COMPARISON BETWEEN DIAZEPAM AND PHENOBARBITAL IN PREVENTION OF FEBRILE SEIZURE: CLINICAL TRIAL

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Abstract
Objective
Febrile convulsions (FC) are the most common convulsive events in childhood, occurring in 2-5% of children. About one third of these children will have a recurrence during a subsequent febrile infection. This sudden neurologic problem is extremely frightening and emotionally traumatic for parents so some physicians try to prevent recurrence of FC by prescribing different drugs.

Materials and Methods
This is a randomized clinical trial in 85 healthy children, aged 6 months to 5 years, who were not treated before. These children received randomly either oral diazepam (0.33 mg/kg/TDS for two days during febrile illness) or continuous oral Phenobarbital (3-5mg/kg /24 h).

Results
Ultimately 64 patients completed the study and were followed up for an average of 13 months (12-18 months). The rate of recurrence of febrile seizure was 18.2% in diazepam group and 32.3% in Phenobarbital group; the difference is not statistically significant (p=0.16).

Conclusion
There was no significant difference between intermittent oral diazepam and continuous oral Phenobarbital for FC prevention.

Keywords: Febrile Seizure, Phenobarbital, Diazepam, Prevention, Recurrence

Introduction
Febrile seizures are defined as seizures that occur in association with a fever in children 6 months to 5 years of age, but in whom there is no evidence of a central nervous system infection or another definable cause of seizure, and which are not preceded by a history of an afebrile seizure (1, 2). Febrile seizures are classified as simple or complex. Simple febrile seizures account for approximately 85% of all febrile seizure. A complex seizure usually lasts longer than 15 minutes, is focal, might recur within the same day, and might have either a prolonged period of postictal drowsiness or be associated with postictal neurologic abnormalities(3).

Although febrile seizures are benign and the neurologic outcome is excellent, this sudden neurologic problem is extremely frightening and emotionally traumatic for parents who sometimes think their child might die during the seizure (4). Approximately 30% to 40% of children who experience a febrile seizure will have a recurrence, but less than 10% will have three or more recurrences (5). The good prognosis for most patients with febrile seizures reduces the need for continuous
prophylactic treatment with anticonvulsant agents, and intermittent prophylactic treatment seems to be a rational approach. Several studies have shown that daily administration of Phenobarbital (5 to 8 mg/kg/day for children 2 years of age and 3 to 5 mg/kg/day for children 2 years of age) or valproic acid (10 to 15 mg/kg/day in divided doses) is effective to prevent febrile seizures (6, 7). Adverse effects of Phenobarbital include transient sleep disturbances, daytime drowsiness, fussiness, attention deficit, hyperactivity, decreased memory, and impaired cognitive function (8). Diazepam, when administered intermittently either rectally or orally in sufficient doses (0.3 to 0.5 mg/kg, maximum 10 mg) at the onset of fever, has been shown to prevent recurrence of febrile seizures (9). A potential drawback of intermittent diazepam therapy is that some seizures occur before a fever is noticed (10). Adverse effects of diazepam therapy include lethargy, drowsiness, ataxia, dizziness, slurred speech, bradycardia, hypotension, and respiratory depression (11).

Currently in Iran 2 methods are commonly practiced for prevention of febrile seizures:
1- Intermittent use of oral diazepam during intercurrent febrile illnesses.
2- Continuous daily administration of oral Phenobarbital for a period of time.

Each of these two methods has its own advantages and inconveniences. For example intermittent use of diazepam and lead to “fever phobia” in the parents and continuous use of Phenobarbital may cause transient decline in attention and behavioral problem in children. The aim of this study was to evaluate the effectiveness of oral administration of diazepam in comparison with continuous oral Phenobarbital to reduce recurrence of febrile seizure in children.

Materials and Methods
This prospective study took place in Mofid children hospital for 2 years from September 2000 to December 2001. The children with first febrile seizure were included if they were aged 6 months to 5 years; if they had no history of neurologic disease; and if only one of the following was true:
1-age less than 1 year at the time of the first seizure;
2-body temperature less than 39 C during the spell;
3- Familial history of epilepsy in first degree relative.

The use of continuous prophylactic treatment in these cases could be justified regarding increased risk of FC recurrence.

This study was a randomized trial of diazepam versus Phenobarbital. Treatment was prescribed and a written monitoring chart was explained to parents during hospitalization for the first seizure. Parents recorded the number of days with temperature greater than 38°C and the number of days of diazepam administration on a special sheet. They also recorded the child’s acceptance of the treatment (easy, difficult).

The oral prophylaxis was one of the following:
A- Diazepam, according to the body weight of the child (0.33 mg/kg every 8 h), during each episode of fever for 48 h.
B- Phenobarbital according to the body weight of the child (3-5 mg/kg, divided in two daily doses), during 1 year.

A statistician randomly assigned each child to Group A or B and the doctors who followed these children did not know the randomization. A monthly telephone follow up is done for the purpose of ensuring parental compliance.

Comparison between two groups was analyzed by independent-sample t-tests for quantitative variables and the x 2 test for categorical variables. P values, 0.05 were considered statistically significant.

Results
There were 85 children who met all the entry criteria. 21 children were excluded because no follow-up information could be obtained after the initial evaluation. This report is, therefore, based on the remaining 64 children for whom a follow-up contact was made. 33 children were in Diazepam and 31 in Phenobarbital group. There was no difference in age, sex, family history of seizure and the characteristics of the first seizure between the Diazepam and Phenobarbital groups (Table I).

The follow up time was between 12-18 months. The mean follow up time in Diazepam and Phenobarbital group was 12.6 and 13.7 months respectively, and there is no significant difference between two groups.
6 children (18.2%) in the diazepam group and 10 (32.3%) in the placebo group, had a recurrence (difference not significant, P=0.16). Risk assessment with other variables (age, seizure type, ) did not show significant results.

Discussion
The aim of this study was to compose two common clinical practices of Iranian physicians for prevention of recurrence of febrile seizure. One of the most important results of this research is that none of these methods can definitely stop febrile seizure reappearance. Although numerically febrile seizure recurrence was less in children who received diazepam intermittently but statistically no difference existed between these two groups.

We didn’t find in our literature review any study who compared these two drugs; indeed in several trials diazepam and Phenobarbital; alone or in comparison with other methods for febrile convulsion prophylaxis, were studied(12, 13, 14, 15, 16, 17, 18).

In a double blind randomized trial of diazepam versus placebo for febrile seizure prevention Antrent and his colleagues didn’t find any difference between the two groups.

But as the authors stated the major problem was noncompliance in the case group of some families made the results unreliable. Rosemane find 82% decrease in probability of febrile seizure recurrence in children who used diazepam versus placebo in a controled trial(13). In a more recent study performed by Verrotti et al in Italy recurrent febrile seizure occurred in 11.1% of children who used diazepam intermittently versus 30.7% in those who didn’t take any medication (16) All of these authors mentioned about some inconvenience of this method, the most important, being late administration of diazepam by parents several hours after start of fever. Lethargy, Ataxia and hypotonia are some relatively common side effects.

Rose W. et al in a controlled trial done in India concluded that intermittent clobazam can be as effective as diazepam and with lower side effects as ataxia (19).

When phenobarbital is being used continuously there is no fear of sudden emergent fever which can be ignored by parents, as in diazepam group; because a long standing therapeutic drug level is already achieved which can prevent seizure. The main problem when prescribing phenobarbital is family noncompliance and mild cognitive impairment in long term use (20).

Mamelle and Ngware in 2 separate randomized therapeutic assays confirmed the efficacy of continuous Phenobarbital usage with a dose 4-5 mg/kg daily for prevention of febrile seizure (14, 15). One of the strength of this study was serum Phenobarbital assays in children who received it. Such measurement could easily separate noncompliant cases from those received Phenobarbital regularly with appropriate dosage.

Overall there is 20%-30% rate of FC recurrence regardless of with risk factors (17). Previous studies using Phenobarbital reported an average decrease recurrence of 4% 13%(15, 20). In our study we found 32% recurrence rate of F.C, which seems to be similar to the natural course of the disease (without any intervention). The explanation is that our patients had at least one risk factor of FC recurrence and sometimes two or three. Indeed the 20-30% recurrence rate is irrespective of having or not any risk factor. We did not measured serum Phenobarbital level in our patients, so the problem of

<table>
<thead>
<tr>
<th>Variants</th>
<th>Diazepam group</th>
<th>Phenobarbital group</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Age (months/SD)</td>
<td>23.7 /13.4</td>
<td>23 /13.4</td>
<td>NS*</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/3</td>
<td>18/1</td>
<td>NS</td>
</tr>
<tr>
<td>Familial febrile seizure (%)</td>
<td>19 (57.6%)</td>
<td>13 (41.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Familial non febrile seizure (%)</td>
<td>3 (9.1%)</td>
<td>2 (6.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Complex seizure</td>
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<td>4</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS: Not significant
family non compliance remains an important factor explaining such relatively high rate of recurrence. Negative effects of Phenobarbital on behavior and cognition restrict its daily usage in many countries (8-9).

In our literature review we didn’t find similar designed study comparing these two methods, but each practice had shown its efficacy for reducing FC recurrence (14-17). Regarding the visible difference between these two methods a double blind trial could not be designed.

Two limitation of our study was first relatively short time of follow up and secondly not measuring serum Phenobarbital level, which should be applied in future researches on this issue. Regarding cognitive side effects of Phenobarbital, if a physician has planed drug therapy for FC prevention, we recommend intermittent diazepam during febrile illnesses.

Reference