IJPSR (2015), Vol. 6, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 15 July, 2014; received in revised form, 06 September, 2014; accepted, 16 February, 2015; published 01 March, 2015

BUCCAL MIDAZOLAM: COULD IT BE AN ALTERNATIVE FOR I/V DIAZEPAM FOR ACUTE SEIZURES IN MALNOURISHED CHILDREN

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Keywords:

Buccal Midazolam, I/V Diazepam, Acute Seizures, Malnourished Children

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ABSTRACT: Acute convulsive disorders are the most frequent neurological disorders in children which require emergency drug treatment. Immediate management of a convulsive episode is must as, delay can lead to status epilepticus, which is a significant cause of neurological morbidity and mortality among children. Benzodiazepines especially diazepam is often used as first line and routinely administered intravenously, but this is not a practical route in many peripheral health care facilities. Midazolam by buccal route is another upcoming mode of treatment in view of difficulties associated with securing an intravenous line in convulsing children with motor activity especially at peripheries, homes or even at schools. Being a developing country, malnourished group forms a significant number in our clinical practice so it was worthwhile to examine the issue of buccal midazolam's safety and efficacy in this subset of malnourished children. It was a prospective double blind randomized control trial. Total 80 children who fulfilled the inclusion criteria were randomly allocated by a computer generated table. One group received buccal midazolam and the other, intra venous diazepam. Response was assessed by termination of motor activity [seizures] within 5 minute and non-recurrence of seizure in next 30min. Any toxic effects of either drug were noted. The mean time elapsed between drug administration from the point of entry to the emergency department was found longer with I/V Diazepam than buccal Midazolam ($p>0.05$), but not quite statistically significant. The time elapsed between drug administration and control of seizures is shorter for diazepam than buccal Midazolam ($p<0.05$) and this difference is statistically significant. The total time elapsed between point of entry to the emergency till control of seizures is almost same for Diazepam and buccal Midazolam ($p<.05$). The non-response rate and recurrence rate was significantly lower with Diazepam group. Malnutrition had no effect on control of seizures.

INTRODUCTION: Acute convulsive disorders are the most frequent neurological disorders in children which require emergency drug treatment [1, 2]. These disorders are common in children admitted to hospitals, with over a fifth of children reporting a history of convulsions in their presenting illness.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(3).1336-41

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(3).1336-41

Peak incidences have been observed during 2nd-3rd year of life [3, 4]. Immediate management of a convulsive episode is must and it needs to be terminated promptly and safely. Better outcome and less sequlae has been observed with rapid control of seizures [5, 6]. Delay in treatment can lead to status epilepticus, which is a significant cause of neurological morbidity and mortality among children[7, 8].

To terminate these convulsive episodes the drug should be easy to administer, have a rapid onset of action, safe, effective and should also have prolonged anticonvulsant action [9, 10]. Various drugs administered through different routes are important

and have been tried in the management of acute seizures[11, 12].

Benzodiazepines are often used as first line for the treatment of convulsions [9, 13, 14]. Diazepam is commonly used as the standard drug in the developing countries, because it is inexpensive, rapidly acting and widely available, but routinely administered intravenously, which is not a practical route in many peripheral health care facilities. Intravenous administration of diazepam though having a rapid onset of action, is rapidly redistributed in to fatty tissues leading to recurrence of convulsions. It's rather quite difficult to secure an intra-venous line among malnourished children. An effective treatment that can be easily administered by a more convenient, socially acceptable route is therefore needed [11].

Another benzodiazepine, Midazolam by buccal route is another upcoming mode of treatment in view of difficulties associated with securing an intravenous line in convulsing children with motor activity especially at peripheries, homes or even at schools. Midazolam has several pharmacokinetic and pharmacological properties that support its use.

It has a rapid onset of action and shorter elimination half-life. It is therefore less likely than diazepam to accumulate and cause respiratory depression on repeated administration. At the same time it is highly convenient and socially acceptable than rectal route and better tolerated than intranasal route. So midazolam by this route of administration could be quite helpful in difficult settings [9]. Several attempts have been made in the past to develop these alternate routes of administration.

Some of the alternative routes tried are Rectal, Intranasal, Sublingual and Buccal. Some studies on safety and efficacy of buccal midazolam in acute convulsions has proved that it is efficacious in controlling acute attack of convulsions and it is safe as well [10, 15, 16, 17, 18]. Buccal midazolam may cause respiratory depression but fatal outcome and respiratory depression are less in number as compare to other routes and Flumazenil, a benzodiazepine may be used as an antidote to buccal midazolam overdose [19,20].But there have been few / no studies focusing on the subset of malnourished children. These studies have been done in countries where nutritional status is not a big issue. Since this malnourished group forms a significant number in our clinical practice we thought it would be worthwhile to examine the issue of buccalmidazolam in this subset of malnourished children. This would go a long way in formulation of guidelines in which buccal route or other non-intravenous routes may become the route of choice for prompt control of acute seizure of any type. So we try to find out whether we can use buccal midazolam as an alternative for intravenous diazepam for the treatment of seizures in malnourished children.

MATERIALS AND METHODS:

It was a prospective double blind randomized control trial, conducted in the department of pharmacology and department of pediatrics, Santosh Medical College and Hospital, Santosh University, Ghaziabad. We took patients from pediatrics emergency. Total80 children were included in the study.

Inclusion criteria:

Children between the age of 6 months to 5 year, who were malnourished by IAP (Indian academy of pediatrics) classification and suffering from acute convulsive episodes, irrespective of type of seizures and who had not received any drug for the current acute episode were included in this study.

Exclusion criteria:

The Children who were < 6 months and > 5 years of age, Who had received any medications in any form, from anywhere for this current acute episode of seizure and having weight more than 80% of the expected (WHO standard) were excluded from this study.

Children who fulfilled the inclusion criteria were randomly allocated by a computer generated table to either of the two groups. One received buccal midazolam and the other, intravenous diazepam. Allocation had not been concealed from emergency staff nurse. To ascertain double blinding the study group that received buccal midazolam had been given intravenous normal saline which acted as placebo and the study group that received intravenous diazepam had been given normal saline by buccal route which acted as placebo. The dose

of midazolam was 0.2 mg/kg via the buccal route. The usual injectable preparation of midazolam hydrochloride was used even for buccal administration[10, 21, 22]. Measured drug was loaded in a syringe and was squirted in the buccal cavity by separating both the lips apart. The dose of diazepam was 0.3 mg/kg and was given intravenously. Verbal consent was taken from parents/ guardian before entering patients in to our study. After the seizure was controlled written consent was completed by parents. Appropriate approval was sanctioned by the institutional ethical committee.

Response was assessed by termination of motor activity [seizures] within 5min and non-recurrence of seizure in next 30min. If a seizure persisted beyond 5min, it was considered as failure / non response and in both the groups standard treatment guidelines were followed to further control seizure [23]. Any adverse drug reactions of either drug were noted.

All the vitals were noted at the time of arrival and after 30 min. Other general measures in management of seizure were taken care of like suctioning, lateral position, 0xygen inhalation, Maintenance and recording of vitals like pulse, respiratory rate, blood pressure and temperature, Securing an intravenous line for further management if required.

The data was analyzed and comparison between the covariates of two study groups that is means and standard deviations for the time needed to control the seizures, time of drug effect according to grades of protein energy malnutrition and vitals were performed by using chi-square test and paired t-test with the help of SPSS version 17 for windows. We considered a p-value of <0.05 to be statistically significant.

RESULT AND OBSERVATIONS:

TABLE 1: DEMOGRAPHIC PROFILE

Demographic profile	I/V Diazepam	Buccal Midazolam
Mean Age	2.84±1.55 yrs.	2.12±1.4 yrs.
M	23 (57.5%)	26 (65%)
F	17 (42.5%)	14 (35%)
M : F Ratio	1.35 : 1	1.85 : 1

TABLE 2: NUTRITIONAL STATUS OF THE STUDY GROUP

Grades of malnutrition	I/V Diazepam N = 40	Buccal Midazolam N = 40
Grade I (71–80% of expected)	22 [55%]	19 (47.5%)
Grade II (61–70% of expected)	12 (30%)	15 [37.5 %]
Grade III (51–60% of expected)	6 [15%]	5 [12.5]
Grade IV (< 50% of expected)	0	1 (2.5%)
Mean	9.55 ± 2.8 Kg	8.3 ± 2.44 Kg

TABLE 3: MEAN TIME OF DRUG EFFECT

Drugs	Mean time from TOA* – TODA	Mean time from TODA# - TOSS	Mean time from TOA –TOSS$
Diazepam	1.75 ± 0.8min (N=40)	1.69 ±0.87min (N=38)	3.17±1.39min (N=38)
Midazolam	1.43 ± 0.64min (N=40)	2.34 ±1.13min (N=35)	3.22±1.84min (N=35)
P value	0.079	0.022	0.947

TOA* = Time of arrival, TODA# = Time of drug administration, TOSS$ = Time of seizure stoppage

TABLE 4: EFFECT OF TREATMENT

	I/V Diazepam	Buccal Midazolam
Response to treatment	38 [95%] N=40	35 [87.5%] N=40
Non-response to treatment.	2 [5%] N=40	5 [12.5%] N=40
Recurrence of seizure	1 [3.33%] N=38	5 [14.2%] N=35

TABLE 5: RESPONSE OF DRUG ACCORDING TO MALNUTRITION

Grades of PEM	I/V Diazepam N = 40	Response	Buccal Midazolam N = 40	Response
71 - 80%	22	20 (90%)	19	16(84.2%)
61 - 70%	12	12 (100%)	15	13(86.6%)
51 - 60%	6	6 (100%)	5	5(100%)
< 50%	0	0	1	1(100%)
Non Responders		2		5

TABLE 6: MEAN TIME OF DRUG EFFECT ACCORDING TO GRADES OF PEM

Grades of PEM	I/V Diazepam N = 38	Buccal Midazolam N = 35	P value
Grade I	1.81±0.98	2.43±1.09	0.106
Grade II	1.50±0.52	2.41±1.24	0.050
Grade III & IV	2.00±1.26	2.16±1.16	0.809

DISCUSSION: The importance of undertaking this study was to access the efficacy of buccal route of midazolam in malnourished children for cessation of seizures. Malnutrition, as an independent variable has never been assessed in any of the studies so far either in western literature or in Indian literature. This is surprising because in the most recent coverage evaluation survey in 2009 – 10 the number of malnourished children in India was to the tune of 54% [24]. Malnutrition was defined by IAP Classification as Grade I, II, III and IV, with grade I considered as mild, II as moderate and III and IV as severe malnutrition. This classification is based on weight for age and the standard reference value was taken from WHO charts (2005-06)[25]. WHO charts was chosen as they are truly representative of Indian Children.

Age group:
The age group included in our study was 6 months to 5 yrs. This age group was chosen because conventionally malnutrition is defined in this particular age group glbally. In a study by Chakrabarty et al the results between < 5 yrs and > 5yrs children do not differ much [26]. Hence the results observed in our study can be applied to older children as well. The maximum cases (31.2%) belonged to age group of 1-2 yrs. This is in concordance with epidemiology of seizures where the peak incidences have been reported in 2nd year of life [3, 4].

Gender ratio: The male: female ratio in the entire study group was 1.58: 1, in the Diazepam group it was 1.35: 1 and in the Midazolam group it was 1.85: 1 (**Table 1**). The M: F ratio in our study groups was comparable.

Nutritional status: 55% patients among Diazepam group were grade I malnutrition v/s 47.5% in Midazolam group. Grade II malnutrition in 30% patients in diazepam group and 37.5% in midazolam group. Severe malnutrition (III & IV) were observed in 15% each of two study groups (**Table 2).** Mean weight in diazepam group was 9.55 ± 2.8Kg while in midazolam group it was 8.3 ± 2.44kg. Weight in the two groups was matched. Ours is the only study available which has considered malnutrition as an independent variable. Hence the results cannot be compared. However in our study the children with severe malnutrition were relatively less, whereas more than half of the patient belonged to grade I malnutrition (51.2%).

Assessment of response (efficacy):
In our study we have considered following parameters to assess response Time of arrival of patient to control of seizure. Non cessation of seizure (no response) within 5 min. Recurrence of seizures within 30 min. Effect of malnutrition on control of seizure

Time of arrival of patient to control of seizures:
The mean time elapsed from arrival of patient in acute seizure to drug administration was 1.75 ± 0.87 minutes (105 sec) with standard error of 0.14 in diazepam group . On the other hand the mean time from arrival of patient to drug administration in midazolam group was 1.43 ± 0.64 min. (85.5 sec) with standard error of 0.10 (**Table 3**). The difference in time was not quite significant statistically though apparently there is a difference in the sense that buccal midazolam takes shorter time to administer than I/V route.

This has far reaching implication. Non intravenous routes take shorter time to administer the drug. This difference is significant because the total duration of seizure can be shorted by faster administration. Lahat et al in his study found that mean time from arrival in hospital to initiation of therapy was significantly shorter in midazolam group [27]. However Midazolam in his study was given by intranasal route.

In our study after drug administration, seizures were controlled in a mean time interval of 1.69 ± 0.87 min. (101 sec) with standard error of 0.15 in Diazepam group, whereas in midazolam group this time was 2.34 ± 1.13 min. (140.5 sec) with standard error of 0.19 (**Table 3**). This statistical significant difference implies that Diazepam has faster onset of action than Midazolam. These findings are in resonance with other studies [26, 28]. The reason could be the maximum bioavailability by I/V route.

The total time required for cessation of seizure from time of arrival in Diazepam group was 3.17 ± 1.39 min. while in Midazolam group it was 3.22 ±

1.84min. The difference was not statistically significant (**Table 3**). This is a very important observation since, though there is a significant difference in the onset of action of the two drugs. However the faster administration of Midazolam compensates for this and the total time for cessation of seizure from the time of arrival of the patient is practically the same. Hence if we consider the practical implication of this observation it is logical to conclude that midazolam by non intravenous routes (buccal) would effectively control seizure in almost the same time as intravenous Diazepam.

Non response and Recurrence:

In our study non response was defined as inability of seizure stoppage within 5min and Recurrence was reappearance of seizure within 30 minutes. In our study only 2 patients (5%) of Diazepam group showed no response as compared to 5 patients (12.5%) of Midazolam group. Recurrence of seizure in our study was noted in 1 patient (3.33%) in Diazepam group and 14.2% in Midazolam group (5 patients) (**Table 4**).

Effect of malnutrition on control of seizures:

In our study only 15% patients in each group were severely malnourished, however all of them showed response in both groups (100%).There was no recurrence and Non response was observed in this severe malnutrition category in both study groups. However in grade I and II there was 90% and 100% response in Diazepam group as compared to 84.2% and 86.6% in Midazolam group .The mean time of drug administration to effect (cessation of seizure) in grades I in Diazepam group was 1.81± 0.98 v/s 2.43 ± 1.09 in Midazolam group.

In grade II it was 1.50 ± 0.52 in Diazepam group and 2.41±1.24 in Midazolam group. whereas in severely malnourished category (grade III + IV) it was 2.00±1.26 & 2.16±1.16 in Diazepam & Midazolam groups respectively (**Table 5 & 6**). There was no statistically significant difference between the time of administration and time of seizure stoppage between two groups depending upon the grades of PEM and hence there is no other study on malnutrition we can conclude from our study that Malnutrition does not affect seizure control.

CONCLUSION: Hence to conclude, our study demonstrated that both Intravenous Diazepam and Buccal Midazolam are equally efficacious for any grade of malnutrition at these particular doses. The non-response and recurrence was observed higher with Buccal Midazolam giving an edge to I/V Diazepam as a superior drug, However our suggestion would be to start the treatment with buccal midazolam specially in situations like homes, peripheries or in schools where securing an I/V line could be quite troublesome or not possible, to give instant control and also to gain time to put an I/V line for diazepam.

ACKNOWLEDGEMENT: Authors would like to acknowledge the role of Mr. Nand Kishore and Sister Shubralata for their help and technical support.

CONFLICT OF INTEREST: None

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How to cite this article:
Sharma J, Agrawal A, Chopra VS, Gaur P and Jhingran S: Buccal Midazolam: Could It Be an Alternative for I/V Diazepam For Acute Seizures In Malnourished Children. Int J Pharm Sci Res 2015; 6(3): 1336-41.doi: 10.13040/IJPSR.0975-8232.6 (3).1336-41.