ORIGINAL ARTICLE

COMPARISON OF BUCCAL AND INTRAVENOUS MIDAZOLAM FOR THE TREATMENT OF ACUTE SEIZURES IN CHILDREN

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Background: Convulsive disorders often present as urgent neurological conditions requiring prompt intervention like IV midazolam. However, establishing an IV line especially in the ER can delay treatment institution. Therefore, rectal, buccal and intramuscular routes for administration are considered in such cases. Objective of this study was to compare the mean time for control of acute seizures by using buccal and intravenous midazolam in children. **Method:** This was a quasi experimental study carried over 6 months in the Paediatric Accident and Emergency Department, PAF Hospital, Mushaf, Sargodha. The study included a total of 60 children in actively fitting state. The subjects were divided into 2 groups of 30 in each, Group A having buccal midazolam and Group B having IV midazolam for control of seizure episode. Repeat dose was given after 5 minutes if seizures were not controlled. Time required to control seizures was noted for each patient. **Results:** Patients included in study had a mean age of 3.93±3.05 years, with 28 (46.6%) males and 32 (53.33%) female patients. Forty-seven (78.33%) had generalized seizures and 13 (21.67%) had partial seizures. Mean time for control of seizures was 198.33±133.19 seconds in Group A and 169.73±115.22 seconds in Group B. The difference was statistically insignificant with *p*=0.377. **Conclusion:** Buccal midazolam is an effective method for controlling acute seizures in children. It can be used as first line therapy instead of intravenous midazolam in pre-hospital and emergency settings.

Keywords: Acute seizures, Buccal, Children, Diazepam, Intravenous, Midazolam, Oral

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INTRODUCTION

In paediatrics, convulsive disorders often present as urgent neurological conditions requiring prompt intervention.[1] Although there are multiple aetiologies for seizures but prolonged seizure activity from any cause may lead to serious consequences in both patients, i.e., children and adults.[1,2] Despite the initial cause of seizures, if they do not stop spontaneously, they most often generate a positive vicious circle in which convulsions become self-perpetuating leading to status epileptics.[3] Timely control of seizures is important to prevent the patients from long term neurological complications.[2]

In the Accident & Emergency Department, the usual first line treatment for patients with seizures is IV midazolam or diazepam.[4,5] But most of the times establishing an IV line in a convulsing patient can be challenging and can delay treatment.[6,7] Therefore alternative routes for administration of midazolam like buccal, rectal and intramuscular routes are being practiced.[8,9] Despite various routes of administration of midazolam no consensus has yet been developed over the preferable route for administration of midazolam.[10–12]

In different studies, mean time for control of seizures has been reported as 225.6±23.4 seconds[13] after buccal midzolam, and 92.69±25.97 seconds[14] after IV midzolam. In another study mean time to control seizures by buccal midazolam group was 96±124.69 seconds with the lowest being 30 seconds and highest being 790 seconds and in IV diazepam group it was 83.40±124.27 seconds with lowest being 30 seconds and highest being 685 seconds. However, the difference in time to control seizures was not statistically significant (*p*=0.641).[15] Caregivers tend to prefer the buccal route over the rectal route, as it is considered safe and effective. If the buccal route is found to be more effective than intravenous administration, it could potentially become a standard approach for seizure control.[16] It offers the advantage of being easily and effectively used at home.[7]

Acute seizures are a frequently encountered emergency in paediatric care, often leading to serious consequences. Witnessing a child experience convulsions can cause significant anxiety for parents. It is urgent responsibility of healthcare professionals to manage and control seizures as quickly as possible.[2] This study aims to evaluate and compare different routes of drug administration for treating this emergency.

METHODOLOGY

This quasi-experimental study was conducted at the Paediatric Accident and Emergency Department, PAF Hospital Mushaf, Sargodha, from 28 Nov 2023 to 27 Nov 2024. Ethical approval was obtained from the hospital's ethical review committee, and informed consent was secured from the parents or guardians of all participants. A sample size of 60 was calculated using the WHO sample size calculator for comparing two means: the mean time to control seizures with buccal midazolam (225.6 Sec)[13] and with IV midazolam (92.4 Sec)[14], 99% power, and 5% level of significance. Non-probability consecutive sampling was employed.

Children aged 6 months to 12 years presenting with acute seizures lasting more than 5 minutes were included in the study. Cases of prior administration of IV diazepam or other benzodiazepines within the past 24 hours, a history of narrow-angle acute glaucoma, known allergy to benzodiazepines, bradycardia (pulse <50/min) at presentation, and congenital anomalies like cleft palate were excluded. The patients were randomly assigned into two groups of 30 each.

Group A received buccal midazolam, while Group B received IV midazolam. Buccal midazolam was dosed according to age as 2.5 mg for ages 6–12 months, 5 mg for 1–4 years, 7.5 mg for 5–9 years, and 10 mg for children 10 years and older.[4] The drug was prepared as a solution in a syringe and administered with the child in the left lateral position, placing the syringe between the gums and cheek followed by gentle massage. The time to seizure cessation was recorded. A second dose was administered, up to a maximum of two additional doses, after 5 minutes if seizures persisted.

For Group B, IV midazolam was administered at a dose of 0.3 mg/Kg via an established IV line. Repeat doses were given after 5 minutes if needed.

The data were recorded on a structured proforma and entered and analysed using SPSS-20. Descriptive statistics (mean and standard deviation) were calculated for quantitative variables. Frequencies and percentages were calculated for qualitative variables. The mean seizure control times between the two groups were compared using the independent sample *t*-test. Data were stratified by age, gender, and seizure type, with post-stratification analysis performed using the Student's *t*-test, and $p<0.05$ as significant.

RESULTS

There were 28 (46.67%) males and 32 (53.33%) female patients. The mean age of patients was 3.93±3.05 years (Range: 5 months to 12 years). Mean time for controlling seizures was 184.03±124.31 seconds (Range: 30 to 500 Sec). Mean number of doses for controlling seizures was 1.30±0.56. Minimum dose was one and maximum dose was three.

Forty-seven (78.33%) seizures were generalized and 13 (21.67%) were partial. Mean time for seizures control was 198.33±133.19 Sec in Group A and 169.73±115.22 Sec in Group B. This difference was not statically significant (p=0.377). (Table-1).

Stratification was performed on the basis of age, gender and type of seizures. There was no significant effect of these effect modifiers on mean time to control seizures between the groups. (Table-2, 3, 4).

Table-1: Mean time for control of acute seizures between the groups

Groups	Time for control of acute seizures		p
	Mean	SD	
Group A	198.33	133.19	0.377
Group B	169.73	115.22	

Table-2: Association of age with mean time for control of acute seizures between the groups

Groups	Time for control of acute seizures		p
	Mean	SD	
0.5–3 years			
Group A	218.18	143.32	0.567
Group B	188.64	138.92	
4–12 years			
Group A	172.38	119.15	0.627
Group B	153.19	91.19	

Table-3: Association of gender with mean time for control of acute seizures between the groups

Groups	Time for control of acute seizures		p
	Mean	SD	
Male			
Group A	172.81	135.67	0.547
Group B	201.67	105.90	
Female			
Group A	227.50	128.92	0.082
Group B	148.44	119.13	

Table-4: Association of type of seizures with mean time for control of acute seizures between the groups

Groups	Time for control of acute seizures		p
	Mean	SD	
Generalized seizures			
Group A	201.17	121.32	0.08
Group B	146.12	86.08	
Partial seizures			
Group A	189.00	177.89	0.457
Group B	264.17	171.88	

DISCUSSION

The main focus of managing an acute episode of seizure is to control it at earliest. Efforts should be made to curtail the time of seizure so as to prevent long term squeal.[2,3] Trau SP *et al*[3] highlighted the prompt and successful acute seizure control to prevent neuronal injury. They also emphasized at providing patients with epilepsy, at home seizure abortive treatment, to decrease the time to initiate therapy.[3] Because of its feasibility and convenient route of administration, infrequent side effects and most significantly social acceptance, buccal midazolam could be the first choice of therapy for seizure control in patients with epilepsy at home and in circumstances in which there is a difficulty in gaining IV access, like less than 12 months old.[7,17]

The most important characteristics for any drug to be used as emergency treatment includes it safety, efficacy and decreasing seizure span.[12] Our study revealed that buccal midazolam is practical in controlling the acute seizure episode in kids with no side effects.

Previous studies had similar convincing results displaying that buccal midazolam is very effective in controlling seizures. Buccal midazolam reached a therapeutic level earlier as compared to intravenous route. Buccal midazolam can be used as an alternative to IV diazepam.[16]

Francesco Brigo *et al*[18] stated that Non-IV midazolam by any route is as effective as intravenous or rectal diazepam in terminating the seizures in children. In fact the time of arrival in Emergency to drug administration and convulsions control are shorter with non-IV midazolam than with IV or rectal diazepam. They also stated that buccal midazolam is easy to administer and socially more acceptable to patients and their parents for seizure control.

Studies conducted in Egypt to compare the efficacy, adverse effects and satisfaction after midazolam administration by buccal, intranasal or intramuscular route for the control of seizures in children at homes and in emergency settings also had interesting results. In their home group 67 patients received midazolam via buccal, 60 via intranasal and 69 via intramuscular route while in the A&E group 37 received buccal, 34 patients intranasal and 34 got intramuscular midazolam. Seizure cessation in 10 minutes was achieved in 94.2% and 85.3% after intramuscular midazolam in home and A&E groups respectively. The buccal route was effective in 91% in the home group and 78.4% in A&E group. The intranasal midazolam was successful in stopping seizures in 93.3% in home 88.2% in A&E group. They concluded that there was no statistical significant differences in efficacy between all groups (p=0.763 and p=0.509) among the home and A&E groups respectively. All of the above routes can be safely used in pre-hospital and emergency settings.[19,20]

McLntyre J *et al*[21] study included 177 patients having a total of 219 separate seizure episodes. The cut-off point for fit control was 10 minutes after the medicine administration. They concluded a success rate of 56% for buccal midazolam and 27% for rectal diazepam. Buccal midazolam had no associated adverse effects.[21]

Another clinical trail performed in Uganda by Mpimbaza A *et al*[22] found out that malaria was the most common cause of acute prolonged seizures (67.3%) in their children. Therapy failed in 71 (43%) of 165 patients who received rectal diazepam in comparison to 50 (30.3%) of 165 patients who received buccal midazolam. The only side effect noted in both groups was respiratory depression. The authors concluded that buccal midazolam is more effective and safer than rectal diazepam for treating seizures in children.[22]

Our study demonstrated that buccal midazolam is effective in terminating all types of seizures, regardless of their underlying aetiology. While the onset of action of IV diazepam is inherently faster due to its direct entry into the bloodstream, the overall initiation of treatment with buccal midazolam was quicker. This is largely because buccal administration can be performed immediately, without the need for IV access, which often delays treatment —especially in infants under 12 months, where establishing an intravenous line can be particularly challenging.

In contrast, buccal midazolam can be readily administered as a prepared solution into the buccal mucosa, allowing for faster overall seizure control. Our paediatric emergency team was well-prepared and efficiently administered buccal midazolam, which contributed to its effectiveness. As a result, buccal midazolam outperformed IV diazepam in terms of early seizure management.

However a few studies conducted on comparison of non-IV routes of midazolam, i.e., buccal, intramuscular, intranasal, and rectal midazolam, stated that the safety and efficacy of intramuscular midazolam is favourable as compare to buccal midazolam.[23,24] This part of research needs to be further investigated and elaborated as intramuscular absorption is slow in comparison to buccal route. The literature also lacks studies comparing buccal and IV midazolam. Most studies are conducted on buccal midazolam and rectal diazepam, appreciating the safety and efficacy of buccal midazolam. The findings of our research also emphasizes on effectiveness of buccal midazolam without any uncertainty.

Buccal midazolam at a dose of 0.2 mg/Kg has proven to be effective in terminating various types of seizures regardless of their aetiology. Given its ease of administration and rapid effectiveness, particularly in situations where IV access is challenging, buccal midazolam can be considered a first line treatment option for managing acute seizures in paediatric patients.

CONCLUSION

Buccal midazolam is as effective as intravenous midazolam in the management of acute convulsions in children. Due to its ease of administration, safety profile, and ability to be delivered without the need for IV access, it can be confidently used as a first line treatment option in both pre-hospital and emergency settings. It is particularly advantageous in young children and in scenarios where rapid IV access is not feasible.

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