged 3 months to12 months who were convulsing and experiencing prolonged seizure (lasted >5 minutes) were included. Patients was randomly assigned to one of the two treatment arms: rectal diazepam and buccal midazolam. Primary and secondary outcome was compared between 2 treatment arms. Primary outcome was: 1. cessation of visible seizure activity within 10 minutes. 2. without recurrence of seizure in the subsequent hour. Secondary outcome included: 1. proportion with cessation of convulsion and exact time needed for cessation of convulsion within 10 minutes2. proportion of seizure recurrence in the sub sequent hours and within 24 hours after initial control and exact time of recurrence within the respective period. Also the safety and adverse effects were also compared.

Results : The two groups did not differ significantly in sex, age, type of seizures, temperature, and baseline RBS, respiratory rate and blood pressure. Comparing the 2-treatment group, 13 (52%) patient experienced treatment failure who received rectal diazepam compared with 7 (28%) who received buccal midazolam ($P>0.05$). For initial cessation of seizures, 18 (72%) seizures terminated within 10 minutes in the diazepam group compared with 19 (76%) in the midazolam and mean time to cessation of the seizure was 4.02 ± 1.03 minutes and 4.4 ± 1.09 minutes respectively ($p>0.05$). Among the 18 children in whom seizure was initially controlled within 10 minutes by rectal diazepam, 6 (33.33%) of them experienced a seizure recurrence in the subsequent hour compared with 1 (5.26%) of 19 children in the buccal midazolam group ($P<0.05$). children who experienced a seizure recurrence within 1 hour after initial control, the mean time torecurrence was 20.0 ± 5.0 vs 25 ± 0.0 minutes in diazepam group and midazolam group respectively ($P=0.478$). Seizure recurrence after initial control during the 24 hours after treatment was 5 (41.36%)vs 6 (33.33%).The mean time to recurrence within 24 hours was$114.00\pm39.11.53$ vs 320.83 ± 173.10 minutes which was highly significant ($P<0.05$)

Conclusion : Buccal midazolam was as safe as and more effective with an improved efficacy over 1 hour ($P<0.05$) and a more prolonged anticonvulsive effect ($P<0.05$) than rectal diazepam for the treatment of prolonged seizure.

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Introduction

Seizure is defined as a paroxysmal, time-limited change in motor activity and/or behavior that result from abnormal electrical activity in the brain. Seizure is the common neurological disorder in children and occurs in approximately 10% of children.[1] Each year, about 150,000 children and adolescents in the United States will come to medical attention for evaluation of a newly occurring seizure disorder of some type. Between 2% and 4% of all children in Europe and United States experience at least 1

convulsion associated with a febrile illness before the age of 5 years. Population based figures of seizure in a developing country are not accurately available. In community-based survey in Bangladesh it was found that incidence of epilepsy was 2.54 per 1000 population.[2]

The cause of seizure in developing countries differ from that of developed countries, because infectious disease are more common underlying factors, in addition to simple febrile convulsions and epilepsy.[3] seizure that last for more than 5 minutes is termed as prolonged seizure.[4] Prolonged seizures have been shown to increase the risk of death and neurological sequel and warrant urgent treatment that is focused on early and safe seizure termination, prevention of recurrence and identification and treatment of precipitating conditions and secondary complications.[5]

Immediate management of a seizure follows the basic principle of emergency care and to terminate the seizure promptly and safely. Ideally, a drug which is used in emergency should be easy to administer, effective, safe and would have a long-lasting anti-seizure action.[4]Rectal diazepam is the established first line drug for this purpose and is effective in 60- 80% of patients, but seizure recurrence and respiratory depression are the two major side effects.[6]

Midazolam is a water soluble benzodiazepine with an anticonvulsive activity that is extremely lipophilic at physiologic pH, which facilitates its effects on brain tissue.[7] Intravenous access is not always possible for emergency anticonvulsive treatment in children. Traditionally, the rectal route has been used for diazepam and recently the midazolam is used in buccal route. Some studies showed that midazolam in buccal route is easy to use, no adverse events were reported in relation to the route of administration.[8] The buccal route is also more easily acceptable to the patient than the rectal route. Oral mucosa allows rapid absorption of drug directly in the systemic circulation. In arandomized controlled trial, buccal midazolam was found as safe as and more efficacious than rectal diazepam for the treatment of seizure in children who presented in a hospital in Great Britain which was further evaluated in Africa and got better result.[9]

During any seizure episodes our immediate goal should be to control seizure and to keep the patient seizure free. Rectal diazepam results variable in different plasma concentration and fails to terminate 30% of seizure.[10] It is difficult to arrange at in public place and to administer in older children with generalized tonic clonicseizure. Buccal midazolam can be used as an effective treatment of severe seizures. It can be easily administered to everyone, younger and older age and at any place.[11] It is well absorbed, socially more accepted and there is low risk for respiratory depression.[12]

The present study tried to further evaluate the efficacy and safety of buccal midazolam controlling prolong seizure in children of Bangladesh.

Materials and methods

This prospective randomized case-controlled study in the Department of pediatrics, Sir Salimullah Medical College and Mitford Hospital, from March 2018 to December 2018. Fifty (50) patients of aged 3 months to12 years presented with convulsion, that lasted >5 minutes, irrespective of cause were included in the study.

A child with seizure was transferred to are suscitation room, where the patient was rapidly assessed toconfirm genuine convulsive activity, examined the patient's airway for gastric contents. Excessive secretion was removed and nasal oxygen was given to all patients. Rapidly screened the patient for enrollment in the study if the patient fulfilled the enrollment criteria, then a parent or legal guardian was briefly informed the study procedures. If they agreed to proceed, then written consent was taken and the patient was randomized by using the randomization table in to two groups, diazepam, and midazolam group.

Diazepam group received per rectal diazepam and Midazolam group received buccal midazolam. Both drugs were administered at 0.5 mg/kg. It was very difficult to attempting accurate weighing of a child undergoing a seizure. Where weight measuring 'was not possible, age of the patient was used to calculate the dose of drugs (2.5 mg for 3-11 months of age; 5 mg for ages 1-4 years; 7.5 mg for ages 5-9 years; and 10 mg for ages 10-12 years). Injections were used Sedil, which contain diazepam 5 mg/ml and Hypno fast, which contain midazolam 5 mg/ml.

For buccal administration, required amount of inj.Midazolam was taken in a syringe, needle was removed. The syringe connected with butterfly tube with needle end cut and placed between the teeth and cheek, the drug was administered, and the cheek was gently massaged.

For rectal administration, the drug was given via a tube inserted 3 to 4 cm into the rectum and the tube was flushed with air to ensure complete delivery of the drug. The buttocks were then held together for 5 minutes to prevent expulsion of drug.

During a seizure, oxygen was administered to all patients by nasal prongs. Blood pressure and respiratory rate were recorded on study drug administration and at 10, 20, 40, and 60 minutes thereafter. All children in the study had a random blood sugar level determined with a glucometer during study drug administration. Patients were followed up for 24 hours after study drug administration.

Ethical permission was obtained from Review committee of department of pediatrics, SSMC and Ethical l review committee

of SSMC to conduct the research work.

Operational definitions

Prolonged seizure: Seizure that last > 5 minutes termed prolonged[5].

Treatment failure: When the convulsion persisted beyond 10 minutes or recurred within one hour after initial treatment and treated with intravenous diazepam.

Outcome measurement

Primary and secondary outcome was compared between two treatment arms. Primary outcome was cessation of visible seizure activity within 10 minutes, without recurrence in the subsequent hour. Secondary outcome measures include proportion with cessation of convulsion and exact time needed for cessation of convulsion within 10 minutes, proportion with seizure recurrence in sub sequent hour and within 24 hours after initial control and exact time of recurrence with in the respective time period. Safety and adverse effects were compared.

After completion of collection of data in a pre- designed and structured questionnaire by interviewing and observing every case and results was analyzed. Table was prepared by the observed value; mean and standard deviation were calculated. Level of significance was tested by independent sample t-test, ANOVA and chi-square (x2) test. The result is considered statistically significant at a p-values 0.05.

Result

Among 50 patients enrolled in the study, 25 were in per rectal diazepam group and 25 were in buccal midazolam group. Twenty three (94.8%) children in diazepam group and 22(88%) in midazolam group were between the ages of 3 months to 5 years and 2(8%) in diazepam and 3(12%) in midazolam group between 5 years to 10 years. None were above 10 years of age (Table-I).

Table-I : Age of the studied children (n-50)

Age	Rectal diazepam (n=25)	Buccal midazolam (n=25)	Total (n=50)
3 mo-5 years	23(92)	22(88)	45(75)
5 years – 10 years	02(8)	03(03)	05(25)

Among 50 patients in both groups combined, 31(62%) were male and 19(48%) were female. Regarding Diazepam vs midazolam group were male 16 (64%) vs 15 (60%) cases and female 09 (44%) vs 10(56%) cases (Table-II).

Table -II : gender distribution of patient (n=50)

Sex	Rectal diazepam (n=25) N(%)	Buccal midazolam (N=25) N(%)	Total (n=50) N(%)	*p* value
Male	16(56)	15(44)	31(62)	0.396
Female	09(44)	10(56)	19(48)	

Baseline characteristics in diazepam vs midazolam group were, mean age of patient was 28.92±13.86 vs 38.08±24.75 months, axillary temperature 100.16±1.59 F vs 100.32±1.60 F, generalized convulsion 19(76%) vs 17(68%) cases, Focal convulsion 6(24%) vs8(32%), random blood sugar level 3.89±.454 vs3.75t.401, respiratory rate 31.52+5.14 vs31.92+4.77 per minute, systolic blood pressure 82.20± 10.4 vs 83.80±7.4 mm of Hg, diastolic blood pressure 51.80+9.34 vs 53.60±7.14 of Hg respectively (p >0.05 for all value). Baseline characteristics of study patients were similar in the 2 treatment arms (Table-III).

Table III : Base line Characteristics of the cases on admission (n=50)

Character	Rectal diazepam (n=25)	Buccal midazolam (N=25)	*p* - value
Age, months (mean ±SD)	28.92±13.86	38.08±24.75)	
Axillary temperature Fahrenheit (meant ±SD)	100.16±1.59	100.32±1.60	0.187*
Nature of convulsion (%)			
Generalized	19((76%)	17(68%)	0.752
Focal	6(24)	8(32%)	
Respiratory rate (meant ±SD)	31.52±5.14	31.92+4.77	0.777*
Blood pressure, mmof Hg(meant ±SD)	51.80+9.34	53.60±7.14	0.768

Comparing the primary outcome of 2 treatment arms, 13 (52%) patients who received rectal diazepam experienced treatment failure compared with 07 (28%) who received buccal midazolam (p = 0.148). The difference was not statistically significant (Table-IV).

Table 1V : Comparison of treatment failure among rectal diazepam and buccal midazolam group

Character	Rectal diazepam (n=25)	Buccal midazolam (N=25)	*p* - value
Treatment failure (%)	13(52%)	07(28%)	0.148

Chi-squared Test (x2) was employed to analyze the data

For initial cessation of seizures, 18 (72%) seizures terminated within 10 minutes in the diazepam arm compared with 19 (76%) in the midazolam arm (p = 1). The mean time to cessation of the seizure was 4.02±1.03 minutes for rectal diazepam and 4.44 minutes (p 0.23) for buccal midazolam. Difference was not statistically significant (Table-V).

Table V : Secondary outcome in initial 10 minutes

Outcome in initial 10 minutes	Rectal diazepam (n -25)	Buccal midazolam (n-25)	*p* - value
Stopped convulsion, 10 minutes N (%)	18(72%)	19(76%)	1
Time to stop convulsing, Minutes (mean ± SD)	4.02+1.03	4.44±1.09	0.238**

Chi-squared Test (x2) was employed to analyze the data

** Independent sample t test done

In thisstudy 18 children whose seizure was initially controlled within 10 minutes by rectal diazepam,

6 (16.66%) experienced a seizure recurrence in the subsequent hour compared with (5.26%) of 19 children in the buccal midazolam arm. Children in rectal diazepam more significantly recurred compared to buccal midazolam (p=0.042). Of children who experienced a seizure recurrence within 1 hour after initial control, the mean time to recurrence was 20±5 minutes for rectal diazepam and 25 minutes for buccal midazolam (p= 0.478). Difference was not statistically significant (Table-VI)

Table VI : Secondary outcome in 1 hour after seizure control with in first 10 minutes

Outcome within 1 hour	Rectal diazepam n= 16	Buccal midazolam n=19	*p*- value
Recurred, No (%)	06(33.33%)	01(5.26%)	0.042
Time to recur, minutes (mean ± SD)	20.0 ± 5.0	25±0	0.478

Chi-squared Test (x2) was employed to analyze the data

Number of recurrence within 24 hours 05(41.66) vs 06(33.33%) diazepam group and Buccal midazolam group in Rectal respectively (p=0.466).The mean time of recurrence within 24 hours was significant between the 2 treatment arms: 114.00±39.99 minutes for rectal diazepam and 320.14±175.17minutes for buccal midazolam (p = 0.029) (Table-7)

Table VII : Secondary outcome 24 hours after seizure control with in first 10 minutes

Outcome within 24 hours	Rectal diazepam	Buccal midazolam n-18	*p*- value n= 12
Recurred N (%)	05(41.66%)	06(33.33%)	0.466*
Time to recurred, minutes mean ±SD	114.00±39.11	320.83±173.10	0.029

Chi-squared Test (x3) was employed to analyze the data# Independent sample t test done

Respiratory rate before and at 10 minutes, 20 minutes, 40 minutes, 60 minutes after treatment between 2 group did not differ significantly. There was no significant respiratory depression. (Table-VIII).

Table VIII : Comparison of respiratory rate before and after therapy

Outcome	Per rectal diazepam	Buccal midazolam	*p*-value
Before treatment, mean ±SD	31.04±5.14	31.92 4.71	0.777*
At 10 minutes, mean ±SD	31.04± 4.82	31.12± 4.08	0.950*
At 20 minutes, mean ±SD	31.16±5.5	31.76±4.2	0.668*
At 40 minutes, mean ±SD	30.72±4.92	31.68 3.85	0.447*
At 60 minutes, mean ±SD	31.24 5.52	30.96±4.11	0.840**

One way ANOVA test done to analyze the data; level of significance was 0.05

Systolic blood pressure before and at10 minutes, 20 minutes,40 minutes, 60 minutes after treatment between 2 groups did not differ significantly in either group and between two groups. There was no significant cardio depression (p>.05). (Table-IX)

Table-1X : Comparison of Systolic Blood pressure before and after therapy

Outcome	Per rectal diazepam (n-25)	Buccal midazolam (n-25)	*p*-value
Before treatment, mm Hg (mean ±SD)	82.20±10.41	83.80+7.11	0.529*
At 10 minutes, mm Hg (mean ±SD)	80.20±8.71	83.20+6.75	0.180*
At 20 minutes, mm Hg (mean ±SD)	80.20±8.95	81.80±8.15	0.512*
At 40 minutes, mm Hg (mean ±SD)	79.60±7.96	82.60±6.63	0.160*
At 60 minutes, mm Hg (mean ±SD)	79.80±7.96	82.60±6.63	0.185*

*One way ANOVA test done to analyze the data; level of significance was 0.05

Diastolic blood pressure before and at10 minutes, 20 minutes, 40 minutes, 60 minutes after treatment between 2 groups did not differ significantly in either group and betweentwogroups. There was nosignificant cardio depression (p>.05). (Table-X)

Table X : Comparison of diastolic blood pressure before and after therapy

Outcome	Per rectal diazepam (n-25)	Buccal midazolam (n-25)	*p*-value
Before treatment, mm Hg (mean ±SD)	51.80+9.34	53.60±7.14	0.448*
At 10 minutes, mm Hg (mean ±SD)	51.0 7.63	53.0+6.45	0.322
At 20 minutes, mm Hg (mean ±SD)	50.60±7.11	52.80+6.30	0.253*
At 40 minutes, mm Hg (mean ±SD)	49.80±6.84	52.80±6.30	0.114*
At 60 minutes, mm Hg (mean ±SD)	49.80±6.84	52.80+6.30	0.114*

*One way ANOVA test done to analyze the data; level of Significance was 0.05.

Discussion

This study was designed to find out the comparative efficacy of per rectal diazepam vs buccal midazolam in the treatment of prolonged seizure. Early termination of seizure is important to prevent adverse consequence. Aim of the treatment was to

ensure rapid seizure termination and to keep persistence of anticonvulsive effects.

In hospital setup intravenous diazepam is commonly used for control of acute seizure, but it requires an intravenous line and has the disadvantages of respiratory depression. When Seizures occur in public place rectal administration may be difficult to arrange in and difficult in older children with generalized tonic clonic seizure. Moreover, diazepam has wide range of serum bioavailability at variableconcentration.[12]

In this study a total of 50 patients were included. Among them 25 patients in diazepam group and 25 in buccal midazolam group. The patient was of both sexes. Number of male patients were higher than female. The fact is also well documented by Lennox.[13] The incidence of seizure slightly higher in male than female in the study done by Golden sohn et al.[14]

Though the pediatric age group in Bangladesh is up to 18 years, most of the patient attend in pediatric emergency is within 12 years of age. Mean age of two group were midazolam 28.92±23.68 months and 38.08±24.75 months, respectively. Majority of patient were under 5 years of age. Similar distribution ware reported by Wattanaoon et al and Islam.[15]

Before therapy there was no significant difference in sex, age, axillary temperature, nature of convulsion, random blood sugar and blood pressure between two group(p>0.05).

It is interesting that although per rectal diazepam and buccal midazolam did not differ in their initial effects, their effect in prevention of seizure recurrences in the subsequent 1 hour after initial control were different.

In our study percentage of seizure controlled within 10 minutes was higher in buccal midazolam group (BMG) in comparison to par rectal diazepam group (PRG), and mean time to control seizures was lower in BMG in comparison to PR group. But this difference was not statistically significant. (p>.05). This finding is similar to the finding of Mpimbaza A et al.[6]

In our study we found that there was no significant difference of treatment Failure in PDG group and in BMG(p>0.05). These findings differ from Arthur Mpimbaza et al who observed treatment failure more in RD group in comparison to BM group.[6] This difference might be due to small sample size.

The risk for seizure recurrence in the subsequent hour with RD was significantly higher. This was similar to other studies.[9] But very different from that in Great Britain, in which buccal midazolam was shown to have superior efficacy over rectal diazepam for control of prolonged seizures but recurrence was not significantly different.[9]

Over 24 hours, the risk for seizure recurrence was higher in diazepam group than in midazolam and time of recurrence in patients who received midazolam was significantly longer (p=0.029). The difference between diazepam and midazolam was likely attributable to the shorter duration of action of diazepam in the brain (active half-life of diazepam:1 hour)[16],'which was explained by the rapid decline in diazepam brain concentration levels during the redistribution of diazepam from cerebral gray matter into white matter, brainstem, and body fat.[17-18]

There was no significant fall in blood pressure and respiratory rate in our study for both the drugs which differ from previous and similar hospital based study that was 5.5%.[19]

A study on 43 children presenting in emergency service of the children hospital, Ankara, Turkey observed Buccal midazolam was found to be as effective as diazepam and the difference was not statistically significant in both RD and MD group.[11] Another study done on 165 children at emergency unit of the national referral hospital of Uganda showed that Buccal midazolam as safe and more effective than the rectal diazepam for the treatment of seizure.[5] Again, study at Alder Hey Children Hospital; Derbyshire Children Hospital; Queen's Medical Centre Nottingham; and Birmingham Children Hospital in 177 hospitalized patient showed buccal midazolam was more effective then rectal diazepam for children and was not associated with an increase incidence of respiratory depression.[9]

Buccal midazolam offers simple administration, no need of refrigeration, and low risk for respiratory depression. Indeed, buccal midazolam provides a more socially acceptable route of drug administration than rectal diazepam and avoids the need for intravenous access, which is often unavailable in many district hospitals in Bangladesh and can be challenging to establish in a convulsing child. Therefore, the buccal route of administration is an alternative for seizure control in the community and in situations where intravenous access is problematic or not possible.

Limitations

1. Smaller sample size
2. Cause of seizure was not identified as a part of the study.

Conclusion

In conclusion buccal midazolam, like rectal diazepam appears to be a practical method in the effective treatment of severe seizure at home or other public places. Buccal administration of the drug is easy for ever one, in younger or older age and everywhere. We found that buccal midazolam was as effective as rectal diazepam and had more prolonged anticonvulsive effect compared to rectal diazepam.

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