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Comparison of the effects of clobazam and diazepam in prevention of recurrent febrile seizures

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ABSTRACT

Febrile seizure is the most common neurological disorder in children and occurs in 2 to 5% of them. The possibility of febrile seizure recurrence induces a grave concern to parents. Prophylactic benzodiazepines are usually used to prevent the recurrence. However, previous studies showed no difference between the preventive effect of clobazam and diazepam. Thus, this study aimed to compare the effects of clobazam and diazepam in preventing febrile seizure recurrence in children. A double blind, randomized, controlled trial was conducted on 160 children from six months to 5 years of age with febrile seizure. Patients were matched for age, sex, underlying diseases and risk factors for recurrence and randomly assigned to two groups to receive either 0.33 mg/kg of oral diazepam, every 8 h for two days, or 1 mg/kg of oral clobazam every 12 h for 2 days. All patients were followed-up for the frequency and time of febrile seizure recurrence, and drug side effects for 12 months. Descriptive statistics were calculated and chi-square and t- tests were used to compare the two groups. The mean age of the children in the diazepam and clobazam groups were 29.61 ± 13.1 and 29.7 ± 11.5 months, respectively (P = 0.755). 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 children.

Keywords: Clobazam, Diazepam, Febrile seizure, Recurrence

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INTRODUCTION

Febrile seizure is the most common seizure disorder in children [1]. It is a convulsion in children of 6 months to 5 years old occur with a fever greater than 38.5 °C, without infection of the nervous system and in the absence of a positive family history of non febrile seizures or other underlying causes [2]. Two to five percent of children experience at least one febrile seizure before the age of 5 years. Febrile seizure mostly occurs between the ages of 3 months to 5 years and the peak age is between 14 and 18 months. It also accounts for about 25% of all seizures in childhood [1-5]. The likelihood of recurrence of febrile seizure 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 [6]. Ten percent of patients experience three or more relapses [5]. About 50% of recurrences occur in the first year and 90% in the first two years after the first attack. Age under 12 months at the time of the first febrile seizure, a family history of febrile seizures in first-degree relatives, a history of low temperature convulsion, and a short interval between the onset of fever and the first seizure attack are all potential risk factors for recurrence of febrile seizure [2, 6, 7].

Although the cause of the febrile seizure is unknown, but an autosomal dominant pattern of inheritance has been proposed for this disease. Mutations in genes responsible for coding of sodium channel and γ-aminobutyric acid receptor (which play a major role in neonatal myoclonic seizures) have been identified in children with febrile seizures and might be suggesting for the role of these genes in this disorder [7, 8].

Given the benign nature of febrile seizure, it usually requires no treatment to prevent the recurrence. However, some experts signify parental anxiety as an indication for the treatment or prevention of recurrence [9]. The aim of treatment is to prevent the recurrence of febrile seizures. This goal is achieved by either long-term or intermittent anticonvulsant therapy. Continuous long-term anticonvulsant therapy may reduce recurrence in children with a history of febrile seizure. However, considering the numerous potential side effects, prophylactic treatment is not usually indicated [2,6, 7]. 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 concern 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 [19]. Diazepam is commonly used orally or as suppositories to prevent febrile seizure. However, it causes dizziness, imbalance and drowsiness in children [10, 11] and often makes the parents to discontinue the drug. Clobazam is a benzodiazepine effective in the treatment of seizures in adults and children [1, 14-12]. The side effects of clobazam are similar to other benzodiazepines, but occur in lower degrees (4). Clobazam has successfully been used in the intermittent prophylactic treatment of febrile seizure [15, 13].

A number of studies have compared the prophylactic effects of diazepam and clobazam in preventing the recurrence of febrile seizure.

In a randomized controlled trial to compare efficacy of oral clobazam with oral diazepam for prophylaxis of febrile seizures, the odds of recurrence in the group received diazepam was 2.3 times more than the group received clobazam [16]. However, two studies by Bajaj et al. [15] and Khosroshahi et al. [17] found that diazepam and clobazam were equally effective in reducing the risk of recurrence.

Given the controversies mentioned, a question still remains that which of these two drugs is more effective in preventing the recurrence of febrile seizure in children. Consequently, this study aimed to compare the effects of clobazam and diazepam in preventing recurrence of febrile seizures in children.

MATERIALS AND METHODS

Design

This double blind, randomized, controlled trial was conducted on all children of six months to 5 years of age with febrile seizure referred to Kashan Shahid Beheshti hospital, during 2014

Sampling

Considering the rate of febrile seizure recurrence at 32%, type I error probability of 0.05 and a statistical power of 0.80, it was estimated that 84 samples would be needed in each group. Furthermore, in a previous study the rates of recurrence were 1.7% and 18.2% in the groups received clobazam and diazepam, respectively. Then, given the type I error probability of 0.05 and a statistical power of 0.80, it was estimated that 51 samples would be needed in each group. However, the greater sample size was selected as our reference in this study [18]. The inclusion criteria were being in the age range of 6 months to 5 years, experiencing febrile seizure for the first time (rectal temperature over 38 °C), lack of a history of non-febrile seizures, lack of a developmental or neurological disorder, and lack of a central nervous system infection and acute electrolyte disturbance. Exclusion criteria included lack of cooperation, the impossibility of follow-up (i.e. changing the living location) and parental participation refusal.

A pediatric neurologist made the diagnosis of febrile seizure using the TLAE criteria. The study subjects were requited sequentially and allocated to the study groups through a Permuted block randomized method. Blocks of 4 and 6 were used in each of the study groups.

Interventions

The children were enrolled after providing the necessary explanations to and obtaining a written informed consent from their parents.

Children received 0.33 mg/kg of oral diazepam, every 8 h for two days, or 1 mg/kg of oral clobazam every 12 h for 2 days, in case of fever.

To keep the study blind form patients, the drugs were prepared in capsules with similar color and shape. Moreover, a nurse who was not

involved in the allocation of patients was trained to calculate and administer the medications in accordance with the children's weight. The medications were administered only for the first 48 h of the febrile illness and then discontinued. All parents were also trained about using antipyretics and body sponge to keep the intervention similar in the both groups. Parents were also trained about recording and reporting the frequency of febrile seizures recurrences and side effects of the drugs. The children were followed for 12 months. Every three months, the mothers were called and questioned about the incidence of febrile seizure, their adherence to the treatment regimen, and adverse effects of the medications. Moreover, the children were visited by the concerned doctor every three months and were assessed regarding the adverse effects of the drugs and frequency of febrile seizures.

Data collection instruments

A two-part instrument was used in this study. The first part was an entry questionnaire consisting questions on the child's age, gender, family history of febrile seizure and epilepsy, developmental status, the cause of fever, the interval from the onset of fever and occurrence of seizure, type of seizure, and the body temperature at the time of febrile seizure.

The second part was a checklist for the periodical assessments during the 12 months follow-up (i.e. every three months). This part included questions on the frequency and time of febrile seizure recurrence, and drug side effects such as imbalance and drowsiness.

Data

Data were summarized using descriptive statistics including frequency, percentages, mean, and standard deviation. Data analysis was performed using the SPSS software version 16. Chi-square and t- tests were used to compare the two groups.

RESULTS

Totally, 160 children were studied in this study. The mean age of the children in the diazepam and clobazam groups were 29.61 ± 13.1 and 29.7 ± 11.5 months, respectively (P = 0.755). The two groups did not significantly differ regarding their demographic characteristics (Table1).

Table 1:- Demographic characteristics of children in the two groups

Characteristics	Group		P value
	Clobazam	Diazepam	
	N (%)	N (%)	
Gender			0.635
Male	41 (51.3)	38 (47.5)	
Female	39 (48.8)	42 (52.5)	
Age			0.378
Under 18 months	14 (17.5)	20 (25)	
36-19 months	44 (55)	36 (45)	
Over 37 months	22 (27.5)	24 (30)	
Family history of febrile seizure			0.499
Yes	13 (16.3)	10 (12.5)	
No	67 (83.8)	70 (85.5)	
Family history of epilepsy			0.442
Yes	7 (8.8)	10 (12.5)	
No	73 (91.3)	70 (87.5)	
Developmental Status			0.50
Normal	80 (100)	79 (98.8)	
Abnormal	0	1 (3)	
Interval between fever and seizure			0.343
Less than 24 hours	43 (53.8)	37 (46.3)	
More than 24 hours	37 (46.3)	43 (53.8)	
Type of seizure			0.99
Simplex	73 (91.3)	73 (91.3)	
Complex	7 (8.7)	7 (8.7)	

Table 2:- Comparison of body temperature during the febrile seizure in the two study groups

Group	Body temperature		P value
	Mean	Standard deviation	
Diazepam	38.69	0.48	0.967
Clobazam	38.64	0.41	

Table 3:- Frequency of recurrence at intervals of 3, 6 and 12 months after the first attack in the studied groups

Time	Recurrence	Group		P value
		Clobazam	Diazepam	
		N (%)	N (%)	
In three months	No	72 (90)	61 (76.2)	0.02
	Yes	8 (10)	19 (23.8)	
In 6 months	No	76 (95)	66 (82.5)	0.012
	Yes	4 (5)	14 (17.5)	
In 12 months	No	76 (95)	68 (85)	0.035
	Yes	4 (5)	12 (15)	

Table 4:- Comparison of the mean number of febrile seizure recurrence in the studied groups

Group	Mean	Standard deviation	P value
Diazepam	0.72	1.19	0.001
Clobazam	0.24	0.64	

The two groups were not significantly different in terms of their body temperature at the time of seizure (p = 0.967) (Table 2).

Urinary tract infection and herpes simplex virus were respectively the most and the least common causes of fever in both groups. The two groups were not significantly different in terms of the causes of fever (p = 0.519).

The two groups were significantly different regarding the frequency of recurrence in 3, 6 and 12 months after the onset of the first febrile seizure. The group treated with diazepam showed a higher frequency of febrile seizure recurrence in all these periods (Table 3).

Comparing the mean frequency of febrile seizure recurrence between the two groups showed that the mean number of febrile seizure recurrence was significantly higher in the group treated with diazepam than those received clobazam (p 0.001) (Table 4).

The majority of children in the both groups experienced no drug side effect. The most common side effect was drowsiness in the group treated with diazepam, and imbalance in the clobazam group. The two groups were not significantly different in terms of drug side effects (p = 0.194).

DISCUSSION

This study demonstrated that clobazam was more effective than diazepam in the prevention of febrile seizure recurrence. So that the rates of febrile seizure recurrence -within a year after the first attack- in the patients treated with diazepam and clobazam were 12% and 5%, respectively. A few studies have compared the effects of diazepam and clobazam in preventing febrile seizure recurrence; and some of them were consistent with the findings of the present study. In a clinical trial, Gulati et al. have compared the efficacy of oral clobazam with oral diazepam for prophylaxis of febrile seizures. The rates of febrile seizure recurrence were 11.3% and 3% in a year, in the patients treated with diazepam and clobazam, respectively [16]. In another study, Khosroshahi et al. studied 72 patients with febrile seizures. 37 patients treated with diazepam and 35 patients were treated with clobazam. Although the rate of recurrence of febrile seizure were not significantly different in the two groups (48% in the clobazam and 52.3% in the diazepam group), however, the researchers concluded that clobazam was more advantageous due to less adverse effects such as drowsiness and sedation [17]. Amouian et al. have also compared clobazam and diazepam in preventing febrile seizure and reported no significant difference between the two groups regarding febrile seizure recurrence [19]. Although the two latter studies showed no statistically significant difference between diazepam and clobazam in terms of recurrence of febrile seizure, however, it seems that clobazam is clinically more effective than the diazepam in the prevention of febrile seizure recurrence.

In the present study, the two groups were not significantly different in terms of drug side effects such as drowsiness and imbalance. However, Khosroshahi et al. reported less drowsiness in the group treated with clobazam than those received diazepam. The difference might be attributed to the higher mean age of our patients than patients in Khosroshahi et al.'s study [17]. It seems that the risk of drug side effects increases with an increase in the child's age. On the other hand, Gulati et al. reported more drowsiness in patients treated with clobazam than in the patients received diazepam [16]. A possible cause might be the use of antipyretic drugs in the two groups. Thus,

it seems that clobazam induces less adverse effects than diazepam.

CONCLUSION

In this study, the group treated with clobazam experienced a lower frequency of febrile seizure recurrence in the 12 months follow-up. Then, it can be concluded that clobazam can be used as an effective medication to prevent febrile seizure recurrence in children. However, more studies with larger sample size and longer follow-up seem to be needed to achieve more accurate results.

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Conflict of Interest
The authors have no conflict of interest to disclose.

Authors' Contribution
Ahmad Talebian developed the study concept and design and the acquisition of data, interpretations of data, and drafting of the manuscript. Shirin Vafaei, Mohammad Reza Sharif, Hossein Akbari, Mojtaba Sehat, Davood Kheirkhah and Motahare Talebian developed the protocol, analysis of data and drafting of the manuscript.

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