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Comparative Efficacy of oral Diazepam Versus oral Clobazam in Preventing Recurrent Febrile Seizures in Children 6 Month to 5 Years of Age

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Abstract:

Background: *Febrile seizure (FS) is the most common seizure in children younger than 5 years of age. In general, FS is benign, and the anti-epileptic drug controversy has not yet been resolved because of its side effects. Recently preferred for intermittent prophylaxis, Diazepam and Clobazam are more efficacious and have fewer side effects than the preceding drugs. The efficacy of diazepam compared to clobazam in preventing recurrent FS was assessed in this study.*

Methods: *This comparative observational study was conducted at the Sir Salimullah Medical College Hospital (Mitford),, Dhaka, from November 2013 to August 2014. A total of 66 children aged 6 months to 5 years with a simple or complex history of FS were included. Patients were randomized into two groups: Group A (n=33) received oral Diazepam (0.33 mg/kg, 8-hourly for 72 h post-seizure, max 10 mg) or Group B (n=33) received oral clobazam (1 mg/kg daily for 72 h, max 20 mg). Follow-up was performed for 6 months, and data were collected from a pretested questionnaire on patients who were followed monthly.*

Results: *Complete data from 61 children (Group A: 31; Group B: 30) showed that males predominated (59.01%) and were higher in children aged 6–24 months (62.29%). Recurrent FS was observed in 3.23% (diazepam) and 10% (clobazam) of the patients, with no difference in recurrence rates or side effects (p>0.05). The most frequent side effect was drowsiness in both the groups.*

Conclusion: *Oral Clobazam and Diazepam are equivalent and safe for the prevention of FS recurrence. However, with more flexible dosing, clobazam comes out a tiny bit ahead.*

Keywords: *Febrile seizure, Antiepileptic drugs, Diazepam, Clobazam, Adverse effects.*

1. INTRODUCTION

Febrile status epilepticus or febrile seizures (FS) are defined as convulsions in children aged between 6 months to 5 years accompanied by fever, but without evidence of any defined cause or concomitant central nervous system (CNS) infection [1,2]. FS are the most commonly reported seizures in children prevalent among 2% to 8%, which differs according to various ethnicity and geographical locations[3]. However, the occurrence in developing countries is likely to be higher because of higher exposure an severity of frequent infections and perinatal insults[4]. The majority of children with FS have rectal temperatures greater than 102o F. Most FS eventuate during the day of onset of child's fever

and lasts about a few minutes, although some can be as momentary as a few seconds while some episodes may continue up to 15 minutes or more[5]. Though the average recurrence rate of febrile seizure is 35%[2,6] but more than 50% risk for recurrence of further FS is observed during the initial following year after the first FS and over 90% FS recorded to be occurred within the subsequent 2 years[6]. Because of high probability of recurrence of FS, it is imperative to implement preventive measures, such as to put the child on prophylaxis during febrile episodes. The treatment options are continuous process with antiepilepticdrugs, antipyretic treatment and intermittent antiepileptic drug prophylaxis during the period of fever[3]. However, previously practiced continuous prophylaxis with anti-epileptic drug till 6 year of age is not recommended nowadays, considering the potential risk of toxicities from those antiepileptic drugs [7]. Besides, intermittent antiepileptic drug prophylaxis during the period of fever may be continued up to 6 year of age. The efficiency of intermittent Diazepam in precluding recurring seizures is widely acceptedat a dose of 0.33 mg/kg of body weight 8 hourly orally, during initial 72 hours of onset of fever [8-12]. However, it is accompanied by side effects which are likely to interfere with normal daily activities such as, lethargy, ataxia, irritability, reduced activity level or excessive sleep [6-13]. On the contrary, oral Clobazam at a dose of 1mg/kg, once daily for 72 hours is as effective and safe as Diazepam in preventing febrile seizure recurrence which offers single dose schedule along with less side effects [14]. Nonetheless, there are limited clinical data in our country focusing on the comparative assessment of the efficacy and side effects between oral Diazepam and oral Clobazam for the prevention of recurrent FS. To unveil a scope to suggest a relatively safe, with fewer side effects and more effective drug, this study attempted to prospectively analyze the efficacy between oral Clobazam and oral Diazepam in preventing recurrent FS among children of age group from 6 month to 5 year.

2. Objective

The objective of this study was to assess the efficacy and safety of intermittent oral Diazepam vs intermittent oral Clobazam in preventing recurrent FS. Methodology & Materials

3. Methodology and Materials

This comparative observational study was conducted at Sir Salimullah Medical College Hospital (Mitford),, Dhaka from November 2013 to August 2014. A total 66 children (aged 6 months to 5 years) having history of single or multiple episodes of simple or complex FS, who got admitted in the paediatric ward, are purposively selected for this study. With prior consent of parents/guardians, patients were randomly apportioned in Group-A and Group B, each group having 33 children. Group-A patients have been prescribed with oral Diazepam tablet with a dose of 0.33 mg/kg of body weight 8 hourly for 72 hours of initial seizure (maximum 10 mg) and Group-B patients have been prescribed with oral Clobazam tablet intermittently 1mg/kg, single daily dose (maximum 20 mg) for the same duration after every febrile episode. Each patient was followed-up on a monthly basis for consecutive 6 months.

4. Selection Criteria

Inclusion Criteria

- Children of both sexes, having one or more episodes of FS
- Agebetween 6 month to 5 year
- Both simple and complex FS were considered.

Exclusion criteria

- Neurological disabilities.
- Progressive neurological disease.
- Afebrileseizure.
- Acute CNS infection diagnosed clinically.
- Symptomatic seizure of other nature.
- Developmental delay.
- Mentalretardation.
- Chromosomal abnormalities.
- Getting long termantiepileptic drug.

5. Data Collection

After acceptance of the research protocol by ethical review committee of SSMC (Mitford Hospital) and reviewed by BCPSA, data were collected with a pretested questionnaire. Written informed consent was obtained from parents before enrollment. After inclusion and exclusion, 66 children were randomly assigned in two groups. Group A received oral Diazepam (0.33 mg/kg every 8 hours for 72 hours, maximum 10 mg per dose) and Group B received oral

Clobazam (1mg/kg as a single dose, maximum 20 mg) for febrile episodes.Among 66 children, 3 were lost follow up and 2 provided incomplete data. Parents were trained to recognize FS, drug toxicities. FS recurrence, drug safety, side effects, compliance and comparative efficacy of Clobazam and Diazepam were assessed over a period of six months with monthly follow up.

6. Ethical Consideration

To conduct this study written approval was taken from the ethical committee of SSMC (Mitford Hospital). Protocol was submitted to BCPS and was accepted by the reviewers. The aim and the objective of the study were elucidated to the gurdians in followed by obtaining informed written consent from them.

7. Statistical Analysis of Data

Statistical analysis, collected data were processed and analyzed using computer based software SPSS 20 (Statistical package for Social science) and Microsoft Office Excel 2007. Student's t-Tests were carried out with a consideration of significance level p=0.05.

8. Results

Table1. *Distribution of the sample by age and sex (N=61)*

Characteristics	Group-A, OralDiazepam n_1=31	Group-B, Oral Clobazamn_2=30	Total N=61	pvalue
Age(in months)				
6-24 n(%)	18 (58.06)	20 (60.67)	38 (62.29)	0.755
25-48 n(%)	11 (35.48)	8 (26.67)	19 (31.15)	
49-60 n(%)	2 (6.45)	2 (6.67)	4 (6.56)	
Sex				
Male n(%)	20 (64.52)	16 (53.33)	36 (59.01)	0.159
Femalen(%)	11 (35.48)	14 (46.67)	25 (40.98)	

Numbers in parenthesis denote percentage value of each category P value reached from Chi-square test after (adjusting with Fisher's exactas required)

Data of 61 samples out of 66 was available for analysis, where Group A comprised of 31 respondents and Group B comprised of 30 respondents. As depicted in Table I, both in Group A and Group B, majority of the children aged between 6 to 24 months of age (58.06% and 60.67% respectively). Male children were more in proportion in both the groups (64.52% and 53.33% respectively). The sample distribution among the groups as per age is in significant asp=0.755(i.e.p>0.5) but it is having significance as per sex, where p=0.159 (i.e. p<0.5).

Table2. *Study groups showing occurrence of seizures and type of seizures during a febrile episode (before enrollment in the study) (N=61)*

Characteristics	Group-A, OralDiazepam n_1=31	Group-B, Oral Clobazamn_2=30	Total N=61	pvalue
Febrileseizure				
Initial	25 (80.65)	27 (90.0)	52 (85.25)	0.977
Recurrent	6 (19.35)	3 (10.0)	9 (14.75)	
Typesoffebrileseizure				
Simple	23 (74.19)	20 (76.67)	43 (70.49)	0.961
Complex	8 (25.81)	10 (23.33)	18 (29.51)	

Numbers in parenthesis denote percentage value of each category P value reached from Chi-square test after (adjusting with Fisher's exactas required)

The history of FS before enrollment in the study have been recorded. In Group A, initial episode havebeen recorded among 80.65% and recurrent episode have been recorded among19.35% of the children. In Group B, initial episode and recurrent episode have been recorded among

90.0% and 10.0% of the children respectively. History of febrile seizure recorded to be simple in 74.19% of the Group A children and 76.67% of the Group Bchildren. History of FS recorded to be complex in 76.67% of the Group A children and 23.33% of the Group B children respectively (Table II).

Table3. *Study groups showing number of febrile episode occurred during 6 months follow- up (N=61)*

Characteristics	Group-A, OralDiazepam n_1=31	Group-B, Oral Clobazamn_2=30	Total N=61	pvalue
Febrileepisodes				
Nil	5 (16.13)	9 (3.0)	14 (22.95)	0.969
One	23 (74.19)	19 (63.33)	42 (68.85)	
Two or more	3 (9.68)	2 (6.67)	5 (8.2)	
Occurrenceof febrileseizure				
Yes	1 (3.23)	3 (10.0)	4 (6.56)	0.981
No	29 (93.54)	28 (90.0)	57 (93.44)	

Numbers in parenthesis denote percentage value of each category P value reached from Chi-square test after (adjusting with Fisher's exactas required)

Over the 6 months follow-up 47 febrile episode have been reported in this sample. Among the patients in Group-A, 23 (37.7%) patients developed single episode and 3 (4.92%) developed multiple episode, again in Group-B, 19 (31.15%) developed single episode and 2 (3.28%) developed multiple episode. In these patients, febrile seizure have been recorded among 1 case (1.64%) in Group A and among 3 cases (4.92%) in GroupB, all of which were simple febrile seizures. Among the groups, the difference of proportion of respondents having febrile episodes or febrile seizures were statistically insignificant (p>0.05) (Table III

Table4. *Study groups showing adverse effects of drugs during 6 months follow-up (N=61)*

Characteristics	Group-A, OralDiazepam n_1=31	Group-B, Oral Clobazamn_2=30	Total (N=61)	pvalue
Vomiting	7 (22.58)	4 (13.33)	11 (18.03)	0.348
Ataxia	2 (6.45)	3 (10)	5 (8.2)	0.668
Drowsiness	12 (38.71)	11 (36.67)	23 (37.7)	0.869
Irritability	5 (16.13)	5 (16.67)	10 (16.39)	0.955
Others	0 (0.0%)	0 (0.0%)	0 (0.0%)	- -

Numbers in parenthesis denote percentage value of each category P value reached from Chi-square test after (adjusting with Fisher's exactas required)

Adverse effects like vomiting, ataxia, drowsiness, irritability have been noticed in both the groups during 6 months follow-up. Drowsiness reported in highest proportion (Group A: 38.71%, Group B: 36.67%). However, the difference in proportion of reported adverse effects among the groups were not statistically significant (p>0.05) (Table IV).

9. DISCUSSION

Planning the management of FS must address the likelihood of its recurrence. For last few decades various regimes like daily Phenobarbitone, Valporate, and intermittent oral or rectal Diazepam have been administered with obtaining various degrees of success. However, such therapeutic managements may convoyed with adverse effects on the child's cognitive and

behavioral development15 Intellectuals were exploring better approaches for the management of FS, which are purposefully effective with lower dosage but having chances of lesser side effects. In this regard, intermittent Diazepam therapy is a widely practiced management for the prevention of recurrent FS.14 In this study, intermittent oral Clobazam therapy have been compared with intermittent oral Diazepam therapy to weigh their therapeutic efficacy. During the work, it is found that children of age group 6-24 month were more prone to FS. It is further noticed that male children were more prevalent with FS, where, 64.52% and 53.33% of the children from Diazepam and Clobazam group respectively weremale. Similar result depicting higher proportion of male than female being affected with FS was also found in the study of Iqbal et al.16 However, Khosroshahi et al also demonstrated analogous result of age and sex in their study on children with FS.10

Among the sample it is revealed that 85.25% of the children reported with initial FS and 14.75% of them with recurrent FS. Out of them, in 70.49% of the cases the seizures were simple and in 29.51% of the cases, the seizure was complex. Other studies also seems to represent analogous distribution of simple and complex FS where it has denoted most cases of FS are simple and only 15%-20% of the cases are complex in nature.17 Assigning the children in different drug groups, during the follow-up, 47 (77.05%) febrile episodes have been recorded out of these sample. On the other hand, single episode of fever has been reported in 23 (74.19%) cases in Diazepam group compared to 19 (63.33%) cases in Clobazam group. Again, multiple episode of fever developed in 3 (9.68%) patients in Diazepam group compared to 2 (6.67%) patients in Clobazam group. In these patients, febrile seizure has been recorded among 1 case (3.23%) in Diazepam group and among 3 cases (10.0%) in Clobazam group, all of which were simple FS. Though both single or multiple episodes of fever were comparatively low in proportion in the group prescribed with Clobazam than the group prescribed with Diazepam group, and the recurrence of FS was comparatively higher in proportion in the Clobazam group than the Diazepam group, the proportion of febrile episodes or FS were not having statistically significant difference between the groups ($p>0.05$).

The adverse drug effects namely, drowsiness was reported in highest proportion in both of the groups. Drowsiness and vomiting were more common in Diazepam group than the Clobazam group, irritability was reported by nearly similar proportion of both groups and ataxia was more common in Clobazam group than the Diazepam group. In case of the adverse effect of drugs only vomiting shows insignificant difference between the groups as $p=0.348$ ($p>0.05$ is considered statistically significant). However, previous studies have found Clobazam to be an effective treatment module compared to placebo or antipyretics while used intermittently during the onset of fever among the children who had previous history of FS.14,18,19 Researchers who portrayed comparative efficacy of intermittent oral Diazepam versus Clobazam also found superior benefits of Clobazam in children with FS. Khosroshahi et al. found in their 12 month follow-up study that, recurrence of FS occurred in 1.7% of the patients in Clobazam group compared to 3.1% patients in the Diazepam group ($p>0.05$); and 14.2% of the Clobazam group patients compared to 54% of the Diazepam group patients reported drowsiness and sedation as drug adverse effect ($p<0.001$).10 Again, Gulato et al, found in their study that, sedation was significantly higher among group of patients treated with Clobazam compared to group of patients treated with Diazepam ($p<0.001$), whereas, recurrence of FS was 2.3 times higher in Diazepam group compared to that of Clobazam group, however their findings concluded with the estimation that both of these drugs have similar efficacy on terms of treating FS.20

10. CONCLUSION

The clinical data of the present study revealed that, intermittent oral Diazepam and oral Clobazam have comparable efficacy in terms of prevention of recurrence of febrile seizure as well as considering for their adverse effects. However, as oral Clobazam offers better dosage schedule providing easiness of administration in children it holds advantage over oral Diazepam.

11. LIMITATIONS OF THE STUDY

Data was availed from a single center, thus, presented data on a small sample, depended completely on the interviewers statement for the required information.

Recommendations

In this study, it has been well recognized that, oral Clobazam is at least as effective and as safe as that of oral Diazepam with some obvious advantages in the sector of its administration (daily dose) on the children. Thus, oral Clobazam is recommended to be used as an effective and safe alternative to oral Diazepam in preventing recurrent FS. To establish the findings as a therapeutic guideline large scale multi-centre study is imperative.

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Conflicts of interest

There are no conflicts of interest.

12. ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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