

ROLE OF PHENOBARBITONE IN PREVENTING RECURRENCE OF FEBRILE CONVULSIONS

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ABSTRACT

A randomized double blind placebo controlled trial was carried out to study the effect of phenobarbitone (PB) in preventing recurrences of simple and atypical febrile convulsions among children in the age group 6 months to 6 years. Children with simple febrile convulsions were randomly allocated to receive either phenobarbitone or placebo. Children with atypical convulsions were treated with phenobarbitone, as a third group. Thirty children were admitted in each group. All the children were followed up for a period of twelve months.

Recurrence of convulsions and side effects of PB were recorded. Recurrence occurred in only 7% (95% confidence interval : 1-22) of children on Phenobarbitone, suffering from either simple or atypical febrile convulsions, compared to 53% (95% confidence interval : 34-72) of children on placebo, suffering from simple febrile convulsions. With Phenobarbitone, 5% of children had intolerable side effects. These results suggest that long term prophylaxis with phenobarbitone, even in simple febrile convulsions will be useful.

Key words: Febrile convulsion, Atypical convulsion, Phenobarbitone therapy.

Febrile convulsion is a common neurological illness of childhood with significant morbidity rate. The reported prevalence of febrile convulsions is 3 to 4%(1). Recurrence of convulsions is the major complication and repeated febrile convulsions are disturbing to the family of the patients.

It is reported that children with febrile convulsions had a five fold excess risk of subsequent unprovoked seizures, when compared to normal children, the incidence of which increased with the number of initial febrile convulsions(2). With regard to the effects of recurrent seizures, results of previous studies are conflicting. Ellenberg and Nelson described recurrent seizures as unharmed(3). However, Smith and Wallace, in their studies, found that recurrent convulsions were likely to be detrimental in terms of overall intellectual development(4).

This study aims to provide a safe and cost-effective method of preventing recurrences in febrile seizures. Phenobarbitone was chosen because it was less expensive than sodium valproate. The specific objectives were: (i) To compare the efficacy of phenobarbitone (along with simple fever control measures) with simple fever control measures alone, in preventing recurrent febrile convulsions; and (ii) To identify whether long-term prophylaxis (12 months) with phenobarbitone reduces the recurrence of febrile convulsions, both

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simple and atypical and to identify the side effects of such long term prophylaxis.

Material and Methods

A randomized double blind placebo controlled trial was conducted for a period of twelve months.

The study population included children in the age group of 6 months to 6 years, with febrile convulsions, admitted to the Inpatient Department or attending Neurology Outpatient of the Institute of Child Health and Hospital for Children, Madras.

Inclusion criteria for patients with simple febrile convulsions (SFC) were, history of two or more episodes of febrile convulsions, of the generalized tonic-clonic type, lasting for less than 15 minutes without postictal weakness. Inclusion criteria for patients with atypical febrile seizures (AFC) were, history of two or more episodes of convulsions with fever. The pattern of convulsion had to be more than one seizure in 24 hours or seizures lasting for more than 15 minutes or focal seizures or seizures with postictal weakness.

Children with abnormal neurological development, those who were already on anticonvulsants, children with epilepsy, chronic medical illness and from outside Madras city were excluded. After case selection, children were examined in detail and basic demographic data were collected from parents. Parents were informed about the trial and their consent was obtained before admitting their children in the trial.

A total of 90 children were admitted to the study. Children with simple febrile convulsions were randomized either to a group receiving placebo (Group A) or to a group receiving phenobarbitone (Group B). All children with atypical febrile convulsions were treated with phenobarbitone (Group C). Children with atypical febrile convul-

sions could not be randomized to receive phenobarbitone or placebo for ethical considerations.

Phenobarbitone was given in the dose of 5 mg/kg/day as a single dose at bed time. Calcium lactate was used as placebo. Both phenobarbitone and placebo were given in powder form in special sachets (one sachet for each day) and were identical in colour, appearance and taste. After allocation, all parents were advised to give the prescribed drug without fail and to attend the follow-up clinic on their specified dates. They were discouraged from giving medications not prescribed under the trial. The parents were advised to give appropriate dose of paracetamol and tepid sponging without fail when the child developed fever. These instructions were given to all the 3 groups with equal emphasis. Follow-up was done once in 15 days. During follow-up visits, history regarding recurrence of convulsions was taken. Detailed physical examination was carried out, side effects of medication were recorded and drugs were distributed for the next fifteen days.

Side effects assessed were: (a) Changes in activity level (hyperkinetic behavior, irritability, aggressiveness, fussiness and lethargy); (b) Changes in sleep pattern (insomnia and excessive sedation); (c) Skin rash; and (d) Gastrointestinal (loss of appetite, nausea and vomiting).

Intolerable side effects were said to be present when a child had persistent side effects on two subsequent visits, *i.e.*, for one month.

At each visit, parents were instructed to bring the empty sachets and the sachets with medication to facilitate sachet counting. Compliance was monitored by counting the sachets containing medication. Sachets were identified by the initials of the investigator which were made before distri-

bution. Even if one sachet with medicine was brought back without consuming, on more than three occasions during the entire duration of the study, the compliance was said to be poor.

The assessment of recurrence, side-effects and compliance were done by one investigator who was blind to the type of treatment throughout the study period. Another investigator followed up the patients with reference to the type and dosage of medication given. Parents were given the name, address and phone number of this investigator and advised to contact the person at any time in case of any emergency. Once a child developed convulsions, while on treatment, it was considered as a drug failure. The drug code was broken, but the child was continued to be followed up till the end of the study. If the child was on placebo then the child was started on phenobarbitone. If the child had been receiving phenobarbitone already then the dose of the drug was adjusted or after a follow-up period another anticonvulsant was started by the second investigator. When intolerable side effects were reported, the dosage of the medication was reduced to 3 mg/kg/day by the second investigator. At the end of the study period, the drug code was broken and analysis was done.

Results

The distribution of variables such as age, sex and number of attacks prior to treatment that could influence the frequency of recurrence of febrile convulsions is presented for the three groups (*Table I*).

With placebo, 53% (95% confidence interval: 34-72) of children developed recurrence of febrile convulsions as against 7% (95% Confidence interval: 1-22) with phenobarbitone treatment for both SFC

and AFC. The difference observed in seizure recurrence between Group A (placebo) and Group B (SFC on PB) as well as the difference observed between Group A and Group C (AFC on PB) was statistically significant ($p < 0.001$). The recurrence rate in children with AFC treated with phenobarbitone was the same as the recurrence rate in children with simple febrile seizures treated with phenobarbitone (*Table II*).

Compliance was poor only in four children, one in Group A, two in Group B and one in Group C, all of whom had a recurrent seizure.

Intolerable side effects were present in two children in Group B and one child in Group C. These were mainly hyperkinetic behavior, extreme irritability, fussiness and aggressiveness. IQ assessment was not done in any of the children.

Totally there were 4 dropouts, one from Group A, two from Group B and one from Group C. Children from Groups B and C dropped out because of intolerable side effects. The child from Group A who was receiving placebo dropped out for an unknown reason.

Discussion

This study has shown that the addition of a single daily dose of phenobarbitone to a programme of antipyretic counselling is effective in preventing recurrence of simple febrile seizures.

In AFC, generally the chances of recurrence is likely to be higher(5). In our study the recurrence in AFC was effectively controlled with phenobarbitone therapy as in the case of simple febrile convulsions. With phenobarbitone therapy the recurrence was only 7% both in SFC and in AFC.

In earlier studies barbiturates have been reported to be either successful

TABLE I—Distribution of Factors According to Regimen

Factors	Group A Simple FC receiving placebo (n=30)	Group B Simple FC receiving phenobarb (n=30)	Group C Atypical FC receiving phenobarb (n=30)
Sex			
Male	12	20	13
Female	18	10	17
Age (mo)			
6-11	16	12	11
12-24	9	13	14
25-60	5	5	5
Total number of attacks child had before treatment			
<2	15	16	17
3-5	14	13	10
≥6	1	1	3

TABLE II—Comparison of Recurrence Among the Three Groups

Recurrence	Number of children		
	Group A (n=30)	Group B (n=30)	Group C (n=30)
Present (Total)	16 (53)	2 (7)	2 (7)
<6 mo	10	2	2
6 mo - 1 yr	6	0	0
Absent	14 (47)	28 (93)	28 (93)

Figures in parentheses indicate percentages.

or unsuccessful as prophylactic agents(6-13). Camfield *et al.* in their research documented a recurrent seizure in 5% of phenobarbital treated patients compared to 25% of patients receiving placebo(6). In the study of Aroor, *et al.*, the proportion of recurrence was 12% in the phenobarbital treated group, compared to 45% in the control group(10). In another study by

Wallace, children with complex febrile seizures were evaluated and it was found that the recurrence was 17% when these children were treated with phenobarbitone or primidone compared to 59% in children who were untreated(8).

The finding from our study that phenobarbitone is effective in preventing recurrences in both SFC and AFC is in

Table III—Comparison of Recurrences Rates among Various Studies

Study	No. of children	Age group	Duration of follow up	Recurrence rate reported (%)	
				Phenobarb	Placebo
Camfield <i>et al.</i>	79	6mo-3 yrs	1 yrs	5	25
Aroor <i>et al.</i>	125	1-2 yrs	2 yrs	12	45
Sheila	108	6 mo-4 yrs	6 mo	17	59
Present	90	6 mo-6 yrs	1 yr	7	53

agreement with some of the earlier studies quoted above (*Table III*).

Heckmatt *et al.* in their study found that the chances of recurrence in the phenobarbitone group was 11% compared to 19% in the control group thereby concluding that regular phenobarbitone therapy does not prevent febrile convulsions(12). This study turned out to be a negative study probably due to the short follow up period of six months. Ramakrishnan *et al.* found the chance of recurrence to be nearly the same in phenobarbital group and control group(13).

In our study, there was little proof that repeated verbal instructions about temperature control decreased seizure recurrences amongst patients with simple febrile seizures, receiving placebo.

The incidence of intolerable side-effects was low in our study (4%) compared to that of Wolf *et al.* (22%), Camfield *et al.* (9%) and Aroor *et al.* (12%)(9,10,14).

In our study, 4 children could not be followed up for the entire study period. This figure compares well with the study of Camfield *et al.* where 12 out of 79 children could not be followed up and that of Heckmatt *et al.* where also 4 children were lost to follow up.

It may be concluded from our study that long term prophylaxis (at least 12 months) with phenobarbitone reduces recurrences both in SFC and AFC. However it is necessary that a much larger number of children need to be followed for a much longer period of time to arrive at a definite conclusion with reference to assessment of IQ and cognitive function.

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NOTES AND NEWS

XIII ANNUAL CONVENTION OF NATIONAL NEONATOLOGY FORUM

The XIII Annual Convention of National Neonatology Forum is to be held at Baroda from *December 17 to 19, 1993*. This Convention is organized jointly by the Department of Pediatrics, Medical College, Baroda and the Indian Academy of Pediatrics, Baroda Branch.

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