Original Article

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Comparative Study of Intermittent Benzodiazepine Prophylaxis Versus Paracetamol Alone for Preventing Recurrence of Febrile Seizures

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Abstract

Objective: To compare the effectiveness of intermittent benzodiazepine therapy with paracetamol alone in preventing the recurrence of febrile seizures and to study the clinical profile of children with recurrent febrile seizures. *Method of Study:* This is a prospective study on 93 neurologically normal children aged from 6 months to 4 years, admitted with a history of febrile seizures during the study period, January - September 2015. Children with history of afebrile seizures and infection of nervous system were excluded. 45 children were prescribed only paracetamol when febrile (assigned as Group 1) and age matched 48 children were given benzodiazepine prophylaxis for initial three days of fever during each febrile episodealong with paracetamol to control fever (assigned as group 2). Oral clobazam and oral diazepam at appropriate doses were used for intermittent prophylaxis. All the patients were followed up for 12 months, for recurrence of seizures during fever. *Results:* Among the 93 children included in the study, 48 were males and 45 were females. 43.8% had positive family history with first degree relative affected in 19.1% and second degree relative in 24.6%. Family history of epilepsy is present in 9.5%. The most common etiology for fever was viral infection (57.5%). Atypical febrile seizures occurred in 28.7%. Multiple episodes of seizure during a febrile episode was also reported (20.5%). 8.2% children had focal seizures. The recurrence of febrile seizure was found in total of 52% children. Recurrence was maximum (31.5%) in the age group of 1-2 years. Among those with recurrence all had typical febrile seizure except 4 children. A recurrence rate of 56% and 53% was noted in group 1 and group 2 respectively, which was not statistically significant. *Conclusion:* We conclude that administration of benzodiazepines along with paracetamol is not superior in efficacy to paracetamol alone in preventing the recurrence of febrile seizure.

Keywords: Febrile Seizure; Benzodiazepine; Prophylaxis.

Introduction

Febrile seizures are the most common seizures in children.Febrile seizures have defined by The International League Against Epilepsy (ILAE) as "a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures" [1]. They usually occur with a temperature of 38^0C or higher,with most cases occurring between 5 months and 60 months of age with peak age of 18 months [2].

Febrile seizures has a high overall recurrence rate of 33%, where half the recurrences occur within six months of the first febrile seizure, 75% within a year and 90% within two years [3]. Despite this high recurrence rate, febrile seizures rarely caused permanent neurological damage [4]. The overall prognosis and behavioral outcome of children with febrile seizures are excellent [5].

However, prophylactic treatment of febrile seizures with intermittent as well as continuous use of antiepileptics, mainly benzodiazepines is quite prevalent in the present era. Benzodiazepine agents through oral, rectal or sublingual route is usually administered as intermittent prophylaxis [6]. This study aims at comparing the effect of benzodiazepine intermittent prophylaxis with treatment of

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paracetamol alone in preventing recurrence of febrile convulsions.

Materials and Methods

This prospective study was conducted on children admitted to Government Medical College, Thrissur, Kerala, with a history of febrile seizures during the study period, January to September 2015. The study was approved by Institutional Ethics committee. The study included all neurologically normal children aged 6 months to 4 years who were admitted to the hospital with febrile seizures. Exclusion criteria included the presence of neurological abnormalities, progressive neurological diseases, complex febrile convulsion, infections of central nervous system and history of afebrile seizures.

Ninety three children who met the inclusion criteria were enrolled in the study. Among them, 45 were randomly assigned to receive only oral paracetamol during the next febrile episode at a dosage of 15mg/kg/dose, three to four times a day, assigned as group 1. The other group of patients (group 2) were given either diazepam 0.33 mg/kg dose every 8 h or oral clobazam at a dosage of 0.3 to 1.0 mg/kg up to a maximum dose of 10 mg b.i.d.), administered only for the first 48 h of each febrile illness along with paracetamol as prescribed for group 1.Tepid sponging in addition to this were advised to both groups. Group 2 had age appropriate randomly selected 48 children. Both groups were followed up for 1 year for recurrence of seizures during fever, since 75% of recurrence of febrile seizures is known to happen in the first one year after initial seizure.

Outcome variable was defined as recurrence of febrile seizure. The fever episodes, recurrence of febrile seizure during fever and need for hospitalisation were assessed during the follow up visits. Data were analyzed using chi-square and fisher-exact tests with significance level set at $p<0.05$.

Results

Among the 93 children included in the study, 48 (51.61%)were males and 45 (48.38%)were females. 43.8% had positive family history with first degree relative affected in 19.1% and second degree relative in 24.6%. Family history of epilepsy is present in 9.5%.The most common etiology for fever was viral infection (57.5%). Atypical febrile seizures occurred in 28.7%. Multiple episodes of seizure during a febrile episode was reported in 20.5% of children. 8.2% children had focal seizures.

The recurrence of febrile seizure was found in 49 children, 52% of the total study population. Recurrence was maximum (31.5%) in the age group of 1-2 years. Among those with recurrence, all had typical febrile seizure except 4 children. 22 children, in whom benzodiazepines were not given since fever developed after the seizure were included in group 2. A recurrence rate of 53.33% (24 children) and 52.08% (25 children) was noted in group 1 and group2 respectively, which was not statistically significant (p=0.9040).Odds ratio with 95% confidence interval was found to be 0.9511 (95% CI: 0.4211 to 2.148).

Table 1: Baseline demographic characteristics of each group

	Group 1 (n=45)	Group 2(n=48)
Mean age(in months)	30 ±2	32 ±3
Males	23 (51.11%)	25 (52.08%)
Females	22 (48.88%)	23 (47.91%)
Total Febrile episodes in one year	127	134
Recurrence of FS	24 (53.33 %)	25 (52.08%)

Discussion

Febrile seizure is a benign neurological condition with genetic factors playing a key role in the etiology and in predicting its recurrence rate. Berg at al reported that young age at onset, a history of febrile seizures in a first degree relative, low degree of fever while in the emergency department, and a brief duration between the onset of fever and the initial seizure were strong independent predictors of recurrent febrile seizures [7]. Among 428 children studied, 136 children had a first recurrence, 73 (17.1%) had only 1 recurrence, 38 (8.9%) had 2 recurrences, and 25 (5.8%) had 3 or more recurrences.With these 4 factors combined, it is possible to define groups of children having very high and very low probabilities of having any recurrences [7].

In our study, we had a 43.8% had positive family history with first degree relative affected in 19.1% and second degree relative in 24.6%. Family history of

epilepsy is present in 9.5%. The recurrence of febrile seizure was found in 49 children, 52% of the total study population. Recurrence was maximum (31.5%) in the age group of 1-2 years.

Despite this high recurrence, studies document that febrile seizures do not cause brain damage or deûcits in cognition or behaviour.Prolonged febrile seizures are of significant concern because a child may later develop mesial temporal sclerosis and intractable epilepsy in rare cases.Otherwise,the risk of subsequent epilepsy is only 2-4%, comparable with general population [8]. Such a clinical situation warrants neither continuous nor intermittent pharmacological interventions to prevent the recurrence. In our study, the group received benzodiazepines intermittently along with paracetamol and the group who received paracetamol alone showed no significant difference in the recurrence. So, oral benzodiazepines may not be sufficiently effective in preventing febrile seizures.

In 46% children, benzodiazepines were not given since fever developed after the seizure. This is a common scenario in children that the increase in temperature is noted only after developing seizures, which makes the timely administration of prophylactic drugs difficult.

Moreover, side effects like drowsiness, weakness and sedation are commonly reported due to benzodiazepines, with a much higher incidence in children treated with diazepam than clobazam. Benzodiazepines are also reported to cause ataxia, about 8.3% with clobazam and around 30% children with diazepam [3,9]. These symptoms are to be taken into concern since they overlap with the clinical picture of meningitis which is the differential diagnosis in a child with fever and seizures.

The frequent occurrence of febrile seizures can impair the quality of life of family members and the parents may experience anxiety and fear whenever child develops a fever. Studies have showed their psychological reactions include fear of reoccurrence, fear of subsequent development of epilepsy, apprehension, and excessive anxiety and worry about low-grade fevers and management of a seizing child [8]. So, parents need to be educated regarding the likelihood of recurrence of seizures during fever especially if strong predictive factors coexist. They should also be educated about the benign nature of the disease and that these seizures will rarely lead to disastrous consequences.

It is also important that health care providers understand potential parental misconceptions, anxieties and fears about fever and febrile seizures and reassure them, which is much more beneficial than overdosing the children with benzodiazepines and other antiepileptics. This study recommends that overuse of benzodiazepines should not be encouraged for prophylaxis of febrile seizures, for fear of inappropriate dosing, significant side effects and overdose. If needed, oral preventive therapy may be considered in children with strong predictive factors of recurrence as mentioned earlier, which is to be decided by the treating paediatrician after proper parental education.

A febrile episode is the only time when a child is at risk of developing seizures. Hence, the primary aim of treatment of febrile convulsion should be reduction of the body temperature via conductive or evaporative cooling of the patient and treatment of the acute infection responsible for the fever [10]. But it is often seen in the routine practice that it is not practically possible to control fever with highest dose of paracetamol and other antipyretics along with tepid sponging. Antipyretics can make the febrile child more comfortable, but does not reduce the frequency of recurrent febrile seizures [11].

The association between iron and febrile seizures had been widely studied and literature reveals iron deficiency as a major risk factor for recurrence of febrile seizures. The role of iron in brain energy metabolism, functioning of neurotransmitters and myelination might point to a decreased seizure threshold in children with iron deficiency [12]. Dawn et al had also made similar conclusions that children with febrile seizures are almost twice likely to have iron deficiency compared to control population [13]. Considering this preventable and treatable condition, iron should be the right drug for prescription in these children.

The limitations of study are that the patients enrolled in the study are followed up only for one year. Any subsequent recurrence of seizures could not be included. The major side effects of drugs used for prophylaxis were also not compared between the groups.

Conclusion

Febrile seizures are benign self limited illness in early childhood. Prevention of recurrent febrile seizures does not reduce the risk of subsequent epilepsy. The risks of pharmacological prophylaxis usually outweigh the benefits since a large proportion of children experience side effects. There is not much evidence to advocate treatment after a first episode of febrile seizures, unless they have strong predictive

factors of recurrence. Hence,the best approach to febrile seizures is to provide education and reassurance to the parents and care takers.

References

1. ILAE. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993; 34:592-596.
2. Mikati MA. Febrile seizures in :Kliegman MR, Behrman RE, Schor NF, Nelson textbook of pediatrics.19th ed.Philadelphia: Saunders. 2011; 2017-2018.
3. Rose W, Kirubakaran C, Scott JX. Intermittent clobazam therapy in febrile seizures. The Indian Journal of Pediatrics. 2005 Jan 1; 72(1):31-3.
4. Verity CM. Do seizures damage the brain? The epidemiological evidence. Arch Dis Child 1998; 78: 78-84.
5. Verity CM,Greenwood R, Golding J. Long term intellectual and behavioral outcomes of children with febrile convulsion. N ENG J MED. 1998; 338: 1723-1728.
6. Pavlidou E, Tzitiridou M, Panteliadis C. Effectiveness of intermittent diazepam prophylaxis in Febrile Seizures: long time prospective controlled study. J Child Neurol. 2006; 21:1036-1040.
7. Berg et al,Arch PediatrAdolesc Med. 1997; 151: 371-378.
8. Epileptic Disord, Vol. 16, Supplement 1, October 2014].
9. Rosman NP, Colton T, Labazzo J et al. A controlled trail of diazepam administered during febrile illness to prevent recurrence of febrile seizures. N EnF: J Med 1993; 329:79-84.
10. Karande S. Febrile Seizures: a review for family physicians. Indian J Med Sci. 2007; 61:161-72.
11. Van Stuijvenberg M, Derksen-Lubsen G, Steyerberg EW, et al. Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. Pediatrics 1998; 102:E51.
12. Kumari PL, Nair MK, Nair SM, Kailas L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures-a case control study. Indian pediatrics. 2012 Jan 1; 49(1):17-9.
13. Dawn SH, Jonatan T, Jerome Y, Don S. The association between iron deficiency and febrile seizures in childhood. Clin Pediatr. 2009; 48:420-6.