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Original article

Do antipyretics prevent the recurrence of febrile seizures in children? A systematic review of randomized controlled trials and meta-analysis

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ABSTRACT

Objectives: To determine the effectiveness of antipyretics use in prevention of subsequent febrile seizures in children.

Data sources: A search for all available electronic databases (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials, Cochrane Methodology Register) from 1950 to July 2011 was done. No language restrictions were applied, but English abstract required.

Study selection: We included randomized controlled trials comparing the efficacy of anti-pyretic drugs to placebo in reducing the recurrence rate of febrile seizures in children (6–72 months) with previous febrile seizures. We excluded reviews, letters, and uncontrolled or non-randomized studies.

Data extraction and synthesis: The literature search was performed by a professional medical librarian. Based of the preliminary search, two reviewers independently pooled studies for detailed manual review per the inclusion criteria. We used the Cochrane Review Manager software (Revman 5) to calculate the odds ratio and 95% confidence intervals (CI) for seizure recurrence, assuming a random-effects model.

Results: Initial search identified 479 citations, five articles underwent further rigorous evaluation by two reviewers and three papers met the inclusion criteria. In these three studies, 540 children were included, of whom 348 received antipyretics (acetaminophen (15 mg/kg), ibuprofen (5–10 mg/kg) or diclofenac (1.5 mg/kg)) and 192 received placebo for

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h The first two authors have made an equal contribution to the manuscript, and are, therefore, co-principal authors. 1090-3798/\$ — see front matter © 2013 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.ejpn.2013.04.008

prevention of subsequent febrile seizures during a 1–2 year follow-up period. Seventy-nine patients (22.7%) in the antipyretics group and forty-seven patients (24.4%) in the placebo group had febrile seizure recurrence during follow up. No statistically significant difference was found between the antipyretics and the placebo groups in the recurrence rate of febrile seizures (OR 0.9, 95% CI: 0.57–1.43).

Conclusion: Antipyretics were ineffective in reducing the recurrence of febrile seizures.

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1. Introduction

Febrile seizures affect 2–5% of children aged 6–60 months. Despite their prevalence and high recurrence rate (30–50%), there is no consensus about optimal prevention approach. Febrile seizures recurrence and anticipation cause great distress and anxiety to affected families and caregivers, and efforts are made to identify effective treatments to prevent their recurrence. The most commonly used drugs for febrile seizure prevention are antipyretics and anticonvulsants. The use of anticonvulsant drugs such as phenobarbital or valproic acid has been previously studied. These drugs are effective in reducing the recurrence rate of febrile seizures. However, safety issues, potential adverse effects, and the need for therapeutic drug monitoring make this option less appealing and controversial.

Antipyretics are considered safe and effective in treating fever in children. 6-8 Since the intuitive precursor of a febrile seizure is fever, physicians commonly recommend antipyretics use during febrile episodes in children with a known history of febrile seizures, in an attempt to prevent their recurrence. A study from Japan, reported that about 40% of experienced pediatricians recommend the use of antipyretics for febrile seizure prevention⁹ and 84% of parents believe that if their child's fever is untreated febrile convulsions will occur. 10 A recent survey amongst 322 Swiss pediatricians identified significant differences in practice patterns related to fever management in toddlers, in respect to height of fever requiring treatment, previous history of febrile convulsions, etc. 11 The objective of this systematic review and metaanalysis of randomized controlled clinical trials is to assess, based on the current literature, the effectiveness of antipyretics in prevention of febrile seizures recurrence in predisposed children.

2. Methods

2.1. Data sources and search methods

Searches were conducted in MEDLINE (1950 to July Week 4, 2011), EMBASE (1947–2011 Week 30), Cochrane Database of Systematic Reviews (2005 to July 2011), ACP Journal Club (1991 to July 2011), Database of Abstracts of Reviews of Effects (DARE) (1st Quarter 2011), Cochrane Central Register of Controlled Trials (1st Quarter 2011), Cochrane Methodology Register (1st Quarter 2011). No language restrictions were applied, but an English abstract was required.

The multipurpose search command for the Ovid SP interface (.mp.), and the topic search command for the ISI Web of Knowledge interface (TS=), were used to search both text and database subject heading fields. To capture variations in suffix endings of search terms, the unlimited truncation symbol "" was used in both interfaces. Search terms included: febrile seizures, and all terms listed under the broader database subject headings Antipyretic analgesic agents (EMBASE), and Anti-Inflammatory Agents, Non-Steroidal (MEDLINE). Additional search terms were identified through the 'Used For' section of the term scope notes in MEDLINE, and the thesaurus in EMBASE.

2.2. Inclusion and exclusion criteria

We included randomized controlled trials comparing the efficacy of antipyretic drugs to placebo in reducing the recurrence rate of febrile seizures in children (<18 years), published in any language with an English abstract. Only full papers were included. We excluded reviews, letters, and uncontrolled or non-randomized studies.

2.3. Data extraction and synthesis

The literature search was performed by a professional medical librarian (TA).

Based of the preliminary search, two reviewers (ER, YF) independently pooled studies for detailed manual review per the inclusion criteria.

We used the Cochrane Review Manager software (Revman 5) to calculate the odds ratio and 95% confidence intervals (CI) for seizure recurrence, assuming a random-effects model.

3. Results

We identified 479 citations, which met the initial search criteria. All were manually reviewed. Five articles reported comparative studies, and underwent further rigorous evaluation. Two of those five articles were excluded from analysis because they did not meet the meta-analysis inclusion criteria: the study by Van Esch et al. ¹² was excluded because it was not a randomized controlled trial (RCT). The RCT by Schnaiderman et al. ¹³ was excluded since the effect of antipyretics was not compared to placebo, but between two dosing regimens of acetaminophen for seizures prevention. There was no interreviewer disagreement regarding study selection for meta-analysis.

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