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Original Research Article

Efficacy of intermittent prophylaxis vis a vis no prophylactic interventions in febrile seizure recurrence: randomised controlled trail

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ABSTRACT

Background: To compare efficacy of intermittent prophylaxis during subsequent febrile episodes with antipyretics alone or antipyretics with anticonvulsant (clobazam) vis a vis no prophylactic interventions except need-based antipyretic measures in preventing recurrence of febrile seizures.
Methods: This prospective randomized controlled interventional study was carried out in neurologically normal children. Study conducted over 14 months (March 2014 - May 2015), tertiary care hospital Mumbai. Inclusion criteria was, children aged from 6 month to 5 years with history of simple febrile seizure, lasting for less than 15 minutes, with Frequency less than one episode in 24 hours. Children with history of afebrile or complex febrile seizure, CNS comorbidity, family history of epilepsy, abnormal electroencephalogram, Unwillingness or non-feasibility of follow up were excluded from study. The patients were randomly grouped in A (No Prophylaxis n= 60), B (Antipyretic prophylaxis n=57) and C (Antipyretics + clobazam prophylaxis n=55). All cases were followed up telephonically every 15 days from date of first seizure as well as personal follow up at 1,3,6 months either in the hospital or at home. End point of study was taken as six months of follow-up from enrolment or lost-to-follow up. Efficacy of intervention was compared using chi-square test, Pearson chi-square test with/without Yates continuity correction and/or Fisher exact test, with p value of <0.05 as test of significance.
Results: Sixty cases in group A developed febrile episodes and 6 of them developed recurrence of febrile seizures, with a recurrence rate of 10% among total cases and 9.67% among all febrile episodes. Recurrence rate was significantly higher (10%) in cases who did not receive any prophylactic intervention (Group A) as compared to pooled recurrence rate in group B and C together 1.78% (p=0.022).
Conclusion: Regular antipyretic prophylaxis, alone or along with clobazam does not reduce the risk of recurrence in simple febrile seizures as compared to those who receive antipyretic intervention.

Keywords: Clobazam, Febrile seizure, Intermittent prophylaxis, Recurrent rate

INTRODUCTION

Febrile seizures are most common seizure disorder in children, affecting approximately 2-10% of children below five years of age relatively more common in developing countries perhaps due to higher incidence of infective illnesses.[1-3] Although these seizures are mostly benign with excellent outcome, a convulsing child is an extremely frightening and stressful situation for parents. A major concern of parents of a febrile seizure patient is to know the risk of recurrence in their child after the first attack. Febrile seizures are often known to recur with recurrence rate of about 30-40%, though reported risk in literature varies widely due to differences in case selection, population characteristics and duration of follow-up.[1] Considering the high risk of recurrence, another important issue in the management of these case

is prevention of further attack of seizure during next febrile episode, if possible.

Antipyretics with or without intermittent anticonvulsant prophylaxis are commonly used to prevent recurrence of simple febrile seizures during subsequent febrile episodes, though efficacy is controversial. However, there is no consistent evidence in favour or in against of these interventions.[4] Given the benign nature of febrile seizures, need for prophylactic interventions, even if to be given intermittently, has to be weighed against the potential risk of the adverse effects of drugs. American Academy of Pediatrics recommends that although there is evidence that both continuous antiepileptic therapy and intermittent therapy are effective in reducing recurrence of febrile seizures, potential toxicities associated with anticonvulsants outweigh the minor risk associated with simple febrile seizures.[2]

Many studies including Indian studies are available to assess the efficacy of intermittent antipyretic and/or anticonvulsant prophylaxis in prevention of the recurrence in febrile seizures, though with conflicting results.[5,6] Clobazam is a preferred anticonvulsant to longer duration of action and lesser side-effects.

This study aims to compare efficacy of intermittent prophylaxis during subsequent febrile episodes with antipyretics alone or antipyretics with anticonvulsant (clobazam) vis a vis no prophylactic interventions except need-based antipyretic measures in averting recurrence of febrile seizures.

METHODS

This prospective prospective randomized controlled interventional study was carried out over 14 months (March 2014 - May 2015) in Dr R N Cooper Municipal General Hospital, Mumbai, India. Children enrolled in the study group was 6 months to 60 months with episodes of simple febrile seizure. Inclusion criteria was, children aged from 6 month to 5 years with history of simple febrile seizure, lasting for less than 15 minutes, with Frequency less than one episode in 24 hours.

Children with history of afebrile or complex febrile seizure, CNS comorbidity, family history of epilepsy, abnormal electroencephalogram, Unwillingness or non-feasibility of follow up were excluded from study. The study was approved by institutional ethics committee, prior to commencement of data collection.

Sample size was calculated with at least 60 patients in each group calculated by a) presuming approximate probability of recurrence in simple febrile seizures as 30% with precision value of 0.05, b) presuming at least 10% difference in recurrence rate between any of the two groups versus controls or non-intervention group, and c) presuming 10% drop- out during the study (Figure 1).

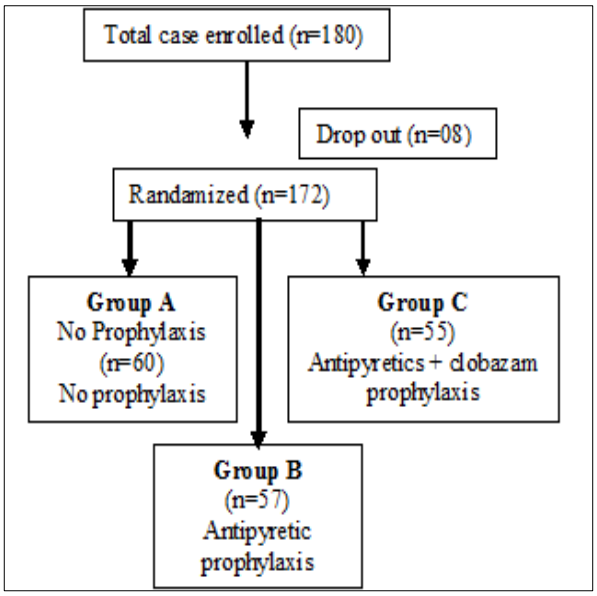

Figure 1: Flow diagram of a clinical trial.

All cases were screened for inclusion and exclusion criteria. A written informed consent was obtained on pre-designed consent form.

All cases were randomly allotted to one of the three groups, using block randomization of 15 with computer-generated list, to ensure nearly comparable number of cases in each group.

After randomization, following preventive interventions for simple febrile seizures were advised Group A.

Group A

As controls, advised to use need-based Oral Paracetamol (15mg/kg/dose) as and when required during the febrile episode (i.e. only after developing fever).

Group B

Advised to start Per Oral Paracetamol (15mg/kg/dose) every 6 hourly as soon as the first fever spike was noted during next episode (not later than 3 hour) and continued till the patient is afebrile for at least 24 hours after last episode of fever, subject to minimum 3 days.

Group C

Advised to start oral Paracetamol (15mg/kg/dose) every 6 hourly along with oral Clobazam in weight-wise dosage (5mg, daily in children ≤5kg; 5mg, twice daily (BD) in children 6-10kg; 7.5mg, BD in children 11-15kg; and 10mg, BD in children >15kg.) as soon as the first fever spike is documented during next episode (not later than 3 hour) and continued till the patient is afebrile for at least 24 hours after last episode of fever, subject to minimum 3 days.

Children were followed up till 6 months. Drop-outs were excluded from the study. Data were analyzed using chi-square test, Pearson chi-square test with/without Yates continuity correction and/or Fisher exact test, with p value of <0.05 as test of significance. Mann-Whitney test and Kruskal Wallis test was used to compare data.

RESULTS

Patients included 110(64.0%) male and 062(36.0%) female subjects, with mean age of 22 months (range 6-60 months). Finally, 60 patients in group A (No prophylaxis), 57 in group B (Antipyretic prophylaxis) and 55 in group C (Antipyretics + Clobazam Prophylaxis) completed the study. Recurrence rate was significantly higher (10%) in cases who did not receive any prophylactic intervention (Group A) as compared to pooled recurrence rate in group B and C together 1.78% (p=0.022). Although recurrence rates in isolated group B (prophylactic antipyretics) (1.75%) and isolated group C (prophylactic antipyretics with clobazam) (1.81%) were apparently less as compared to group A (no intervention), the differences were not significant (p=0.11).

Table 1: Recurrence rate among total cases in different study groups.

Group	A	B^	C^	Total
Total cases	60	57	55	172
Total recurrences	6	1	1	8
% Recurrence among all cases	10.00%	1.75%	1.81%	4.65%

Fisher's exact test (A vs B): p = 0.11
Fisher's exact test (A vs C): p = 0.11
Fisher's exact test (B vs C): p = 1
Fisher's exact test^ (A vs B+C): p = 0.022

Table 2: Recurrence rate among all febrile episodes in different study groups.

Group	A	B^	C^	Total
Total cases	60	57	55	172
Total febrile episodes	62	57	58	177
Total recurrences	6	1	1	8
% Recurrence among all Febrile episode	9.67%	1.75%	1.72%	4.5%

Fisher's exact test (A vs B vs C): p = 0.10
Fisher's exact test (A vs B): p = 0.11
Fisher's exact test (A vs C): p = 0.11
Fisher's exact test (B vs C): p = 1
Fisher's exact test^ (A vs B+C): p = 0.022

There was no significant difference in recurrence rates between group B and C (p=1.00)Recurrence rate was significantly higher (9.67 %) in cases who did not receive any prophylactic intervention (Group A) per number of febrile episodes as compared to pooled recurrence rate in group B and C together (1.73%),which was statistically significant (p=0.022) (Table 1). Recurrence rates per number of febrile episodes in isolated group B (prophylactic antipyretics) 1.75% and isolated group C (prophylactic antipyretics with clobazam) 1.72% were less as compared to group A (no intervention), but the differences were not significant (p=0.11).There was no significant difference in recurrence rates per number of febrile episodes between group B and C (p=1.00) (Table 2).

DISCUSSION

The role and efficacy of benzodiazepines in the prevention of recurrence of febrile seizures has been well documented in litrature.[7-9] Some studies have compared clobazam against placebo as prophylaxis for febrile seizure, and there are few studies comparing diazepam with clobazam.[10-13] Intermittent short-term use of an anticonvulsant e.g. Diazepam or clobazam is a common practice to prevent recurrence of febrile seizures, though with variable outcome. Bajaj, in a double-blind placebo-controlled study found that recurrence of febrile seizure was observed in 30% patients in the clobazam group vs 83.3% in the placebo group.[11] Manreza performed a study on fifty 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).[14] In our study the recurrence rates in antipyretics group was 1.75%. Rose and coworkers found 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).[5] Karande S. in their study notice that oral diazepam and clobazam are equally effective and safe in the prophylaxis of recurrence of febrile seizure. They found that oral clobazam is more effective in preventing febrile seizure recurrence as compared to diazepam in children with history of at least one episode of febrile seizure.[13] Camfield et al, reported that although treatment with acetaminophen and Phenobarbital was effective in preventing recurrent febrile seizures, acetaminophen and placebo were not.[15] Which was consistent with our study, prophylactic antipyretics are not effective in preventing recurrence. Many studies have also shown efficacy of intermittent oral or rectal diazepam prophylaxis in prevention of the recurrence of febrile seizures with conflicting outcome.[16-19] In recent study systematic review of randomized controlled trials and meta-analysis, antipyretics were ineffective in reducing the recurrence of febrile seizures.[20] Which is consistent with our study. Uhari et al, in a placebo-controlled double-blind study demonstrated that the intermittent use of acetaminophen or diazepam has no effect on recurrence of febrile seizure.[21] We found similar finding in our study, antipyretic prophylaxis, along or along with clobazam does not reduce the risk of recurrence. To conclude, regular antipyretic prophylaxis, alone or along with

clobazam does not reduce the risk of recurrence in simple febrile seizures as compared to those who receive only need based antipyretics during next febrile episode. Further large-scale study needed to study the effectiveness of interventions.

CONCLUSION

Both antipyretic prophylaxis and antipyretic plus anticonvulsant prophylaxis do not affect the recurrence rates in febrile seizures vis a vis child who received only need-based antipyretic therapy during next febrile episode.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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