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Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children

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ABSTRACT

A Prolonged convulsive seizure is the most common neurological medical emergency with poor outcome. An ideal anticonvulsant should be easy-to-use, effective, and safe, and it should also have a long-lasting effect. Benzodiazepines, give via the intravenous or rectal route have generally been used as first-line drugs. In small children, IV access can be difficult and time consuming. Midazolam is a potent anticonvulsant and is rapidly absorbed from the rectal, nasal, and buccal mucosa. Our aim was to evaluate the efficacy and usability of buccal midazolam in controlling seizures in children with acute prolonged seizures, by comparing it with rectal diazepam. Ninety-eight patients were enrolled, with 49 patients in each treatment group. In the buccal midazolam group, 42 (88%) patients were controlled in less than 4 min of drug administration, and all of the patients were controlled within 5 min of drug administration. In the rectal diazepam group, 24 (49%) patients were controlled in less than 4 min and 40 (82%) patients were controlled within 5 min of drug administration. The time for drug administration and drug effect was significantly less with buccal midazolam than with rectal diazepam (p *value* < 0.001). In the buccal midazolam group, 46 (94%) parents were satisfied with their child's treatment and route of drug administration while in the rectal diazepam group, 7 (14%) parents were satisfied. Buccal midazolam was significantly more acceptable than rectal diazepam (p *value* < 0.001). In conclusion, buccal midazolam may be as effective as rectal diazepam but more convenient to use in the controlling acute prolonged seizures in children, especially in situations in which there is a difficulty in gaining IV access, for example, in infants.

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1. Introduction

Seizures that last longer than 5 min are termed prolonged.[1] A prolonged convulsive seizure is the most common neurological medical emergency, and unlike brief seizures, it has an increased risk of morbidity and mortality along with a poor outcome.[2–6] The primary determinants of the outcome for prolonged convulsive seizures include the aetiology and seizure duration; therefore, prolonged convulsive seizures warrant urgent treatment, involving anticonvulsants.[1] An ideal anticonvulsant should be easy-to-use, effective and safe, and it should also have a long-lasting effect. Benzodiazepines, give via the intravenous or rectal route have generally been used as first-line drugs. In small children, IV access can be problematic and time consuming, and it usually requires trained personnel. In these situations, other routes such as rectal, buccal, and nasal ones are the established choices for drug administration.[7–9]

Although rectal diazepam is effective in controlling acute seizures in children and adults, its plasma concentrations are variable. Moreover, this route of diazepam administration fails to terminate seizures in about 30% of the patients.[3,10] Repeated doses of rectal diazepam can cause accumulation of the drug in the adipose tissue, which can lead to marked respiratory depression.[11] Not only in our country but also in developed countries, the oral route is better accepted. Many teachers and parents are reluctant to administer rectal medication in developed countries; therefore, a more convenient route of drug administration is needed.[6]

Midazolam is a potent anticonvulsant. This drug is highly water soluble and is rapidly absorbed from rectal, nasal, and buccal mucosa.[12,13] It has been reported that the mouth and the rectum have similar surface areas and pH, and they also have rich blood supplies.[14,15] Studies in some developed and developing countries have shown that buccal midazolam can be used to control convulsions.[3,6,8,16] In a recent study in India, buccal midazolam has been found to be as effective as IV diazepam in the control of prolonged convulsive seizures.[17] In our country, no study has been performed to show the efficacy of buccal midazolam in controlling acute prolonged convulsive seizures in children. In this study, we tried to evaluate the efficacy and usability of buccal midazolam in controlling seizures in children with acute prolonged convulsive seizures by comparing it with rectal diazepam.

2. Methods

2.1. Study location, sample, and study design

The study was conducted between April 2007 and April 2008 in 2 major referral paediatric hospitals of Tehran, Iran (Children's Medical Centre and Bahrami hospital). Children aged 3 months and older with an acute prolonged convulsive seizure (lasting for more than 5 min) and those convulsing while attending the emergency rooms of these 2 hospitals were enrolled in this study, irrespective of the cause of the seizure. Patients who already had IV access or were younger than 3 months were excluded. All types of convulsive seizures were included. Consecutive patients were enrolled and were randomized to receive either buccal midazolam or rectal diazepam. A random number table was used for randomization.

2.2. Dose and mode of administration of drugs

Buccal midazolam (Epistatus, Midazolam Buccal liquid, and Midazolam Maleate; Orion House, 49 High Street, Addlestone, Surrey KT15 1TU, UK) was used with a dose of 0.3–0.5 mg/kg and rectal diazepam was used with a dose of 0.5 mg/kg.[8] For ease of practice and because a child with active convulsion is difficult to weigh, we tried the following doses for either buccal midazolam or rectal diazepam: 2.5 mg for children aged 3–12 months, 5 mg for 1–4 years, 7.5 mg for 5–9 years, and 10 mg for 10 years or older.[3,8] drugs were administered by trained personnel. As soon as the decision was made to treat, buccal midazolam in the appropriate dose was drawn into a syringe. Children received buccal midazolam by placing the syringe between their teeth and cheek, and after drug administration the cheek was gently massaged. In the diazepam group, the drug in the appropriate dose was drawn into a syringe, a tube was inserted into the rectum and the syringe was attached to the tube, following which the diazepam was expelled into the tube. To ensure that the full dose was given, the tube was pinched while the syringe was removed and the diazepam was then flushed through with normal saline and then the buttocks were held together for 5 min to prevent expulsion. We did not use tubes of rectal diazepam; instead, we used vials of IV diazepam for ease of dose calculation. Patients were admitted to the hospital for at least 48 h, depending on the cause of seizures.

2.3. Response assessment

The main outcome variable was cessation of all motor activity, and this should be achieved in less than 5 min without respiratory depression and without another seizure within 1 h. Otherwise, the treatment was considered to be a failure and the patient was treated with IV diazepam, which is the standard therapy. Respiratory depression was defined as a decrease in respiratory effort sufficient to require assisted breathing either via face-mask inflation or mechanical ventilation. For every episode of convulsion, time spent in preparing the drugs before administration (treatment initiation time) and time of cessation of all convulsions after drug administration (drug effect time) were measured. These time periods were noted in minutes by an assistant.

Convenience of drug use, parents' acceptance of the drug, and route of administration also were noted.

2.4. Monitoring adverse effects and patient evaluation

In all patients the respiratory rate, heart rate, and blood pressure were recorded just before drug administration and 10 min after drug administration. All complications in patient management were recorded till the patients were discharged. All patients were evaluated for seizure aetiology and, if needed, special treatment was given. In all patients blood sugar, serum electrolytes, and serum calcium levels were

evaluated. Cerebrospinal fluid (CSF) analysis, computed tomography (CT) or magnetic resonance imaging (MRI), and electroencephalogram (EEG) were performed if indicated. All patients were referred to the child neurology clinic for follow-up.

2.5. Ethics

The study was approved by the Tehran University of Medical Sciences Ethics Committee and informed consents were taken during drug administration as soon as the trial was explained to the parents.

2.6. Data recording and analysis

On the basis of previous data and by using two-tailed tests, it was calculated that 49 episodes would be needed in each treatment group to detect a difference in efficacy and usability.[6] Data were recorded in forms previously explained to nurses and staff. Statistical analysis was performed by applying the Mann–Whitney *U*-test for continuous data. Categorical variables were analyzed by the χ^2-test or Phi and Cramer's V. A *p-value* < 0.05 was considered significant.

3. Results

3.1. Baseline characteristics (Table 1)

In this study, 98 patients (58 male (59%) and 40 female (41%)) were enrolled, with 49 patients in each treatment group. In the rectal diazepam group, 32 patients were male and 17 were female while in the buccal midazolam group, 26 were male and 23 were female. There were no statistically significant differences between the sexes in the 2 treatment groups (*p-value* $= 0.218$ *by the* χ^2*-test*). Fifteen patients (15%) were aged below 1 year, 59 (60%) were between 1 and 5 years and 24 (25%) were between 6 and 12 years. Median age (24 months) in the buccal midazolam group was less than that in the rectal diazepam group (48 months), although this difference was not statistically significant (*p-value* $= 0.217$ *by Mann–Whitney U-test*). The major type of seizure in both treatment groups was generalized tonic-clonic (42 patient in each group). In the rectal diazepam group, 5 patients had myoclonic seizures, 1 had focal tonic seizure, and 1 had focal clonic seizure. In the buccal midazolam group, 7 patients had myoclonic seizures and no patient had clonic or tonic seizure. There was no statistically significant difference in the seizure types between the 2 groups (*p-value* $= 0.506$ *by the* χ^2*-test or Phi and Cramer's V test*).

3.2. Treatment response

In the buccal midazolam group, 42 (88%) patients were controlled within 4 min of drug administration, and all of the patients were controlled within 5 min of drug administration. In the rectal diazepam group, 24 (49%) patients were controlled within 4 min and 40 (82%) patients were controlled within 5 min of drug administration. All the patients were controlled within 8 min after drug administration in the rectal diazepam group. Medians of drug effect time of two treatment groups were shown in Table 2. Distribution of data was not normal; therefore medians of data were shown. As is shown in Table 1, no patient with partial seizure was enrolled in the buccal midazolam group, and statistical analysis was not done for these seizures. In both treatment groups no recurrent seizures were recorded within 1 h after drug administration.

3.3. Drug usability

In the buccal midazolam group, the drug was administered in 40 (82%) patients (treatment initiation time) 2 min after entering the emergency room. In the rectal diazepam group, the drug was administered in 11 (22%) patients 2 min after entering the emergency room. Within 3 min after entering the emergency room, the drug was administered to 46 (94%) patients in the buccal midazolam group and to 44 (90%) patients in the rectal diazepam group. In the buccal midazolam group, 10 (20%) patients received the drug within 1 min. Medians of drug initiation time of two treatment groups were shown in Table 2. Distribution of data was not normal; therefore medians of data were shown.

3.4. Parent satisfaction

In the buccal midazolam group, 46 (94%) parents were satisfied with their child's treatment and route of drug

Table 1 – Baseline characteristics of patients in two groups.

Parameter	Buccal midazolam	Rectal diazepam	*p-value*
Age in months (median)	24	48	0.217
Males (n)	26	32	0.218
Females (n)	23	17	0.218
GTCS	42	42	0.506
Myoclonic seizure	7	5	0.506
Focal tonic seizure	0	1	0.506
Focal clonic seizure	0	1	0.506

n, number of patients; GTCS, generalized tonic-clonic seizures.

Table 2 – Control of convulsions, treatment initiation time, and drug effect time.

Parameter	Buccal midazolam	Rectal diazepam	*p-value*
Frequency of control (in 5 min):	49/49 (100%)	40/49 (82%)	<0.001
Treatment initiation time (in minutes): Median	2	3	<0.001
Drug effect time (in minutes): Median	4	5	<0.001

p-values of treatment initiation time and drug effect time by Mann–Whitney *U*-test.

administration while in the rectal diazepam group, 7 (14%) parents were satisfied. Buccal midazolam was significantly more acceptable than rectal diazepam (p *value* < 0.001).

3.5. *Adverse effects*

Control of vital signs in our patients did not show any adverse effects in either group.

4. Discussion

The aim of this study was to determine the efficacy and usability of buccal midazolam as compared to that of rectal diazepam in controlling acute prolonged convulsive seizure. Overall frequency of response within the first 5 min after drug administration in the buccal midazolam group was significantly greater than that in the rectal diazepam group, and all the patients were controlled in less than 5 min after drug administration in the buccal midazolam group, although the drug effect time after 5 min and less than 10 min was similar in both groups.

The drug was administered faster in the buccal midazolam group than in the rectal diazepam group. This difference could be explained by possible delays resulting from the need to remove clothing and to position the patient appropriately for the administration of rectal diazepam. Similar considerations do not apply for the administration of buccal midazolam.

The majority of the parents (94%) were satisfied with drug administration in the buccal midazolam group. This is probably because of the greater social acceptance of the oral route of drug administration in our country as against the rectal route.

Previous studies have shown that the first and foremost aim in treating an acute episode of convulsion is controlling it as quickly as possible.[1] Every effort should be made to prevent prolonged seizures from developing into status epilepticus.[5] Pellock JM et al. have emphasized timely and effective acute seizure control to prevent neuronal damage.[5] They also have emphasized equipping patients with epilepsy with an at—home seizure—abortive treatment option to shorten the time to initiate treatment.[5,18] Because of its usability and easy—to—understand route of administration, infrequent adverse effects, and most importantly, social acceptance, buccal midazolam could be the first choice of treatment for seizure control in patients with epilepsy in their homes and in situations in which there is a difficulty in gaining IV access, for example, in infants.

Safety, efficacy, and long-lasting antiseizure activity are important characteristics of any drug for emergency treatment of seizures.[19] Our study showed that buccal midazolam is effective in controlling acute seizures in children. Moreover, no adverse effects were recorded in our patients.

Previous studies have shown that transmucosal midazolam is rapidly effective.[14,15] We did not measure serum concentrations of midazolam and diazepam in our patients, although seizure control in our patients established the therapeutic serum level after buccal and rectal routes. In a recent study, IV diazepam was more effective than buccal midazolam. The findings of that study suggested that buccal midazolam can be used as an alternative to IV diazepam.[17]

Our results are comparable to previous studies. In a randomized trial reported by Scott RC et al., buccal midazolam was used to treat 40 seizures in 14 students, and rectal diazepam for 39 seizures in 14 students. In their study, midazolam ceased 75% of the seizures and diazepam ceased 59% of the seizures (p-*value* $= 0.16$). In their study, drug effect time did not differ significantly.[6]

In another study by Kutlu NO et al., the efficacy of buccal midazolam was examined in children with prolonged seizures. Nineteen children with prolonged seizure were treated with buccal midazolam with a dose of 0.3 mg/kg. Of these 19 seizures, 16 (84.2%) ceased within 10 min of buccal midazolam administration. In their study, all patients with convulsions shorter than 30 min showed a complete response (100%) and no clinically important adverse effects were seen in any patient.[16]

In a randomized controlled trial reported by McIntyre J et al., the safety and efficacy of buccal midazolam versus diazepam for emergency treatment of seizures in children were studied. In their study, 219 separate episodes of seizures involving 177 patients were obtained. The cut-off point for seizure control was 10 min after drug administration. Therapeutic success was 56% (61 of 109) for buccal midazolam and 27% (30 of 110) for rectal diazepam. buccal midazolam was not associated with more adverse effects.[8]

A randomized clinical trial was performed in Ugandan children by Mpimbaza A et al. They compared buccal midazolam with rectal diazepam in the treatment of prolonged seizures in children. In their study, malaria was the most common (67.3%) underlying aetiology for acute prolonged seizures. This was a single-blind trial and 330 patients were enrolled. Treatment failure occurred in 71 (43%) of 165 patients who received rectal diazepam as compared to 50 (30.3%) of 165 patients who received buccal midazolam. Respiratory depression occurred infrequently in both treatment groups. The researchers concluded that buccal midazolam was as safe as and more effective than rectal diazepam for the treatment of acute prolonged seizures in children.[3]

A telephone survey was carried out by Wilson MT et al. to evaluate the effectiveness and convenience of nasal/buccal midazolam in terminating prolonged seizures in the community. In this survey, 40 families were evaluated. A total of 33/40 (83%) families who had used it found it effective and easy to use.[20]

The results of our study must be interpreted in the face of certain limitations. This study was not blinded and placebo was not administered, although we think in situations as prolonged convulsive seizures with high risk of morbidity and mortality, placebo administration without any other controlling drug may not be ethical.

Doses of drugs in our study were comparable to those in previous studies and have proved practical.

Our results suggest that buccal midazolam at a dose of 0.3–0.5 mg/kg may be as effective as and more convenient to use than rectal diazepam for the treatment of acute prolonged convulsive seizures in children, especially in situations in which there is a difficulty in gaining IV access, for example, in infants.

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