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# **Original Research Article**

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# Intermittent clobazam prophylaxis in simple febrile convulsions: a randomised controlled trial

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## **ABSTRACT**

**Background:** Febrile seizure (FS) is the most common type of childhood seizure disorder with a prevalence of 2-5% in children less than 5 years. Although the prognosis of febrile seizure is usually good, however, the possibility of recurrence keeps many parents and families in a state of anxiety and concerned, for years after the first seizure. Thus, intermittent prophylactic treatment might be advised in children with high risk of recurrence.

Methods: The study was a prospective randomized, double blind, placebo-controlled trial conducted at Department of Pediatrics, Umaid Hospital, Dr S N Medical College, Jodhpur on neurologically normal children aged from 6 months to 5 years with a history of simple febrile seizures and normal electroencephalogram without any evidence of acute central nervous system infection. Subjects were randomly prescribed oral clobazam according to weight of child and placebo when they developed a febrile disease during the first 48 h of the onset of fever. Temperature reduction measures with paracetamol and tepid sponging were also advised. Patients were followed up for the frequency and time of febrile seizure recurrence, febrile episodes and side effects of drugs for 12 months.

Results: Ten (3.8%) of 257 episodes in clobazam group and 38 (14.07%) episodes 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).

Conclusions: Intermittent oral clobazam therapy is a very effective measure in preventing recurrence of febrile seizures.

**Keywords:** Febrile convulsions, Febrile seizure recurrence, Fever, Intermittent oral clobazam therapy

# INTRODUCTION

Febrile seizure (FS) is the most common type of childhood seizure disorder, which occurs in an agespecific manner with a prevalence of 2-5% in children less than 5 years. Febrile convulsion is defined as a seizure occurring in children between the ages of 6 and 60 months with fever >38°C, who do not have an intracranial infection, metabolic disturbance, or history of a febrile seizure. Most cases occur between 3 months and 5 years of age with peak age of 14-18 months.3 It accounts for approximately 25% of childhood status epilepticus.4 Genetic factors are important in the etiology of febrile seizures. Children of parents who had febrile

seizures have a risk 4 times that of the general population and siblings of probands have a risk 3.5 times that of general population.5

Febrile seizures frequently recur, the likelihood of recurrence is 50% in children under 12 months and would decrease to 30% thereafter. The chance of recurrence would increase to 50% in children who experience febrile seizures for the second time.<sup>6</sup> Febrile seizures recur 3 or more times in 10% of cases.4

About 50% of recurrences occur in the first year and 90% in the first two years after the first attack.<sup>2,6</sup> The overall prognosis for febrile seizures is excellent.<sup>7</sup> The intellectual and behavioural outcome of febrile seizure is excellent.<sup>8</sup> The risk of developing epilepsy in children who have had febrile seizures is increased compared to that of general population. The risk is 2% at 5 years, 4.5% at 10 years, 5.5% at 15 years and 7% at 25 years.<sup>9</sup>

Although the prognosis of febrile seizure is usually good, however, the possibility of recurrence keeps many parents and families in a state of anxiety and concerned, for years after the first seizure. Thus, intermittent prophylactic treatment might be advised in children with high risk of recurrence. Oral benzodiazepines such as diazepam or clobazam can be used in these cases. 10 Diazepam is commonly used orally or as suppositories to prevent febrile seizure. However, it causes dizziness, imbalance and drowsiness in children and often makes the parents to discontinue the drug.<sup>11</sup> Clobazam is another benzodiazepine effective in the treatment of seizures, with fewer side effects. Clobazam has successfully been used in the intermittent prophylaxis of febrile seizures. 12 -<sup>14</sup> Only a few studies determining efficacy of intermittent clobazam in FS are available. The present study was undertaken with the objective of determining efficacy of intermittent clobazam prophylaxis in FS as compared to placebo and determine its safety.

## **METHODS**

This study was a double blind, randomized, placebo-controlled trial conducted at Department of Pediatrics, Umaid Hospital, Dr S N Medical College, Jodhpur. Children (aged 6 months to 5 years) with one or more episodes of simple febrile seizure who were referred to Umaid Hospital were enrolled in the current study. The study was approved by the Institutional ethical committee and duration of the study enrolment was one year.

## Inclusion criteria

 The patients were recruited sequentially and allocated to the study groups through a permuted block randomized method.

# Exclusion criteria

 The presence of acute CNS infection, abnormal electroencephalogram, developmental retardation, CNS malformation, progressive neurological disease, chromosomal abnormalities and those on any anticonvulsant medication.

Sample size was calculated with at least 85 patients in each group, considering alpha error of 5%, and a statistical power of 80% and rates of recurrence were 1.7% in clobazam group and 12.5% in placebo group based on the results of previous study conducted by Rose W et al.  $^{13}$ 

To keep the study double blind, sachets of clobazam and placebo with similar color and shape were prepared and labelled by pharmacist who knew the code of drug which was disclosed at the end of the study. The investigator was given only random numbers to be assigned to the patients.

The therapeutic dosage of clobazam ranges from 0.3 to 1mg/kg/day. The dosage schedule for the purpose of this study was allocated according to the subject's weight as follows: up to 5kg: 5mg per day; 6kg to 10kg: 5mg twice daily; 11kg to 15kg: 7.5 mg twice daily and >15 kg: 10 mg twice daily.

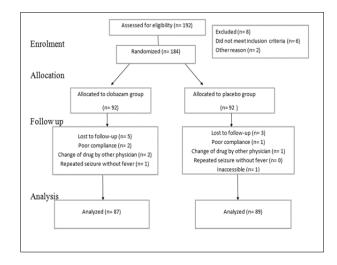


Figure 1: Flow diagram of our clinical trial comparing clobazam vs placebo for intermittent prophylaxis for febrile seizures.

The parents then received a diary and were instructed to annotate further febrile episodes, with their degree, associated symptoms, medication used, adverse effects and seizure recurrence. They were also instructed to administer the dispensed medicine at the beginning of each febrile episode for a period of 48 hours from the start of fever, irrespective of whether the fever persists or not. The parents were also instructed to administer paracetamol and institute temperature control measures at the onset of fever and continue it through the duration of the illness. The children under the study were followed up every month from the time of induction into the study till 1 year. During each visit they were evaluated for the number of febrile episodes, frequency of recurrence of febrile seizure and adverse effect profile of drug.

# Stastical analysis

Statistical analysis was performed with Windows SPSS version 23, Chi-square and t- tests. Significance level was set at p < 0.05.

#### **RESULTS**

Finally, 87 children in clobazam group (Male/Female: 56/31) with mean age of 23.20±10.54 months and 89 children in placebo group (Male/Female: 59/30) with

mean age of  $22.22\pm10.54$  months completed the study. No significant difference was observed in demographic characteristics (age, gender, family history, temperature) of both the groups (p>0.05), so all base line parameters were comparable in two groups (Table 1).

Table1: Demographic characteristics of children in the two groups.

Chanastanistics	Groups		P value
Characteristics	Clobazam	Placebo	
Age (months)	23.20±10.54	22.22±10.54	0.537
Gender			
Male	56	59	0.912
Female	31	30	
Family history o			
Yes	7	10	0.644
No	80	79	0.644
Interval between			
fever and seizure			
<24 hours	84	88	0.763
>24 hours	3	1	
Temperature			
during febrile	101.63±0.9	101.63±0.94	0.978
seizure			

Mean number of febrile episodes in clobazam group was 2.95 and in placebo group- 3.03. Ten (3.8%) of 257 episodes in clobazam group and 38 (14.07%) of 270 episodes in placebo group had seizure recurrence. This was statistically significant (p=0.001) (Table 2).

Table 2: Frequency of seizure recurrence according to treatment of febrile episodes.

	Recurrence		
Groups	Yes (%)	No (%)	febrile episodes
Clobazam (N=87)	10 (3.89)	247 (96.10)	257
Placebo (N=89)	38 (14.07)	232 (85.92)	270
Total	48 (9.10)	479 (90.89)	527

 $[\chi^2=15.285; d.f. =1; p < 0.0001]$ 

In the present study, 0.038 seizures per febrile episodes were observed in the group treated with clobazam and 0.140 seizures per febrile episodes in the placebo group. There was significant fall in frequency of febrile seizure recurrence at 3,6,12 months of follow up period in the clobazam group when compared to the placebo group. The risk of seizure recurrence is 27 % lower in clobazam group (RR=0.27). Clobazam reduces the absolute risk of recurrence by 10.27% and also reduces the risk of recurrence by 73% relative to that occurring in placebo group (RRR=0.73). Odds ratio of clobazam compared to placebo with 95% confidence interval was 0.27 and number needed to treat was 9.7.

The majority of children in both the groups experienced no significant side effects because of the drugs. The most common side effect was sedation in the group treated with clobazam, and irritability in the placebo group (Table 3). The two groups were not significantly different in terms of side effects (p > 0.05).

Table 3: Comparison of side effects in both the groups.

Side effects	Clobazam (n=87) N (%)	Placebo (n=89) N (%)	P value
Vomiting	03 (3.44)	04 (4.49)	0.722
Irritability	03 (3.44)	06 (6.74)	0.631
Sedation	05 (5.74)	03 (3.37)	0.970
Anorexia	02 (2.29)	03 (3.37)	0.668
Headache	01(1.14)	04 (4.49)	0.181
Abdominal pain	01(1.14)	01 (1.12)	0.987

#### **DISCUSSION**

Intermittent benzodiazepines therapy for the prevention of recurrence of febrile seizures has been well studied and showed a unique role and efficacy. 4,12,15 This study was aimed at evaluating clobazam in prevention of recurrence of febrile seizure. Some studies have compared clobazam against placebo as prophylaxis for febrile seizure and there are few studies comparing diazepam with clobazam in this regard. 13-16

Bajaj, in a double-blind placebo-controlled study reported that recurrence of febrile seizure was observed in 30% patients in the clobazam group vs 83.3% in the placebo group (p<0.05).14 In another double blind randomized controlled trial Rose and co-worker reported 1.7% recurrence of seizure in the clobazam group vs 12.5% in the placebo group (P=0.01).13 Similarly, Manreza performed 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 patients who received only antipyretic (P<0.0001).<sup>17</sup> In present study, a high recurrence of febrile seizure in placebo group was reported. There was a significant difference between treated with clobazam (3.8%) and placebo (14.07%) (p = 0.001). In our study, no significant adverse effects were observed in the patients and the drug was well tolerated (p=0.05). The patients who were in placebo group showed greater incidence of irritability, vomiting and headache, presumably due to higher rate of recurrence of seizures in this group. Bajaj et al, in their study also reported no significant difference in adverse effects.<sup>14</sup> Rose et al reported that side effects were not significantly different in clobazam and placebo group except for ataxia. They also reported that ataxia due to clobazam was much lower than that seen with diazepam.<sup>13</sup> Such findings were not observed in the present study.

## **CONCLUSION**

The observations and results of this study very emphatically prove that children receiving clobazam

experienced lower febrile seizure recurrence as compared to placebo. The easiness of oral intake, better compliance (2 doses for 2 days), greater efficacy and fewer side effects make clobazam superior for prophylaxis of febrile seizure.

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Institutional Ethics Committee

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