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Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD003031.
DOI: 10.1002/14651858.CD003031.pub4.

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[Intervention Review]

Prophylactic drug management for febrile seizures in children

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Editorial group: Cochrane Epilepsy Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2021.

Citation: Offringa M, Newton R, Nevitt SJ, Vraka K. Prophylactic drug management for febrile seizures in children. *Cochrane Database of Systematic Reviews* 2021, Issue 6. Art. No.: CD003031. DOI: 10.1002/14651858.CD003031.pub4.

ABSTRACT

Background

Febrile seizures occurring in a child older than one month during an episode of fever affect 2-4% of children in Great Britain and the United States and recur in 30%. Rapid-acting antiepileptics and antipyretics given during subsequent fever episodes have been used to avoid the adverse effects of continuous antiepileptic drugs.

This is an updated version of a Cochrane Review previously published in 2017.

Objectives

To evaluate primarily the effectiveness and safety of antiepileptic and antipyretic drugs used prophylactically to treat children with febrile seizures; and also to evaluate any other drug intervention where there is a sound biological rationale for its use.

Search methods

For the latest update we searched the following databases on 3 February 2020: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to 31 January 2020). CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane Review Groups including the Cochrane Epilepsy Group. We imposed no language restrictions and contacted researchers to identify continuing or unpublished studies.

Selection criteria

Trials using randomised or quasi-randomised participant allocation that compared the use of antiepileptics, antipyretics or recognised Central Nervous System active agents with each other, placebo, or no treatment.

Data collection and analysis

For the original review, two review authors independently applied predefined criteria to select trials for inclusion and extracted the predefined relevant data, recording methods for randomisation, blinding, and exclusions. For the 2016 update, a third review author checked all original inclusions, data analyses, and updated the search. For the 2020 update, one review author updated the search and performed the data analysis following a peer-review process with the original review authors. We assessed seizure recurrence at 6, 12, 18, 24, 36, 48 months, and where data were available at age 5 to 6 years along with recorded adverse effects. We evaluated the presence of publication bias using funnel plots.

Main results

We included 42 articles describing 32 randomised trials, with 4431 randomised participants used in the analysis of this review. We analysed 15 interventions of continuous or intermittent prophylaxis and their control treatments. Methodological quality was moderate to poor in most studies. We found no significant benefit for intermittent phenobarbital, phenytoin, valproate, pyridoxine, ibuprofen, or zinc sulfate versus placebo or no treatment; nor for diclofenac versus placebo followed by ibuprofen, paracetamol, or placebo; nor for continuous phenobarbital versus diazepam, intermittent rectal diazepam versus intermittent valproate, or oral diazepam versus clobazam.

There was a significant reduction of recurrent febrile seizures with intermittent diazepam versus placebo or no treatment at six months (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.48 to 0.85; 6 studies, 1151 participants; moderate-certainty evidence), 12 months (RR 0.69, 95% CI 0.56 to 0.84; 8 studies, 1416 participants; moderate-certainty evidence), 18 months (RR 0.37, 95% CI 0.23 to 0.60; 1 study, 289 participants; low-certainty evidence), 24 months (RR 0.73, 95% CI 0.56 to 0.95; 4 studies, 739 participants; high-certainty evidence), 36 months (RR 0.58, 95% CI 0.40 to 0.85; 1 study, 139 participants; low-certainty evidence), 48 months (RR 0.36, 95% CI 0.15 to 0.89; 1 study, 110 participants; moderate-certainty evidence), with no benefit at 60 to 72 months (RR 0.08, 95% CI 0.00 to 1.31; 1 study, 60 participants; very low-certainty evidence).

Phenobarbital versus placebo or no treatment reduced seizures at six months (RR 0.59, 95% CI 0.42 to 0.83; 6 studies, 833 participants; moderate-certainty evidence), 12 months (RR 0.54, 95% CI 0.42 to 0.70; 7 studies, 807 participants; low-certainty evidence), and 24 months (RR 0.69, 95% CI 0.53 to 0.89; 3 studies, 533 participants; moderate-certainty evidence), but not at 18 months (RR 0.77, 95% CI 0.56 to 1.05; 2 studies, 264 participants) or 60 to 72 months follow-up (RR 1.50, 95% CI 0.61 to 3.69; 1 study, 60 participants; very low-certainty evidence).

Intermittent clobazam compared to placebo at six months resulted in a RR of 0.36 (95% CI 0.20 to 0.64; 1 study, 60 participants; low-certainty evidence), an effect found against an extremely high (83.3%) recurrence rate in the controls, a result that needs replication.

When compared to intermittent diazepam, intermittent oral melatonin did not significantly reduce seizures at six months (RR 0.45, 95% CI 0.18 to 1.15; 1 study, 60 participants; very-low certainty evidence).

When compared to placebo, intermittent oral levetiracetam significantly reduced recurrent seizures at 12 months (RR 0.27, 95% CI 0.15 to 0.52; 1 study, 115 participants; very low-certainty evidence).

The recording of adverse effects was variable. Two studies reported lower comprehension scores in phenobarbital-treated children. Adverse effects were recorded in up to 30% of children in the phenobarbital-treated groups and 36% in benzodiazepine-treated groups. We found evidence of publication bias in the meta-analyses of comparisons for phenobarbital versus placebo (seven studies) at 12 months but not at six months (six studies); and valproate versus placebo (four studies) at 12 months. There were too few studies to identify publication bias for the other comparisons.

The methodological quality of most of the included studies was low or very low. Methods of randomisation and allocation concealment often did not meet current standards, and 'treatment versus no treatment' was more commonly seen than 'treatment versus placebo', leading to obvious risks of bias.

Authors' conclusions

We found reduced recurrence rates for intermittent diazepam and continuous phenobarbital, with adverse effects in up to 30% of children. The apparent benefit for clobazam treatment in one trial needs to be replicated. Levetiracetam also shows benefit with a good safety profile; however, further study is required. Given the benign nature of recurrent febrile seizures, and the high prevalence of adverse effects of these drugs, parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management, and, most importantly, the benign nature of the phenomenon.

PLAIN LANGUAGE SUMMARY

Prophylactic drug management for febrile seizures in children

Background

Seizures occurring with a fever (febrile seizures) in children are common and affect about one in 30 children under the age of six years. On average, one out of three children who have had a febrile seizure will have at least one more. We reviewed the evidence about the effect of drugs to prevent seizures (antiepileptics), drugs to lower temperature (antipyretics), and zinc in children with febrile seizures.

Objective

We wanted to know in how many children these drugs would prevent a recurrence of febrile seizures or cause unwanted effects.

Methods

We included 32 studies with a total of 4431 children in the review. Children who had had at least one febrile seizure were assigned to one of two or more treatment groups. The studies recorded any further seizures at various time intervals between six months and up to six years of age in each group. Unwanted medication effects were also noted.

Results

The study design and evidence quality in the studies of antiepileptic drugs was often low or very low. Poor methods known to lead to obvious risks of bias were used. One issue was with the methods used to assign children to study groups and how random this allocation was. Other issues included whether the parents or doctors, or both, knew which group each child was in or if a treatment was compared to no treatment with no placebo (dummy pill) used. The quality of the trials of antipyretics or zinc was better, with the evidence assessed as moderate to high.

Zinc therapy was found to provide no benefit. We also found no benefit in treating children just at the time of the fever with either antipyretic drugs or most antiepileptic drugs.

A significant result was noted in some instances. For example, at times between 6 and 48 months follow-up, intermittent diazepam (an antiepileptic drug) led to a reduction in the number of recurrent seizures by about a third. Continuous phenobarbital resulted in significantly fewer recurrences at 6, 12, and 24 months, but not at 18 and 60 to 72 months. One study showed that intermittent oral levetiracetam compared to placebo significantly reduced recurrent seizures at 12 months. When compared to intermittent diazepam, intermittent oral melatonin did not significantly reduce seizures at six months.

However, as recurrent seizures are only seen in about a third of children, this means that up to 16 children would have to be treated over a year or two to save just one child a further seizure. As febrile seizures are not harmful, we viewed these significant findings to be unimportant, in particular because adverse effects of the medications were common. Lower comprehension scores in phenobarbital-treated children were found in two studies. In general, adverse effects were recorded in up to about a third of children in both the phenobarbital- and benzodiazepine-treated groups. The benefit found for treatment with clobazam in one study published in 2011 needs to be repeated to test its reliability. Levetiracetam may be useful in treating children where family anxiety over possible seizure recurrence is high, but further study is required.

Authors' conclusions

There is currently insufficient evidence to support the use of continuous or intermittent treatment with zinc, antiepileptic or antipyretic drugs for children with febrile seizures. Febrile seizures can be frightening to witness. Parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management, and, most importantly, the benign nature of the phenomenon.

The evidence is current to February 2020.