EBEM Commentator
Lisa M. Evered, MD, FRCP(C)

From the Division of Pediatric Emergency Medicine, University of Alberta, Edmonton, Alberta, Canada.

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Does Acetaminophen Treat Fever in Children?

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Meremikwu M, Oyo-Ita A. Paracetamol for treating fever in children (Cochrane Review). In: *The Cochrane Library.* Issue 3. Oxford, United Kingdom: Update Software; 2002.

The *Annals'* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To assess the effect of paracetamol (acetaminophen) on fever clearance time, febrile convulsions, and the resolution of symptoms associated with fever in children. The primary outcomes were fever clearance time and febrile convulsion.

DATA SOURCES

The Cochrane Infectious Diseases Group specialized trials register, The Cochrane Controlled Trials Register, Index Medicus (MEDLINE), Excerpta Medica (EMBASE), La Literatura Latinoamericana y del Caribe de Informacion en Ciencias de Salud (LILACS), Science Citation Index, and reference lists of articles were searched. Reviewers also contacted researchers in the field. This review is considered updated to January 2002.

STUDY SELECTION

Randomized and quasirandomized trials of children with fever caused by infections comparing: (1) paracetamol versus placebo or no treatment; and (2) paracetamol versus physical cooling methods (eg, sponging, bathing, fanning) were selected.

DATA EXTRACTION

Two reviewers independently extracted data on methods, types of participants, interventions, and outcomes. The meta-analysis was conducted using relative risk (RR) with

95% confidence intervals (CIs) for discrete variables, and weighted mean differences (WMD) for continuous outcomes.

MAIN RESULTS

Twelve trials (n=1,509 participants) met the inclusion criteria. Outcomes varied between trials. No data were available on the primary outcome. There is insufficient evidence to show whether paracetamol influenced the risk of febrile convulsions. In a meta-analysis of 2 trials (n=120), the proportion of children without fever by the second hour after treatment did not differ significantly between those given paracetamol and those sponged (RR=1.84; 95% CI 0.94 to 3.61, random effects model). The statistical test showed significant heterogeneity between the groups receiving paracetamol or physical methods. No severe adverse events were reported. The number of children with mild adverse events did not differ significantly between paracetamol and placebo, or paracetamol and physical methods, but numbers were small.

CONCLUSIONS

Trial evidence that paracetamol has a superior antipyretic effect than placebo is inconclusive. There is limited evidence that there is no difference between the antipyretic effect of paracetamol and physical methods. Data on adverse events in these trials were limited. Establishing standard outcomes will help comparisons between studies and meta-analysis.

Cochrane Systematic Review Author Contact

M. Meremikwu, MB BCh, MSc, FMCPaed
Department of Paediatrics
University of Calabar
Calabar, Cross River State, Nigeria
E-mail meremiku@skannet.com

COMMENTARY: CLINICAL IMPLICATIONS

Fever accounts for a significant proportion of emergency department visits in children. Fever may be caused by infectious or inflammatory processes, which may, albeit infrequently, result in serious sequelae. The negative outcomes known to be caused directly by fever itself are: (1) feeling unwell, (2) convulsions caused by a rapidly rising temperature in a predisposed child, and (3) caregiver or parental concern.[1] Parents, caregivers, and health care professionals strive to minimize the malaise associated with fever and prevent febrile convulsions using both physical and pharmaceutical techniques to reduce temperature. Cooling methods, such as fanning and tepid sponging, conduct heat from the skin[2]; however, in some cases these measures actually cause the core temperature to rise. The most commonly used medication to treat fever is acetaminophen. Fever has also been treated with acetylsalicylic acid in the past, but this treatment has largely been abandoned because of its strong association with Reye's syndrome. More recently, nonsteroidal anti-inflammatory drugs, such as ibuprofen, have been used.[3]

Fever is the body's natural response to infections, and some experts argue that treating fever may interfere with its beneficial role.[4-6] If in fact this is true, reducing fever has the potential to prolong the infectious illness and may adversely affect the outcome of the illness.[4-6] In addition, there are known risks associated with antipyretic medications, such as the potentially fatal liver failure that results from overdose with acetaminophen or use of acetylsalicylic acid in association with varicella infection. Adverse effects of the physical methods of reducing fever include the associated discomfort and the potential paradoxical conservation of heat.

As part of a larger plan to evaluate these approaches to fever, this systematic review searched for the best available evidence on the risks and benefits of treating fever (≥37.5°C [≥99.5°F] axilla or ≥38.0°C [≥100.4°F] core) in children aged 3 months to 15 years using acetaminophen (8 to 15 mg/kg per dose). The analysis did not demonstrate whether acetaminophen has benefit over placebo or physical cooling methods in the time to clearance of fever or in reducing the risk of febrile convulsions. Because febrile convulsions are a relatively rare consequence of fever, much larger sample sizes than those found here (n=1,509) would be required to detect a meaningful difference. The authors did demonstrate that, although acetaminophen is significantly better than placebo at resolving fever within 2 hours, the overall time to resolution of symptoms did not significantly differ between the 2 groups. Evaluation of defervescence at 2 hours comparing acetaminophen versus cooling yielded inconsistent results. Meta-analysis showed no significant difference in adverse events between the comparison groups.

This review addresses preliminary and, ultimately, tangential issues to do with rapid ED lowering of temperature in febrile infants. Other clinically important issues in fever management (eg, effect of sponging, use of nonsteroidal anti-inflammatory drugs, prevention of febrile seizures) will be addressed in the subsequent reviews in the series by these authors.

TAKE HOME MESSAGE

These findings indicate that there is a paucity of adequate research in this area and that treatment of fever with acetaminophen may or may not be

effective for children. Although no significant evidence of harm exists from the short-term use of acetaminophen at doses of 8 to 15 mg/kg every 4 hours, the burden is on the medical community to prove that it is actually beneficial. More research is clearly indicated, and emergency physicians should exercise common sense in the use of acetaminophen, reserving it primarily for analgesia and discomfort.

EBEM Commentator Contact

Lisa M. Evered, MD, FRCP(C)
Division of Pediatric Emergency Medicine
University of Alberta
Edmonton, Alberta, Canada
E-mail lisaevered@shaw.ca

EVIDENCE-BASED MEDICINE TEACHING POINTS

Quasi-randomized control trials. In the hierarchy of study designs, systematic reviews and meta-analyses of randomized controlled trials represent the highest levels of evidence in therapeutic interventions. Individual randomized control trials are ranked below systematic reviews when evaluating evidence, unless they are mega-trials.[7] Quasi-experimental (also referred to as pseudorandomized trials) use other nonrandomized methods to decide on the treatment allocation. For example, allocations based on flipping a coin, day of the week, month of the year, and so on are examples of quasi-experimental methods. Because these methods do not use randomization, their potential to produce a biased estimate and error is higher than true randomized controlled trials. Some researchers, including the authors of this review, include quasirandomized controlled trials in their systematic reviews. Readers should be careful when interpreting the results of reviews with nonrandomized control trial designs, and a subgroup examining the effect of the addition of quasi-experimental designs on the pooled estimates should be provided.

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