The Effectiveness and Safety of Midazolam and Diazepam via the Buccal and Rectal Route for the Emergency Treatment of Seizures among Children at the Philippine Children's Medical Center: A Randomized Controlled Trial

Principal Investigator	:	**CHERRY LOU M. ANTONIO, MD** Child Neurology- Fellow-in training, Child Neuroscience Center
Supervising Investigator	:	**MEL MICHEL G. VILLALUZ, MD** Visiting Consultant, Child Neuroscience Center
Research Advisers	:	**JOSEFA R. PANLILIO, M.D.** Training Officer, Child Neuroscience Center
		MADELEINE GRACE M. SOSA, M.D Consultant, Child Neuroscience Center
Technical Board Adviser	:	**PAUL MATTHEW D. PASCO, M.D.** Consultant, Office of the Research Development
Location of the Study	:	**Philippine Children's Medical Center**
Endorsed by:	:	**TERESITA N. RABANAL, M.D.** Chairman, Child Neuroscience Division, PCMC
	:	**MARILYN H. ORTIZ, MD** Head - Section of Child Neurology Child Neuroscience Division, PCMC

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ABSTRACT

BACKGROUND: Prolonged seizures are one of the most distressing pediatric emergencies. Prompt management with anticonvulsants is necessary to prevent significant morbidity and mortality. However, the transport from the home to hospital has numerous factors that can be problematic, especially in remote regions, which could further delay treatment initiation. Alternative modes of administration of benzodiazepines as first line anti-epileptic medications, would be lifesaving. OBJECTIVES: *General Objective:* To compare the effectiveness & safety of buccal midazolam and buccal diazepam against rectal diazepam and rectal midazolam for the treatment of children 1 month to 18 years presenting with an acute seizure at Philippine Children's Medical Center. *Specific Objectives:1)*To determine the time duration of seizure cessation among children 1 month to 18 years of age when midazolam or diazepam via the buccal route against the rectal route in PCMC; 2) To determine the side-effects of midazolam and diazepam when given via the buccal route against the rectal route when given for acute seizures among children 1 month to 18 years of age in PCMC.

METHODOLOGY: This is a randomized single-blinded open label controlled trial. Data collection was done from April to September 2013 at the PCMC. Eligible patients were aged 1 month to 18 years who were admitted in the emergency room, service wards or intensive care unit; and patients seen in the out-patient department and diagnostic center (under going EEG or prolonged video EEG monitoring) with continuous, either afebrile or febrile, seizures and children with or without established intravenous access.

RESULTS: All the treatment groups were similar based on the age, weight, sex, seizure types and admission temperature. However, those patients on buccal midazolam group who were receiving anti-epileptic drugs prior to the occurrence of seizure showed significant difference among the treatment groups with p value of 0.039. The seizure cessation has a trend favoring buccal diazepam however difference among the groups were not statistically significant because of small sample size. No adverse effects were noted.

CONCLUSION: The study showed that there is no statistical difference among the four treatment groups as to their effectiveness and safety in the treatment of acute seizures.

KEYWORDS: Seizures, Epilepsy, Therapeutic Success, Status Epilepticus, Buccal, Rectal, Treatment failure

INTRODUCTION

Prolonged seizures are one of the most distressing reasons among pediatric emergencies. This condition requires immediate management to prevent convulsive status epilepticus which causes significant morbidity and mortality. Immediate management of a continuing seizure follows the basic principles of emergency care with the role of anti-seizure medications to terminate the seizure promptly and effectively. Ideally, the medications should be easy to administer, effective, safe, and would have a long anti-seizure effect. However, transfer of a child from home to the hospital can delay treatment substantially. If treatment is delayed, the chances of a successful response to a single medication are diminished.

For the immediate management of prolonged seizures, benzodiazepines are often used as first-line drugs; and the intravenous route is the most suitable in an emergency room setting. In other countries, intravenous lorazepam has been used widely utilized for the treatment of status epilepticus both in the emergency room (for children) and out of the hospital (for adults). Unfortunately, this medication is not available in our country. Locally, diazepam and midazolam are available as first line medications for prolonged seizures. However, intravenous access can be a problem when the seizure event occurs out of the hospital or in small children. In these situations, alternate routes of administration should be employed.

SIGNIFICANCE OF THE STUDY

Buccal midazolam was more effective than rectal diazepam for treating children with acute seizures. (McIntyre, et. al. 2005) Presently, only one prospective study used rectal midazolam for treatment of seizures in children is available.

Anecdotal reports from India (Sridharan, 2005) claimed that buccal diazepam may also be as effective treatment for serial seizures. This was applied at a primary care level in tribal and rural areas of Karnataka, India. They have been running a community based epilepsy control program for the last 15 years, and have used buccal diazepam to control serial or cluster attacks of both convulsive and non convulsive seizures, and claimed the results have been very good.

However, there are currently no local data which could demonstrate the applicability of these different alternative treatment approaches in our present local setting particularly in remote areas and non-hospital setting.

REVIEW OF RELATED LITERATURE

Diazepam is very efficacious for all seizure types because of its rapid onset. However, modes of administration are limited to the intravenous and rectal routes. Intramuscular administration leads to variable absorption. Repeated doses of diazepam accumulate in the serum, which can lead to respiratory depression.

Midazolam, the first water soluble benzodiazepine, is widely accepted as a parenteral anxiolytic and premedicant. It is the only anti-seizure medication which could be given by intramuscular, intranasal or buccal routes. Intranasal midazolam has been shown to be safe and effective in children undergoing various diagnostic studies and minor surgical procedures. Intranasal midazolam has shown to suppress epileptic activity and improves the background of electroencephalograms in epileptic children. However, seizures were controlled more quickly by intravenous diazepam compared to intranasal midazolam (Lahat, 2000).

Intravenous access for benzodiazepines is very difficult during an active seizure. Rectal diazepam has been shown to be as effective as intravenous diazepam. Buccal midazolam may offer a suitable alternative to rectal diazepam. The mouth and the rectum have similar surface areas and pH, have rich blood supplies, and absorption is directly into the systemic circulation, which avoids high first-pass metabolism. Midazolam is effective in the treatment of acute repetitive seizures, with 80% of the episodes ending within 10 minutes of buccal administration. (Scott et. Al.,1999) However, rectal administration may prove problematic in the adolescent and adult population. Oral and sublingual drug administration during a

seizure is not recommended for risk of aspiration and injury. The buccal route has been shown to be an effective alternate route among patients in active convulsions. (Sridharan, 2005)

The overall frequency of response within the first 5 minutes 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 minutes after drug administration in the buccal midazolam group, although the drug effect time after 5 minutes and less than 10 minutes was similar in both groups. The drug was administered faster in the buccal midazolam group than in the rectal diazepam group. (Mpimbaza, 2012)

Treatment failure for buccal midazolam may reach approximately 40%, in contrast to rectal diazepam which averages 30%. Respiratory depression occurred uncommonly in both of the treatment arms. They concluded that buccal midazolam was as safe as and more effective than rectal diazepam for the treatment of seizures in Ugandan children, although benefits were limited to children without malaria. (Mpimbaza, 2012)

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. Buccal diazepam was utilized in one rural community to treat serial seizures. (Sridharan, 2005)

Midazolam introduced into the buccal cavity is as effective as rectal diazepam in aborting prolonged seizures (roughly 8–10 min). The study was done at a residential centre for children and young people with severe epilepsy. All the patients included in the study had received rectal diazepam previously for acute seizures. The investigators found the buccal cavity easy and safe to reach, and there were no significant adverse cardio-respiratory events. Because of the small volume of liquid given and the rapid absorption of midazolam, aspiration was not an issue in the study. The buccal administration of midazolam seems to have some distinct advantages over rectal administration of diazepam. Although no difference in efficacy between buccal midazolam and rectal diazepam was noted in this study, further work was recommended before this mode of therapy is totally adopted. The patients ranged in age from 5–18 years, but a single dose of each treatment was used for every patient. Whether differences in response rate would have emerged if the dose was based on weight (as is usual for children) was not clear. (Scott et. Al.,1999)

The efficacy of buccal midazolam in children aged 1 month to 15 years with seizures of more than 5 minutes duration showed that the drug efficacy for status epilepticus was 50%. The children were given buccal midazolam at a dose of 0.3mg/k/dose. However, all patients with seizures less than 30 minutes showed a 100% response, wherein the seizures stopped within 3.89 ± 2.22 min (median 3 minutes). No clinically important side effects were reported in this study. (Kutlu, et. al. 2003)

A multi-center randomized controlled trial was done to compare buccal midazolam with rectal diazepam for emergency treatment of children aged 6 months and older presenting with active seizures without intravenous access. The dose utilized for both medications was 0.5 mg/k/dose (ranging from 2.5 mg to 10 mg). The therapeutic success was defined as cessation of seizures within 10 minutes and for at least 1 hour, without respiratory depression. They reported a therapeutic success rate of 56% for buccal midazolam and 27% for rectal diazepam. Thus, they stated that buccal midazolam was more effective than rectal diazepam. (McIntyre et. Al, 2005)

Currently, there is only one study which utilized rectal midazolam for the treatment of acute seizures. A study conducted in Nigeria, comparing the efficacy of rectal midazolam against intramuscular paraldehyde in the control of seizures in 55 children with febrile convulsion. Children aged 5 months to 6 years presenting with febrile convulsion were assigned to either of two treatment groups - rectal midazolam or intramuscular paraldehyde. Rectal

midazolam had an onset of action of 4.9±0.5 minutes. as against 5.2±0.4 minutes in the intramuscular paraldehyde group, though the difference is insignificant ($p>0.10$). The effect of paraldehyde lasted 85±16 minutes compared to 22±5 minutes in those who received rectal midazolam ($p<0.001$). The temperature, pulse and respiration were insignificantly different in the two groups after the administration of the drugs ($p>0.10$), but midazolam significantly lowered the mean arterial blood pressure compared to paraldehyde ($p<0.05$). They concluded that rectal midazolam is as effective and efficacious as intramuscular paraldehyde in the control of seizures in children with febrile convulsion. The ease of administration made it suitable for use in their primary health care setting. (Ojuawo et al. 2001)

RESEARCH OBJECTIVES

General Objective

1. To compare the effectiveness & safety of buccal midazolam and buccal diazepam against rectal diazepam and rectal midazolam for the treatment of children 1 month to 18 years presenting with an acute seizure at the Philippine Children's Medical Center.

Specific Objectives

1. To determine the time duration of seizure cessation among children 1 month to 18 years of age when midazolam or diazepam via the buccal route against the rectal route at the Philippine Children's Medical Center.
2. To determine the side-effects of midazolam and diazepam when given via the buccal route against the rectal route when given for acute seizures among children 1 month to 18 years of age at the Philippine Children's Medical Center.

OPERATIONAL DEFINITION OF TERMS:

1. **Non-invasive administration of medications** – the utilization of the alternative routes of administration of either midazolam or diazepam other than the intravenous or intramuscular route, i.e. buccal, intranasal, sublingual or via rectal routes.
2. **Seizure or convulsion** – episodes of excessive, abnormal muscle contractions, either focal or generalized, which may be sustained or interrupted which are manifestation of excessive or hyper-synchronous (usually self-limited) activity of neurons in the brain.
3. **Status epilepticus** – seizure or a recurrence of seizures that lasts for 30 minutes or more during which the patient does not regain consciousness. However, for management purposes, the operational definition of status epilepticus proposed by Lowenstein & Alldredge (1998) will be utilized in this study. Lowenstein et. al. proposed that institution of treatment for status epilepticus should start for continuous lasting for at least 5 minutes, or there are two or more discrete seizures in between which there is incomplete recovery of consciousness.
4. **Serial seizures** – occurrence of two or more seizures occurring for a relatively brief period (i.e. minutes to hours), but the patient regains consciousness between seizures.
5. **Seizure Recurrence-** recurrence of motor seizure activity from the end of the IV drug infusion after enrollment in the study.

METHODOLOGY

Research Design

This research is a randomized single-blinded open label controlled trial. The data collection was done from April to September 2013 at the Philippine Children's Medical Center. The trial design allowed for entry of a patient more than once because of the potential delay in the treatment if the clinician will still check for prior enrollment into the study.

Population:

Inclusion Criteria:

Eligible patients were aged 1 month to 18 years who were admitted in the emergency room, service wards or intensive care unit; and patients seen in the out-patient department and diagnostic center

(under going EEG or prolonged video EEG monitoring) with:

1. continuous, either afebrile or febrile, seizures
2. children with or without established intravenous access

Children with epilepsy were not excluded in this study (Scott 1999, Kutlu, 2003 and McIntyre, 2005)

Exclusion Criteria:

The following patient were excluded in the study:

1. Patients with proven impaired hepatic, renal and cardiac dysfunction.
2. Patients with seizures who received prior emergency anti-seizure medications from another hospital.

Sample Size Calculation:

By use of two-tailed tests, the estimated sample size is twenty five (25) for each group to detect a difference of at least 2.5 minutes in seizure cessation between groups with 80% power, 5% level of significance, based from previous data.[9]

Calculation:

$$\frac{4C}{(\Delta/\sigma)^2}$$

Where: $C = 7.85$ *(at 80% power)*
$\Delta = 2.5$ *minutes*
$\sigma = 2.22$ *mins*

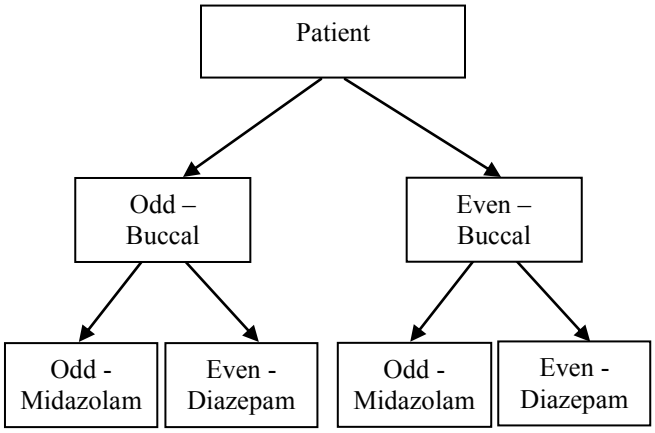
$$N = \frac{4\,(7.85)}{(2.5/\,2.22)^2}$$

$$= \mathbf{24.9 \sim 25}$$

PROCEDURE

Randomization:

Randomization sequence were generated using the random generation tool of Microsoft Excel Program. Generated odd numbers utilized the buccal route, while even numbers were assigned to rectal route. These two groups were further subdivided to either use midazolam or diazepam. For the subgroups, even numbers were assigned to use midazolam, while the odd numbered group used diazepam. The treatment regimen were placed with preassigned schedule and were directly communicated with the senior residents on duty on their respective posts.



Informed Consent:

Patients who arrived at the emergency room in active seizures were verbally given an option to utilize the alternative non-invasive routes of midazolam or diazepam while trying to put an intravenous access. Written consent from the parents or guardians were obtained as soon as practicably possible after treatment and seek consent to use their data in the study.

For those patients with risk factors for recurrent seizures in the service wards, diagnostic center, ICU, an informed consent were obtained from the parents or guardians prior to enrollment into the study.

Drug Preparation and Administration:

A. Preparation:

For the study, the following drug preparations were utilized in the study: 1) Midazolam 15mg/3ml IV ampule and 2) Diazepam 10 mg/2 ml. To avoid confusion, a prepared kit containing either diazepam or midazolam were provided for each target area, with the mode of administration clearly indicated outside the kit.

B. Buccal Routes of Administration:

Based on the study by McIntyre (2005), the dose of midazolam or diazepam were based on the child's age and were designed to give about 0.5mg/kg of midazolam or diazepam (maximum of 10mg/kg/dose). Based on the age, the following projected doses for buccal midazolam and diazepam were followed:

AGE GROUP	DOSE	Buccal/ Rectal **Midazolam** 15 mg/3 ml Volume	Buccal/ Rectal **Diazepam** 10 mg/2 ml Volume
1 month to 5.9 mos old	2 mg	0.4 ml	0.4 ml
6 mos to 12 mos	2.5 mg	0.5 ml	0.5 ml
1 to 4 yrs old	5 mg	1 ml	1 ml
5 to 9 yrs old	7.5 mg	1.5 ml	1.5 ml
10 years and older	10 mgs	2 ml	2 ml

The intravenous preparation of midazolam hydrochloride or diazepam was filtered through a needle. And after removing the needle, the medicine was squirted into the buccal cavity between the gum and cheek mucosa.

C. Rectal Routes of Administration

Even though, the gel form of diazepam or midazolam is not available in the country, diazepam given as a solution rectally has been shown to be as effective (Knudsen, 1977), and the intravenous solution of Midazolam has been utilized for rectal administration (Ojuawo, 2001). The therapeutic dose was similar to the buccal route, i.e. 0.5mg/kg/dose. Thus, the desired dose of diazepam or midazolam was obtained and mixed with distilled water to make 1 to 2 ml solution, and the tip of the tuberculin syringe was inserted per rectum. After giving diazepam or midazolam per rectum, the buttocks were pressed together to prevent escape of the medication.

The investigator was the one who administered the medications in either route after proper coordination with the parents and to the patient.

Outcome Measure:

The primary outcome measure or therapeutic success is defined as cessation of visible signs of seizure activity within 10 minutes of administration of the randomized drug without respiratory depression and without another seizure within 1 hour. Respiratory depression is defined as a fall in oxygen saturation or decrease in respiratory effort sufficient to require assisted breathing either via face mask inflation or intubation after the administration of the drug. This effect however is rare, and is usually managed by transient bag-mask ventilation.

The time of administration of all medications and the start and termination of the seizures were recorded. Observations of oxygen saturation, respiratory rate and supportive interventions were recorded at every 5, 15, 30 and 45 min by the investigator. The total number of seizures within the first 6 hours and first 24 hours were recorded. Seizure duration before treatment were obtained from the report of the child's parents or care-givers.

Intention-to-treat analysis was done and those who left treatment against medical advice was included in the study.

Treatment Failure

If the child had a seizure for 10 minutes after giving buccal midazolam, buccal diazepam, rectal diazepam or rectal midazolam, and intravenous access has been established, then IV diazepam was

was administered, and the status epilepticus protocol of the hospital was followed. The requirement of another anti-convulsant at this stage is classified as treatment failure.

ETHICAL CONSIDERATION

This study was performed in accordance with the current version of the Declaration of Helsinki for medical research involving humans and according to the principles of the European Union and the International Conference of Harmonization Guidelines for Good Clinical Practice and regulations application in our country.

The study protocol, the subject information and the informed consent and assent forms were submitted to and were approved by the Institutional Review Board- Ethics Committee (IRB-EC) of the Philippine Children's Medical Center.

Informed consent was taken by the primary and/or co- investigator from the parents of patients under 18 years of age who fulfilled the criteria of enrolling the patients to the study after thorough explanation of the clinical trial. Likewise, informed assent was taken by the primary and/or co- investigator as soon as possible if feasible from patients 7 – 18 years of age.

The patients and their parents or caregivers were informed that the data gathered in this study were part of the hospital medical records and will be kept confidential to the extent imposed by law.

They were informed that the risks associated with this study are related to the administration of both drugs, midazolam and diazepam. These would include hypotension, respiratory depression, hepatotoxicity and hypersensitivity reactions as noted by rash, hives, itching, difficulty of breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue. Strict measures were employed to prevent the incidence of such adverse events, however they were also informed that there is no guarantee that these will not occur. They were also informed that adverse events during the study period were addressed by the clinical investigators.

Statistical Analysis

For the analysis of data, ANOVA test was utilized to compare the means of seizure cessation of the four test groups.

RESULTS

Table 1. Comparison of the Treatment Groups according to Baseline Characteristics

Characteristics		Treatments				P value
		Midazolam rectal (N=8)	Midazolam buccal (N=9)	Diazepam rectal (N=8)	Diazepam buccal (N=9)	
Age (mean)		4.4	5.9	3.1	3.1	.062
Weight (mean)		14.6	15.2	13.1	12.9	.921
Sex	Male	50.0%	22.2%	25.0%	44.4%	0.545
	Female	50.0%	77.8%	75.0%	55.6%	
Seizure type	Generalized tonic-clonic	62.5%	55.6%	62.5%	66.7%	0.738
	Focal	37.5%	44.4%	37.5%	22.2%	
	Myoclonic	.0%	.0%	.0%	11.1%	
Previous seizures	Yes	37.5%	55.6%	25.0%	66.7%	0.320
	No	62.5%	44.4%	75.0%	33.3%	
Admission Temperature	Febrile	62.5%	33.3%	12.5%	33.3%	0.217
	Afebrile	37.5%	66.7%	87.5%	66.7%	
Receiving Anti-epileptic drugs	Yes	.0%	55.6%	12.5%	44.4%	0.039
	No	100.0%	44.4%	87.5%	55.6%	
Episode with pre-hospital treatment	None	37.5%	44.4%	25.0%	33.3%	0.783
	Once	.0%	22.2%	12.5%	11.1%	
	Twice	62.5%	33.3%	62.5%	55.6%	

Table 1 showed that when the treatments were compared based of age, weight, sex, seizure types, presence or absence of seizures, admission temperature and the number of episode with pre-hospital treatment, they were not statistically significant to each other. However, those patients who were receiving anti-epileptic drugs prior to the occurrence of seizure showed significant difference among the treatment groups with p value of 0.039. The group with the highest number of received anti-epileptic drugs are the midazolam buccal group.

Table 2. A. Comparison of the Treatment Groups according to the Duration of Seizure Before Drug

Treatment Groups	N	Mean (Minutes)	Std. Deviation
Midazolam rectal	8	3.6250	.91613
Midazolam buccal	9	3.1111	1.29368
Diazepam rectal	8	2.1875	.65124
Diazepam buccal	9	3.3333	1.19896

Table 2.A showed that the group with the shortest duration of seizure before drug administration is the rectal diazepam followed by buccal midazolam and buccal diazepam with mean duration of 2.1, 3.1 and 3.3 minutes respectively. The group with the longest duration is the rectal midazolam with 3.6 minutes.

Table 2.B Multiple Comparison of the Treatment Groups according to the Duration of Seizure Before Drug Administration

(I) Treatments	(J) Randomization	Mean Difference (I-J)	P value	95% Confidence Interval	
Midazolam rectal	Midazolam buccal	.51389	1.000	-.9416	1.9693
	Diazepam rectal	1.43750	.066	-.0601	2.9351
	Diazepam buccal	.29167	1.000	-1.1638	1.7471
Midazolam buccal	Midazolam rectal	-.51389	1.000	-1.9693	.9416
	Diazepam rectal	.92361	.499	-.5318	2.3791
	Diazepam buccal	-.22222	1.000	-1.6342	1.1898
Diazepam rectal	Midazolam rectal	-1.43750	.066	-2.9351	.0601
	Midazolam buccal	-.92361	.499	-2.3791	.5318
	Diazepam buccal	-1.14583	.203	-2.6013	.3096
Diazepam buccal	Midazolam rectal	-.29167	1.000	-1.7471	1.1638
	Midazolam buccal	.22222	1.000	-1.1898	1.6342
	Diazepam rectal	1.14583	.203	-.3096	2.6013

Table 2.B. showed that the duration of seizure prior to the institution of treatment was not statistically significant when compared to all the treatment groups.

Table 3. Comparison of the groups according to the Effectiveness of Treatment

Characteristics		Treatments								P value
		Midazolam rectal		Midazolam buccal		Diazepam rectal		Diazepam buccal		
		N	%	N	%	n	%	n	%	
Therapeutic success	Yes	6	75.0%	8	88.9%	8	100.0%	9	100.0%	0.230
	No	2	25.0%	1	11.1%	0	.0%	0	.0%	
Stopped seizure within 10mins	Yes	6	75.0%	7	77.8%	8	100.0%	9	100.0%	0.207
	No	2	25.0%	2	22.2%	0	.0%	0	.0%	
Given benzodiazepines to stop seizure	Yes	3	37.5%	2	22.2%	2	25.0%	2	22.2%	0.879
	No	5	62.5%	7	77.8%	6	75.0%	7	77.8%	
Seizure recurrence within 6hrs	Yes	1	12.5%	0	.0%	0	.0%	1	11.1%	0.544
	No	7	87.5%	9	100.0%	8	100.0%	8	88.9%	
Seizure recurrence within 24hrs	Yes	1	12.5%	0	.0%	0	.0%	3	33.3%	0.098
	No	7	87.5%	9	100.0%	8	100.0%	6	66.7%	
Respiratory distress	Yes	1	12.5%	1	11.1%	0	.0%	0	.0%	0.544
	No	7	87.5%	8	88.9%	8	100.0%	9	100.0%	

Table 3 showed that the cessation of visible signs of seizure activity within 10 minutes of administration of the randomized drugs without respiratory depression and without another seizure within one hour were not statistically significant. Likewise, the patients enrolled in the treatment groups were not statistically significant whether they were given long acting benzodiazepines after the seizure and the recurrence of seizures within six hours. However, the recurrence of seizures within 24 hours was found to be borderline significant with a p value of 0.098.

Table 4. A. Comparison of the Treatment Groups according to the duration to stop seizure after treatment

	N	Mean (Miniutes)	Std. Deviation
Midazolam rectal	8	5.9187	5.05401
Midazolam buccal	9	3.4648	3.27190
Diazepam rectal	8	3.1500	.95115
Diazepam buccal	9	2.3722	1.22636

Table 4.A. showed that the group with the shortest duration of seizure after administration of the drug is the buccal diazepam followed by rectal diazepam and buccal midazolam group with mean duration of 2.3, 3.1 and 3.4 minutes respectively. The rectal diazepam having a 5.9 minutes has the longest duration.

Table 4.B. Multiple comparison of the Treatment Groups according to the duration to stop seizure after treatment

(I) Randomization	(J) Randomization	Mean Difference (I-J)	Sig.	95% Confidence Interval
Midazolam rectal	Midazolam buccal	2.45394	.663	(-1.7603-6.6681)
	Diazepam rectal	2.76875	.488	(-1.5676-7.1051)
	Diazepam buccal	3.54653	.144	(-.6677-7.7607)
Midazolam buccal	Midazolam rectal	-2.45394	.663	(-6.6681-1.7603)
	Diazepam rectal	.31481	1.000	(-3.8994-4.5290)
	Diazepam buccal	1.09259	1.000	(-2.9958-5.1810)
Diazepam rectal	Midazolam rectal	-2.76875	.488	(-7.1051-1.5676)
	Midazolam buccal	-.31481	1.000	(-4.5290-3.8994)
	Diazepam buccal	.77778	1.000	(-3.4364-4.9920)
Diazepam buccal	Midazolam rectal	-3.54653	.144	(-7.7607-.6677)
	Midazolam buccal	-1.09259	1.000	(-5.1810-2.9958)
	Diazepam rectal	-.77778	1.000	(-4.9920-3.4364)

The table 4.B. showed that the multiple comparisons of all the treatment groups based on the time duration to stop the seizure after giving the drug were not statistically significant with each other.

DISCUSSION

Previous studies have shown that the first and foremost aim in treating an acute episode of convulsion is controlling it as quickly as possible. Every effort should be made to prevent prolonged seizures from developing into status epilepticus.

This is a randomized single-blinded open label controlled trial research conducted from April to September 2013 at the Philippine Children's Medical Center. This study aimed to compare the effectiveness and safety of buccal midazolam and buccal diazepam against rectal midazolam and rectal diazepam for the treatment of children 1 month to 18 years presenting with an acute seizures. There were only 34 subjects enrolled in this study instead of 100 subjects based on the 5% level of confidence with 80% power.

As to the baseline characteristics of the patients such as age, weight, sex, seizure type, presence and absence of previous seizures, temperature on admission and the number of seizure episodes prior to hospitalizations were found to be not statistically significant. However, patients who received anti-epileptic drugs prior to the occurrence of seizure among the treatment groups showed significant difference with a p value of 0.039.

As to the seizure type, majority of the subjects presented with generalized tonic-clonic seizure but were not statistically significant between the groups. Majority of the patients were afebrile at the time of admission but was not statistically significant when compared to the treatment groups. The results of the comparison of the treatment groups to the baseline characteristics are comparable to the study of Scott et al in 1999.

The number of subjects who were maintained on or receiving anti- epileptic drugs were statistically significant between the treatment groups.

The therapeutic success or the cessation of visible signs of seizure activity within 10 minutes of administration of the drugs without signs of respiratory depression and without another seizure within 1 hour was found to be highest among the diazepam buccal and rectal groups. However, when compared to other treatment groups, it is not statistically significant.

All the subjects under the diazepam buccal and rectal groups showed cessation of seizure within 10 minutes however some of the patients were given long acting benzodiazepines after 1-2 hours of giving the medication.

The duration of seizure prior to the institution of treatment and the time duration to give the drug after arrival to hospital were not statistically significant among the treatment groups.

The time to stop the seizure after giving the drug among the treatment groups were found to be not statistically significant. The group with the shortest duration to stop the seizure activity was buccal diazepam group (mean= 2.3 minutes) and the longest was rectal midazolam (mean= 5.9 minutes). Among the route, the buccal group particularly that of Diazepam group has the shortest duration of seizure after giving the medication.

Overall, the author found out that there is a trend of not having significant differences between the drugs according to its efficacy, time from arrival at the patient to drug administration, time from administration to end of seizure, or total seizure length. No subjects had adverse cardiorespiratory events, which suggests drug safety.

Safety, efficacy, and long-lasting anti-seizure activity are said to be important characteristics of any drug for emergency treatment of seizures. The result of this study showed that buccal diazepam has been proved superior to the other drugs in the treatment of acute repetitive seizures which was justified in this report. Since there were no differences between the efficacy of the drugs, buccal diazepam is also likely to be superior to the other drugs. Use of buccal diazepam has clear practical and social advantages over rectal diazepam, buccal midazolam and rectal midazolam.

CONCLUSION

The results of this study showed that there is no statistical difference among the four treatment groups as to their effectiveness and safety in the treatment of acute seizures.

Based also on this preliminary report, the author can conclude that both drugs (diazepam and midazolam) of either routes (rectal and buccal) can be used as alternative treatment in patients with acute seizures in a setting with no intravenous access. There were no cardio-respiratory events noted in all the treatment groups, which suggests drug safety.

RECOMMENDATION

In this study, samples recruited were not enough. Thus, it should be continued by the co-authors to have a larger population for a better reflection of the results.

Likewise, it is to be recommended for future research to include sub-analysis of the anti-epileptic drugs given prior to giving the medications.

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