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ORIGINAL ARTICLE

Diazepam Versus Clobazam for Intermittent Prophylaxis of Febrile Seizures

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Abstract
Objective To compare the effectiveness of intermittent clobazam versus diazepam therapy in preventing the recurrence of febrile seizures and assess adverse effects of each drug.
Methods This prospective randomized controlled trial was performed 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. The patients were randomly prescribed with oral clobazam (37 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.
Results Overall, 243 episodes of fever occurred during the period, including 116 episodes in the clobazam group and 127 episodes in the diazepam group. Recurrence of seizures occurred in 2 (1.7%) subjects in the clobazam group, and in 4(3.1%) cases in the diazepam group. (P value=0.474). Twenty cases (54%) in the diazepam group and 5 (14.2%) cases in the clobazam group developed drowsiness and sedation during the follow-up period (P value=0.0001).
Conclusions Intermittent clobazam therapy seems advantageous to diazepam due to similar efficacy but significantly lower adverse effects such as drowsiness and sedation.

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Introduction

Febrile seizures are the most common types of seizure among children, with a prevalence of 2–5% in children aged less than 5 years.

Most cases occur between 3 months and 5 years of age with peak age of 14–18 months [1–3]. It accounts for approximately 25% of childhood status epilepticus [4].

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 cases [4].

More than one half of recurrences are experienced during the first year and over 90% develop 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°C [2]. The risk of recurrence is about 30% for simple febrile seizures and over 50% for complex febrile seizures [6].

Treatment of Febrile seizures consists of controlling the convulsions with anticonvulsants in dosages analogous to those recommended for the treatment of status epilepticus, reduction of the body temperature *via* conductive or evaporative cooling of the patient and treatment of the acute infection responsible for the fever [2].

The recurrence rate of 30–50% and family anxiety rationalize the prophylaxis [6].

Benzodiazepine agents through oral, rectal or sublingual route can be administered as intermittent prophylaxis [7–9].

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 epilepsy. 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 severity [3].

In this study, the authors compared the effectiveness and adverse effects of clobazam *vs* diazepam in the prevention of recurrence of febrile seizure.

Material and Methods

This prospective, randomized, superiority, intention to treat method controlled trial study was conducted in children aged 6–60 months with one or more episodes of simple febrile seizures, who were referred to the Bahrami Children Hospital, Tehran, Iran, from March 2006 until one year.

The study was approved by the ethics committee of the university. Children with simple febrile seizure whose parents had severe anxiety (residing far from medical center, having multiple caregivers and poor accessibility to medical personnel) are included in study.

Exclusion criteria included the presence of neurological abnormalities, progressive neurological diseases, complex febrile seizures, symptomatic seizures of other nature, seizures during a central nervous system infection and cases of simple febrile seizure that had abnormal electro-encephalogram.

Sample size was calculated with at least 18 patients in each group, considering alpha error of 5%, power of 80% and effectiveness of 35% for diazepam group and 1.7% for clobazam based on the results of reference no. 7 [7, 8].

Patients were randomly assigned to receive oral diazepam 0.33 mg/kg/ dose every 8 h for 2 days or oral clobazam for 2 days with the following dosage: 5 mg, daily in children ≤ 5 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 kg.

The medicines were administered only for the first 48 h of each febrile illness and stopped after 48 h, irrespective of the persistence of fever. Using antipyretics and body sponge in addition for specific management of the disease, were advised to both groups.

The children were visited every 3 months for 12 months. Outcome variables were occurrence of febrile seizures and adverse effects of the drugs. On each visit, the frequency of febrile illness and adverse effects of the therapy were evaluated. (Fig. 1)

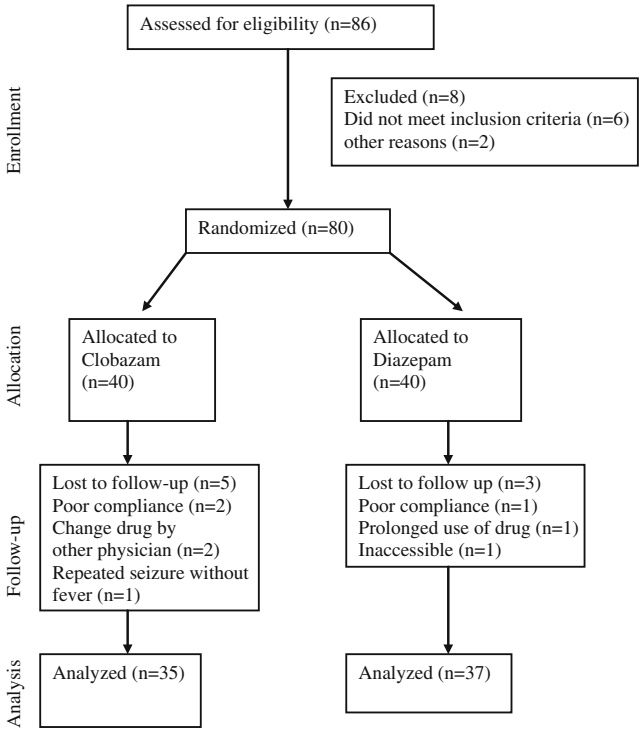

Fig. 1 Flow diagram of a clinical trial comparing clobazam *vs* diazepam for intermittent prophylaxis of febrile seizures

Data were analyzed using *chi-square* and fisher-exact tests with significance level set at <0.05.

Results

Finally, 37 patients in diazepam group and 35 patients in the clobazam group completed the study.

Patients included 41 (56.9%) male and 31 (43.1%) female subjects, with mean age of 21 months (range 7–60 months). (Table 1)

During 12 months follow-up period, 243 episodes of fever occured which included 116(47.7%) episodes in the clobazam group and 127 (52.3%) episodes in the diazepam

Table 1 Baseline Demographic characteristics of trial group (clobazam *vs* Diazepam)

Characteristic	Clobazam group *n*=35	Diazepam group *n*=37
Mean age	21 ± 3.1	21 ± 5
Sex		
Male	19(54.28)	22(59.45)
Female	16(45.71)	15(40.54)
Episode of fever	116(47.73)	127(52.26)
Episode of seizure	2(1.7)	4(3.1)

Figures in parenthesis indicate percentage

group. Two patients (1.7%) in the clobazam group and 4 patients (3.1%) in the diazepam group developed febrile convulsions in their febrile episodes. (P=0.474).

Odds ratio of clobazam compared to diazepam with 95% confidence interval was 0.54(0.01–3) and number needed to treat was 71.43.

Discussion

The role and efficacy of benzodiazepines in the prevention of recurrence of febrile seizures has been well established [2–4, 6, 8–10].

Some studies have compared clobazam against placebo as prophylaxis for febrile seizure [7, 10, 11], and there are few studies comparing diazepam with clobazam in this regard [3, 10, 12].

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 seizures and is superior to the use of intermittent antipyretics alone [11].

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) [13].

Rose and coworkers evaluated the 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].

Gulati S in a randomized controlled trial compared efficacy of oral clobazam (75 cases) with oral diazepam (75 cases) for prophylaxis of febrile seizures. They reported a rate of febrile illness in 86.7% and 93.3% of patients in the diazepam and clobazam group respectively, during 3 years. The odds ratio of seizure recurrence was 2.3 in the diazepam group as compared to clobazam group [12].

This study is similar to our study with a difference in sample size and duration of study.

Sunil barande believed that oral diazepam and clobazam are equally effective and safe in the prophylaxis of recurrence of febrile seizure [3].

They 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 seizure [3].

The present study also showed that oral clobazam for the recurrence of febrile seizure is comparable to that of oral diazepam. (P=0.474)

However, adverse effects of clobazam were lower than diazepam. Sedation was more often in patients who received diazepam compared to clobazam (P<0.0001).

Rose *et al* reported that ataxia due to clobazam was much lower than that of diazepam [7]. Such finding did not show in the present study. Other side effects such as nausea and vomiting are not mentioned in present patients.

The easiness of oral intake, better compliance (2 doses for 2 days), and fewer adverse effects besides the equal efficacy of clobazam as compared the diazepam makes clobazam superior to diazepam, for prophylaxis of febrile seizures.

References

1. Johnston MV. Seizures in childhood. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson's textbook of pediatrics. 18th ed. Philadelphia: Saunders; 2007. p. 2457–8.
2. Sankar R. Paroxysmal disorders. In: Menkes JH, Sarnat HB, Maria BL, eds. Child neurology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 919–22.
3. Karande S. Febrile seizures: a review for family physicians. Indian J Med Sci. 2007;61:161–72.
4. Shinnar S. Febrile seizures. In: Swaiman KF, Ashwal S, Ferriero DM, eds. Pediatric neurology principles & practice. 4th ed. Philadelphia: Mosby; 2006. p. 1079–82.
5. Fenichel CM. Clinical Pediatric Neurology: A signs and symptoms Approach. 4th ed. Philadelphia: Saunders; 2001. p. 18–9.
6. Gupta S. Febrile seizures. An overview and use of clobazam as intermittent therapy. Pediatr Today. 2002;7:244–9.
7. Rose W, Kirubakaranc C, Scott JX. Intermittent clobazam therapy in febrile seizures. Indian J Pediatr. 2005;72:31–3.
8. Pavlidou E, Tzitiridou M, Panteliadis C. Effectiveness of intermittent diazepam prophylaxis in febrile seizures: long-term prospective controlled study. J Child Neurol. 2006;21:1036–40.
9. Verrotti A, Latini G, Dicorcia GD, et al. Intermittent oral diazepam prophylaxis in febrile convulsions: its effectiveness for febrile seizure recurrence. Eur J Pediatr Neurol. 2004;8:131–4.
10. Akman CI. Febrile seizures: the role of intermittent prophylaxis. J Pediatr Neurol. 2005;3:1–3.
11. Bajaj AS, Bajaj BK, Vinod P, Girish T. Intermittent clobazam in febrile seizures; an Indian experience. J Pediatr Neurol. 2005;3:19–23.
12. Gulati S, Saini D, Pandey RM, Kalra V. Randomized controlled trial to compare efficacy of oral clobazam with oral diazepam for praphylaxis of febrile seizures. Neuropediatrics. 2006;37:13.
13. Manreza MLG, Gherpelli JLD, Machado HLR, Pedreire CCC, Diament A, Heise CO. Treatment of Febrile seizures with intermittent clobazam. Arq Neuropsiquiatr. 2007;55:757–61.