

Comparison of Prophylactic Effect of Clobazam and Diazepam in Children with Simple Febrile Convulsion (SFC)

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Abstract: To compare the effectiveness of intermittent clobazam versus diazepam therapy in preventing the recurrence of febrile seizures and assess adverse effects of each drug. This prospective randomized controlled trial was performed on neurologically normal children aged from 6-60 months with a history of simple febrile seizures and normal electroencephalogram without any evidence of acute central nervous system infection. The patients were randomly prescribed with oral clobazam (36 cases) or diazepam (35 cases) when they developed a febrile disease. They were advised to use the medications during the first 48 h of the onset of fever. All the patients were monitored regarding developing seizure and adverse effects of the drugs. All patients were followed for 12 months. Overall, recurrence of seizures occurred in 1 subject in the clobazam group and in 3 cases in the diazepam group ($p = 0.296$). The 15 cases in the diazepam group and 7 cases in the clobazam group developed drowsiness and sedation during the follow-up period ($p = 0.03$). Ataxia occurs in 4 cases of diazepam group and one patient in clobazam group ($p = 0.17$). Intermittent clobazam therapy seems advantageous to diazepam due to similar efficacy but significantly lower adverse effects such as drowsiness and sedation.

Key words: Randomized, neurologically, monitored, seizures occurred, diazepam group

INTRODUCTION

Febrile seizure is the most common type of seizure in childhood and its prevalence is 2-5% in children younger than 5 years old. Most cases occur between 3 months and 5 years of age. Febrile seizure is the reason of 25% of status epilepticus in children (Johnston, 2007; Sankar, 2006).

Febrile seizure is defined as a simple generalized seizure which related to fever with <15 min duration in patients without neurological deficit.

Febrile seizure frequently recurs and the risk of recurrence is higher in infants under 1 year old. Febrile seizure recurs three or more times in 10% of cases (Shinnar, 2006; Reuter and Brownstein, 2002).

The likelihood for recurrence is greater among infants who convulse at temperatures below 40 degree centigrade. The risk of recurrence is about 30% for simple febrile seizures and over 50% for complex febrile seizures (Beaumanoir and Gupta, 2002).

Prevention of febrile seizures is highly desirable, since seizures are upsetting to both parents and children and since the medical costs can be considerable. Any child with a convulsion is at risk for brain injury due to falls caused by seizures or due to hypoxia if there is accompanying respiratory compromise. Most studies, though not all have found a relation between the number

of febrile seizures, particularly those that are complex and the risk of later afebrile seizures. Hence, prevention of febrile seizures might also lessen that risk (Annegers *et al.*, 1987).

For two decades, daily phenobarbital has been the drug of choice for the prevention of febrile seizures and in most studies, it has been effective. More recently, however, its role in prophylaxis has been questioned. Concern has centered on the frequency of behavioral side effects and consistently poor compliance with the drug regimen (Farwell *et al.*, 1990; Wolf, 1981).

Diazepam is the most common agent used for this purpose but has side effects such as drowsiness, ataxia and sedation (Pavlidou *et al.*, 2006).

Clobazam is the first and only benzodiazepine in the management of epilepsy. It is used as effective antiepileptic agent in adults and children. The side effects of are similar to other benzodiazepines but with lower severity (Rose *et al.*, 2005).

In this study, we compared the effectiveness and adverse effects of clobazam versus diazepam in prevention of recurrence of febrile seizure.

MATERIALS AND METHODS

Subjects: Beginning on January 2012, we recruited subjects from Motahari hospital in Urmia, Iran. The

criteria for eligibility were a history of at least one simple febrile seizure; no history of afebrile seizures; no neurological abnormalities; age from 6-5 years; no anticonvulsant medication or a willingness on the part of the physician and parents to discontinue such medication and an absence of liver disease.

The study was approved by the ethics committee of the Urmia University of Medical Science and informed consent was obtained from all the parents.

Procedures: Discussion with the family emphasized the following steps to be taken by the parents and other care givers: taking the temperature promptly whenever the child seemed ill; giving study medication as soon as the child became febrile (rectal temperature $>38.1^{\circ}\text{C}$) and continuing the medication until the child had been afebrile for 24 h following instructions from the child's pediatrician including those on the use of other medications and keeping the study medication available at all times. Each child was then randomly assigned to a treatment group and the family was provided with the study medication.

Medication: Patients were randomly assigned to receive oral diazepam 0.33 mg kg^{-1} dose every 8 h for 2 days or oral clobazam for 2 days with the following dosage: 5 mg, daily in children $<5\text{ kg}$; 5 mg, twice daily (BD) in children 6-10 kg; 7.5 mg, BD in children 11-15 kg and 10 mg, BD in children $>15\text{ kg}$.

The children were followed up every 3 months for 12 months. Outcome variables were occurrence for febrile seizures and adverse effects of the drugs. On each follow up, the frequency of febrile illness and adverse effects of the therapy were evaluated.

Data were analyzed using Chi-square and Fisher Exact tests and $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Finally, 35 patients in diazepam group and 36 patients in group completed the study. Patients included 42 (59.2%) male and 29 (40.8%) female subjects with mean age of $22.01 \pm$ months (min. 6 and max. 60 months).

During 12 months follow up period, 253 episodes of fever occurred which included 122 (47.7%) episodes in the clobazam group and 131 (52.3%) episodes in diazepam group (Table 1).

The 3 (75%) patient in diazepam group and one patient (25%) in clobazam group developed febrile convulsion in their febrile episodes ($p = 0.296$).

Table1: Demographic characteristics of patients in the study

Characteristic	Clobazam group	Diazepam group
Mean age	21.86 \pm 13.25 months	22.17 \pm 14.55 months
Male	19 (54.2%)	23 (63.9%)
Female	16 (45.8%)	13 (36.1%)
Episode of fever	122 (47.7%)	131 (52.3%)
Episode of seizure	3 (75%)	1 (25%)

Ataxia was seen in five patients, four patients in diazepam group and one patient in clobazam group. There is no significant difference between two groups ($p = 0.17$).

The 22 patients had sedation in two groups, 15 patients in diazepam group and 7 patients in clobazam group. Significantly, sedation as a side effect occurred less in clobazam group.

The role and efficacy of benzodiazepines in the prevention of recurrence of febrile seizure has been well established (Verrotti *et al.*, 2004; Akman, 2005).

In this study, we conducted a randomized, controlled clinical trial to compare the efficacy and side effects of these two drugs, diazepam and clobazam. Our results showed no difference in the rate of seizure control between two drugs. In addition, ataxia is similar in both but drowsiness and sedation was significantly less occurred by clobazam.

Diazepam is a standard treatment for control and prevention of recurrent seizures in children who already had a history of febrile seizure. But its side effects such as drowsiness and ataxia limited using this medication. Thus, recent studies were done to find an alternative medicine in the same efficacy but fewer side effects. One of these drugs is clobazam. Clobazam is a new antiepileptic and in clinical studies, efficacy and tolerability by patients has been proven.

The effects of this drug in the prevention of febrile seizures in some studies have been investigated. For example, Beaumanoir and Gupta (2002) reviewed clobazam as the treatment of intermittent prophylactic treatment of children with febrile seizures, he indicated that introduced that the effectiveness of clobazam, the benefits of ease of oral administration, the fast pharmacological activity and low side effects make it appropriate in these patients.

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. They concluded that clobazam is efficacious and well tolerated as intermittent prophylaxis of febrile seizure and is superior to the use of intermittent antipyretic alone (Bajaj *et al.*, 2005).

The similar study which confirmed our results was Khosroshahi's study in which they compare the efficacy of clobazam and diazepam in children with a history of febrile seizure. They showed that seizure rate in both groups was the same but side effects such as sedation was significantly lower in patients whom received clobazam (Khosroshahi *et al.*, 2011).

The present study showed that oral clobazam for the recurrence of febrile seizure is comparable to that of oral diazepam; however, adverse effects of clobazam were lower than diazepam. Sedation was more often in patients who received diazepam compared to clobazam.

Rose *et al.* (2005) reported that ataxia due to clobazam was much lower than that of diazepam. Such finding did not show in the present study. Other side effects such as nausea and vomiting are not mentioned in present study.

CONCLUSION

These results showed that clobazam could be an Alternative treatment for diazepam as a prophylaxis in children with a history of febrile seizures with similar effectiveness in controlling seizures but lower drowsiness effect in patients using clobazam.

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