



Original Article

Recurrence of Simple Febrile Seizure who follows Intermittent Prophylaxis: A Comparative Study Between Clobazam and Diazepam

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Abstract:

Background: Febrile seizures are common among children, with a prevalence of 2–5% aged less than 5 years. The recurrence rate of febrile seizures 30–50%. Intermittent or continuous prophylaxis by using anticonvulsant along with antipyretics have been prescribed rationally to prevent recurrence. **Objective:** To compare the recurrence rate of simple febrile seizure who follows intermittent prophylaxis; between clobazam & diazepam and adverse effects of each drug therapy. **Methods:** This prospective comparative observational study done in children with aged 6–60 months with one or more than one episodes of simple febrile seizure. Children with simple febrile seizure diagnosed after hospitalization were included in this study after exclusion of intracranial infection, epilepsy and other causes of seizures. During discharge of that simple febrile seizure cases; intermittent prophylaxis given rationally and proper counselling done. Among them 30 cases were given clobazam and 30 cases were given diazepam as both drugs can be used in prophylaxis. Clobazam 1 mg/kg/day once daily orally and diazepam 0.5 mg/kg/day eight hourly orally for 3 days along with antipyretics were given. The children were visited every 3 months for 6 months. Episodes of fever, recurrence of seizures and adverse effect of therapy noted. **Results:** Seventeen (56.7%) male and 13 (43.3%) female, with mean age of 25.7±13.6 months, with mean weight 12.8±3.5 kilograms were in clobazam group. Fourteen (46.7%) male and 16 (53.3%) female, with mean age of 21.3±13.8 months, with mean weight 11.1±2.9 kilograms were in diazepam group. Since first attack of simple febrile seizure; 115 episodes of fever occurred which included 55 (47.8%) episodes in the clobazam group and 60 (52.2%) episodes in the diazepam group. Eleven (36.7%), 9 (30.0%), 9 (30.0%) in the diazepam group and 4 (13.3%), 2 (6.7%), 1 (3.3%) cases in the clobazam group developed sedation, drowsiness and incoordination respectively ($P < 0.05$). Recurrence of seizures occurred in 10 (33.3%) cases in the clobazam group and in 3 (10%) cases in the diazepam group. ($P = 0.029$). **Conclusions:** Recurrence of simple febrile seizure who follows intermittent prophylaxis is more in clobazam group but adverse effect like sedation, drowsiness & incoordination more seen in diazepam group.

Key words: Febrile Convulsion, Intermittent Prophylaxis, Recurrence, Adverse effect, Clobazam, Diazepam

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Introduction:

Febrile seizures are common among children, with a prevalence of 2–5%, aged less than 5 years. Mostly 3 months to 5 years of age with peak age of febrile seizure of 14–18 months^{1,2,3}.

It accounts 25% of childhood status epilepticus⁴. Febrile seizures frequently recur, with a recurrence rate of 50%, when the first attack occurs before one year of age. In general, one third of infants will develop a second attack following subsequent febrile illness; half of the latter group will experience a third febrile seizure as well^{5,6}. Febrile seizures recurs 3 or more times in 10% of cases⁴.

More than one half of recurrences are experienced during the first year and over 90% developed within two years, following the first attack, with the higher risk within the first 6 to 12 months. The likelihood for recurrence is greater among infants who convulse at temperatures below 40°C².

The risk of recurrence is about 30% for simple febrile seizure⁶. Treatment of febrile seizures consisting of controlling the convulsion by anticonvulsant, reduction of the body temperature by sponging and using paracetamol, treatment of the acute infection responsible for the fever and prophylaxis to prevent recurrence².

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The recurrence rate of 30–50% and family anxiety rationalize the prophylaxis⁶. Benzodiazepine agents through oral, rectal route can be administered as intermittent prophylaxis⁷⁻⁹. Diazepam is the most common agent used for this purpose but it has side effects such as drowsiness, ataxia and sedation^{8,9}.

Clobazam is the first and only^{1,5} benzodiazepine in the management of seizures. It is used as effective antiepileptic agent in adults and children^{6,7}.

The side effects of clobazam are similar to other benzodiazepines, but with lower severity³. In this study, the authors compared the recurrence of simple febrile seizure who follows intermittent prophylaxis and adverse effects of drugs between clobazam and diazepam.

Materials & Methods:

This prospective comparative observational study was conducted in children aged 6–60 months with one or more than one episodes of simple febrile seizures. Study was done in Eastern medical College, Cumilla and Dr. M R Khan Shishu Hospital & ICH, Mirpur 2, Dhaka from January 2019 to June 2019.

Children with simple febrile seizure diagnosed after hospitalization were included in this study. Presence of neurological problems, progressive neurological diseases, complex febrile seizures, other symptomatic seizures, meningitis, encephalitis and simple febrile seizure with abnormal electroencephalogram findings were excluded. During discharge of those simple febrile seizure cases, intermittent prophylaxis given rationally and proper counselling done. Among them 35 cases were given clobazam, 35 cases were given diazepam as both drugs can be used in prophylaxis. Clobazam 1 mg/kg/day once daily orally and diazepam 0.5 mg/kg/day eight hourly orally for 3 days along with antipyretics were given.

The children were visited every 3 months for 6 months. Five cases in every group were lost of follow up, but maximum cases followed intermittent prophylaxis very cautiously with follow up schedule. Outcome variables were occurrence of febrile seizures and adverse effects of the drugs. On each visit, the frequency of febrile illness, recurrence of seizure and adverse effects of the therapy were evaluated. Data were collected by seeing previous discharge certificate, details history, through examination and plotted in a preform data sheet. Finally total 60 cases, where 30 in clobazam (Group A) group and 30 in diazepam (Group B) group were found. Data were analyzed using chi-square and unpaired t-test with significance level <0.05.

Results:

Seventeen (56.7%) male and 13 (43.3%) female, with mean age of 25.7±13.6 months, with mean weight 12.8±3.5 kilograms in clobazam group. Fourteen (46.7%) male and 16 (53.3%) female, with mean age of 21.3±13.8 months, with mean weight 11.1±2.9 kilograms in diazepam group. Since first attack of simple febrile seizure; 115 episodes off ever occurred which included 55 (47.8%) episodes in the clobazam group, 60 (52.2%) episodes in the diazepam group (Table-I & II).

Table-I: Age and weight distribution of the study population

Variable	Group A (n=30) Mean±SD	Group B (n=30) Mean±SD	P value
Age (months)	25.7±13.6	21.3±13.8	0.219 ^{ns}
Weight (kg)	12.8±3.5	11.1±2.9	0.054 ^{ns}

ns= not significant
p value reached from unpaired t-test

Table-II: Sex distribution and episode of fever in the study population

Variable	Group A (n=30)		Group B (n=30)		P value	
	n	%	n	%		
Sex	Male	17	56.7	14	46.7	0.303 ^{ns}
	Female	13	43.3	16	53.3	
Episode of fever	55	47.8	60	52.2	0.303 ^{ns}	

ns= not significant
p value reached from chi square test

Eleven (36.7%), 9 (30.0%), 9 (30.0%) in the diazepam group and 4 (13.3%), 2 (6.7%), 1 (3.3%) cases in the clobazam group developed sedation, drowsiness and incoordination respectively (P value<0.05%) (Table-III).

Table-III: Side effects of drugs between the study populations

Side effects	Group A (n=30)		Group B (n=30)		P value
	n	%	n	%	
Nausea & vomiting	0	0.0	1	3.3	0.500 ^{ns}
Ataxia	2	6.7	7	23.3	0.073 ^{ns}
Sedation	4	13.3	11	36.7	0.036 ^s
Drowsiness	2	6.7	9	30.0	0.021 ^s
Incoordination	1	3.3	9	30.0	0.006 ^s
Insomnia	2	6.7	4	13.3	0.335 ^{ns}
Anorexia	0	0.0	2	6.7	0.246 ^{ns}
Headache	0	0.0	2	6.7	0.246 ^{ns}
Abdominal pain	0	0.0	4	13.3	0.056 ^{ns}

s= significant, ns= not significant
p value reached from chi square test

Ten patients (33.3%) in the clobazam group and 3 patients (10%) in the diazepam group developed febrile convulsions in their febrile episodes. ($P=0.029$) (Table-IV).

Table-IV: Recurrence of seizure of the study population

Recurrence of seizure	Group A (n=30)		Group B (n=30)		P value
	n	%	n	%	
Yes	10	33.3	3	10.0	0.029 ^s
No	20	66.7	27	90.0	

s= significant

p value reached from chi square

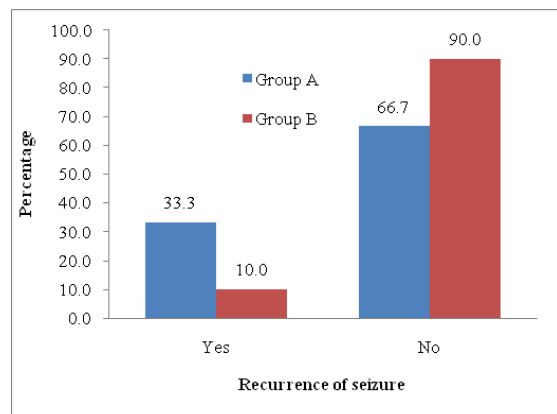


Figure-1: Bar diagram showing recurrence of seizure of the study population

Discussion:

Role and efficacy of benzodiazepines in the prevention of recurrence of febrile seizures has been well established^{2-4,6,8-10}.

The present study showed that recurrence of simple febrile seizure is more in oral clobazam group comparable to that of oral diazepam group ($P=0.029$). Some studies done clobazam vs placebo as prophylaxis for febrile seizure^{7,10,11} and there are few studies comparing diazepam with clobazam in this regard^{3,10,12}.

A double blind placebo-controlled study reported that recurrence of febrile seizure 30% in the clobazam group and 83.3% in the placebo group. They concluded that clobazam is efficacious, well tolerated and superior to use of antipyretics alone as intermittent prophylaxis¹¹.

A study on 50 children with febrile seizures and found that clobazam is an effective prophylaxis for febrile seizures. Recurrence rate was 1.7% in the clobazam group and 22.9% in the antipyretic alone group ($P<0.0001$)¹³. Efficacy and safety of intermittent clobazam prophylaxis for febrile seizures in a prospective randomized double-blind

placebo controlled trial and reported 1.7% recurrence of seizure in the clobazam group vs 12.5% in the placebo group ($P=0.01$)⁷.

A randomized controlled trial among 75 children compared efficacy of oral clobazam with oral diazepam for prophylaxis of febrile seizures. The odds ratio of seizure recurrence was 2.3 in the diazepam group as compared to clobazam group¹². Recurrence of seizures occurred in 1.7% subjects in the clobazam group, and in 3.1% cases in the diazepam group (P value=0.474)^{14,18}.

Oral diazepam and clobazam are equally effective and safe in the prophylaxis of recurrence of febrile seizure³. The authors found that oral clobazam is more effective in preventing febrile seizure recurrence as compared to diazepam for this purpose in children with history of at least one episode of febrile seizure³.

Intermittent oral clobazam therapy is a very effective measure in preventing recurrence of febrile seizures. Ten (3.8%) in clobazam group and 38 (14.07%) in placebo group had seizure recurrence (p value <0.001). The two groups were not significantly different in terms of side effects ($p >0.05$)¹⁵. One recurrence to a second or more are low age at onset and especially positive family history of febrile seizure. Additionally, low temperature prior to the initial seizure is a powerful predictor for three or more recurrences¹⁶; but our study did not match with this study.

In clobazam group, the frequencies of febrile seizure recurrence were 10%, 5% and 5% at 3, 6 and 12 months after the first attack. At the same time, the frequencies of the recurrence in the diazepam group were 23.8%, 17.5% and 15%, respectively ($p < 0.05$).

The two groups were not significantly different in terms of the drug side effects ($p = 0.194$). The group treated with clobazam experienced less febrile seizure recurrence in the 12 months follow-up. Thus, clobazam can be used as an effective medication to prevent febrile seizure recurrence in children¹⁷.

Some authors found reduced recurrence rates for children with febrile seizures for intermittent diazepam and continuous phenobarbitone prophylaxis, with adverse effects up to 30%¹⁹.

In present study adverse effects of clobazam were lower than diazepam like Sedation, drowsiness, incoordination ($P<0.0001$). A study reported that ataxia due to clobazam was much lower than that of diazepam⁷. Fifty four percent in the diazepam group and 14.2% cases in the clobazam group developed

drowsiness and sedation during the follow-up period (P value=0.0001)^{14,18}.

Treatment by clobazam has been caused recurrent and complications like ataxia, drowsiness and other side effects (vomiting, anorexia and irritability) less than diazepam²⁰.

Single dose, fewer adverse effect of clobazam as compared the diazepam makes clobazam superior to diazepam; but recurrence rate more in clobazam as compared the diazepam makes clobazam inferior to diazepam for prophylaxis of simple febrile seizures.

Conclusion:

Recurrence of simple febrile seizure who follows intermittent prophylaxis significantly more in clobazam group but adverse effect of drugs like sedation, drowsiness & incoordination significantly seen in diazepam group. Limitation of this study was epilepsy could not be excluded in subsequent simple febrile seizure. Further study recommended by doing Electroencephalogram in every follow up cases.

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