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[Intervention Review]

Paracetamol versus placebo or physical methods for treating fever in children

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ABSTRACT

Background

Paracetamol (acetaminophen) is widely used for treating fever in children. Like ibuprofen, aspirin, and physical methods (such as fanning), paracetamol aims to provide relief from symptoms and prevent febrile convulsions. Uncertainty exists about the benefits of using it to treat fever in children.

Objectives

To assess the effects of paracetamol for treating fever in children in relation to fever clearance time, febrile convulsions, and resolution of associated symptoms.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (May 2004), CENTRAL (*The Cochrane Library* Issue 2, 2004), MEDLINE (1966 to May 2004), EMBASE (1988 to May 2004), LILACS (May 2004), Science Citation Index (May 2004), and reference lists of articles. We also contacted researchers in the field.

Selection criteria

Randomized and quasi-randomized trials of children with fever from infections comparing: (1) paracetamol with placebo or no treatment; and (2) paracetamol with physical cooling methods (eg, sponging, bathing, or fanning). The primary outcomes were fever clearance time and febrile convulsion.

Data collection and analysis

Two reviewers independently extracted data on methods, types of participants, interventions, and outcomes. The meta-analysis was conducted using risk ratio with 95% confidence intervals for discrete variables, and mean differences for continuous outcomes.

Main results

12 trials (n = 1509 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 two 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 (risk ratio 1.84; confidence interval 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.

Authors' conclusions

There are few trials that have directly compared the antipyretic properties of paracetamol against placebo or physical methods. Data on adverse events are limited. Establishing standard outcomes will help comparisons between studies and better meta-analysis.

23 April 2019

No update planned

Other

This is currently not a priority for update

PLAIN LANGUAGE SUMMARY

Paracetamol for treating fever in children

Plain language summary pending.

BACKGROUND

Fever is common within infections. It is caused by the body responding to disease or invasion by pathogens (Kluger 1992). Fever results in people feeling unwell, and occasionally in children, a rapidly rising temperature results in a convulsion (Behrmann 2000). Febrile convulsions are the most common type of convulsions in childhood, and are known to affect about two to five per cent of all children (Verity 1985). About 30 per cent of those who have had an episode of febrile convulsions have additional convulsions (Stuijvenberg 1998).

The physiological mechanism that results in fever is not clear. However, several immunological factors are known to interact in the process that leads to fever, notably the chemical factors called cytokines produced by white blood cells. Experts suggest that cytokines act on the centre in the brain that regulates temperature (thermoregulatory centre) to initiate the physiological responses that result in fever (Kwiatkowski 1995). Fever also increases the rate at which the body uses its energy reserve, especially when it occurs with chills and rigor (Mackowiak 1998).

The drugs most commonly used for treating fever are paracetamol, aspirin, and ibuprofen (Autret 1997). These drugs exert their effects by blocking different points in the chemical pathway that leads to fever. While aspirin and ibuprofen exert their effects on the central pathway (in the brain) as well as the peripheral (in other parts of the body), paracetamol is believed to act only on the central pathway (Mackowiak 1998). The action of these drugs on the temperature control pathway results in the peripheral blood vessels dilating to dissipate heat (Meyers 1980, Mackowiak 1998). People also use physical cooling methods, such as fanning and tepid sponging, which conduct heat from the skin (Agbolosu 1997).

Although the disease process that leads to fever is obviously harmful, some experts suggest that fever may have a beneficial effect of enhancing host resistance to infection (Kramer 1991, Kluger 1992, Roberts 1991). Some of these experts argue that interventions specifically targeted at resolution of fever may interfere with the beneficial role of fever during illness and adversely affect the outcome of the illness. One report suggests that treatment with antipyretic drugs could increase mortality in severe infections, prolong viral shedding, and impair antibody response to viral infection (Shann 1995). Another researcher has observed that giving paracetamol to African children with malaria fever prolonged the parasite clearance time (Brandts 1997). A Cochrane review has however shown that there is insufficient evidence to support the view that paracetamol prolongs parasite clearance in people with malaria (Meremikwu 2001).

In addition to the potentially harmful effects of reducing fever, there are harms associated with specific drugs. The ingestion of a high dose of paracetamol is known to cause liver damage (Meredith 1981, Plotz 1981). For instance, paracetamol toxicity from overdosing is the commonest cause of acute liver failure in the United Kingdom (Newsome 2001). Paracetamol overdose has also been reported to cause disorders of the kidneys, heart, blood cells, and metabolism (Jones 1997). Aspirin is reported to cause metabolic acidosis (which presents with rapid breathing), very low blood sugar (hypoglycaemia), lethargy, coma, and fits; symptoms which are common in severe malaria. Therefore its use in malaria patients may lead to diagnostic confusion, complications, and increase the risk of death (English 1996). Another major limitation to the use of aspirin in children is its association with Reye's syndrome, a rare adverse event that may lead to coma and death in children. The association of aspirin with Reye's syndrome has led to official ban on the use of aspirin for treating children in the United Kingdom and many other countries (Hall 1988, Porter 1990). Other reported adverse effects of antipyretic drugs (including ibuprofen) are gastrointestinal bleeding, heartburn, dyspepsia, nausea, and vomiting (Done 1983, Meyers 1980).

The common adverse effects of physical methods include shivering, crying, and discomfort. Sponging with cold water may cause peripheral cooling but the constriction of the blood vessels can actually cause heat conservation (Mackowiak 1998). The axillary temperature will fall and the rectal temperature will rise.

The uncertainties associated with antipyretic drugs and physical methods have led to a debate about the benefits and harms of methods of reducing fever (Choonara 1992, Done 1983). Most caregivers and many clinicians believe that treatment of fever will relieve symptoms and prevent harmful effects such as febrile convulsions (Stuijvenberg 1998). A recent study has shown that parental fear about presumed harmful effects of fever in children (also called "fever phobia") is still common, and in most cases, due to misconceptions (Crocetti 2001). Given that these drug and physical methods are widely recommended for treating children with a fever, we sought to examine reliable research evidence of the benefits and harms for each method through the following individual reviews.

1. Paracetamol for treating fever in children (this review).
2. Physical methods for treating fever in children (in preparation)
3. Ibuprofen for treating fever in children (in preparation).
4. Aspirin for treating fever in children (in preparation).

Comparisons between interventions in each review are structured in as follows.

1. PARACETAMOL
Paracetamol compared to placebo.
Paracetamol compared to physical methods.

2. PHYSICAL METHODS
Physical methods compared to nothing or drug placebo.
Physical methods added to any other drug intervention compared to the drug intervention alone.

3. IBUPROFEN
Ibuprofen compared to placebo.
Ibuprofen compared to physical methods.
Ibuprofen compared to paracetamol.

4. ASPIRIN REVIEW
Aspirin compared to placebo.
Aspirin compared to physical methods.
Aspirin compared to against paracetamol.
Aspirin compared to non-steroidal anti-inflammatory drugs (NSAIDs).

Paracetamol for treating fever in children

Paracetamol (acetaminophen) is widely used for treating fever in children. This drug is reputed to be both effective and well tolerated (McIntyre 1996). On the other hand, some experts argue that the use of paracetamol may prolong the duration of certain infections

(Brandts 1997). Some epidemiological reports suggest that the incidence of acute paracetamol poisoning may have increased in recent times owing probably to widespread use of the drug for treating fever (Meredith 1981). Children may develop paracetamol toxicity due to unintended inappropriate dosing, giving standard dose of the drug to children at increased risk of toxicity, or giving paracetamol concurrently with other drugs that are also capable of damaging the liver (AAP 2001).

There are obvious reasons for concern about the safety of this drug and uncertainties about its actual benefits in the treatment of childhood fever. We have addressed these questions in this systematic review with a view to providing reliable evidence for clinical practice and identifying areas for further research.

OBJECTIVES

To assess the effects of paracetamol for treating fever in children in relation to fever clearance time, incidence of febrile convulsions, and resolution of associated symptoms.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials.

Types of participants

Children aged 1 month to 15 years with fever of presumed infectious origin. Fever is defined as temperature of 37.5 °C or more (axillary); or 38.0 °C or more (core body temperature).

We excluded trials that studied only children who have had episodes of febrile convulsions in the past. A Cochrane review of prophylactic treatments for decreasing likelihood of future febrile convulsions is being prepared (Offringa 2001).

Types of interventions

Intervention

Paracetamol (acetaminophen).

Control

Placebo or physical methods (sponging, bathing, or fanning).

Types of outcome measures

Primary outcomes

1. Fever clearance time (time between onset of treatment and return of temperature to normal <37.5 °C).
2. Children who have febrile convulsion after treatment started.

Secondary outcomes

1. Rate of temperature fall between 30 minutes and 6 hours of treatment, (expressed in °C per hour).
2. Proportion without fever by first, second, and sixth hour of starting treatment.
3. Proportion in whom associated symptoms (discomfort, shivering, chills, anorexia, vomiting, irritability, headache, myalgia) resolved within six hours of starting treatment.
4. Adverse events.
5. Number of caregivers dissatisfied with treatment regimen.

Search methods for identification of studies

We selected the following search terms for searching all trial registers and databases for relevant trials: fever; anti-pyretic drugs; non-narcotic analgesic; paracetamol; acetaminophen; panadol; tylenol; tepid sponging; and fanning.

We searched the Cochrane Infectious Diseases Group (CIDG) Specialized Register for relevant trials (published, in press, or in progress) up to May 2004. Full details of the CIDG methods and the journals hand searched are published in The Cochrane Library in the section on Collaborative Review Groups.

We searched The Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 2, 2004). This contains mainly reference information to randomized controlled trials and controlled clinical trials in health care.

We searched the following electronic databases in combination with the search strategy developed by The Cochrane Collaboration and detailed in the Cochrane Reviewer's Handbook (Clarke 2000): MEDLINE (1966 to May 2004); LILACS (1982 to May 2004); EMBASE (1988 to May 2004); Science Citation Index (May 2004).

We checked the citations of all the trials identified by the above methods.

The external referees were asked to check the completeness of the search strategy, and to identify any additional unpublished, ongoing, or planned trials.

We contacted researchers who have done notable studies in infectious diseases and fever to check the completeness of the search strategy and supply information on any unpublished and ongoing trials not yet identified.

Data collection and analysis

Selection of studies

We independently applied the inclusion criteria for this review to the potentially relevant trials identified with the search strategy. Where there was any doubt, we consulted the Cochrane Infectious Diseases Group (CIDG) co-ordinating editor. We included those trials that met the inclusion criteria.

Data extraction and management

We independently extracted data using a standard form. We wrote to the trial authors for additional data or clarification of analyses and outcomes where required using a standard form.

Assessment of risk of bias in included studies

We independently assessed the quality of included trials using the guidelines of the CIDG. The CIDG Co-ordinating Editor was consulted where there were doubts. We planned to exclude any included trials subsequently shown to be of very poor methodological quality.

Data synthesis

We entered the data we extracted from the included trials into Review Manager 5 for the meta-analysis. We prepared a narrative summary on groups of data or information considered

inappropriate for meta-analysis. We performed subgroup analysis of the incidence of febrile convulsion for children aged 6 months to 6 years (preschool children), since the risk of febrile convulsion is known to be particularly high in this age group (Behrmann 2000). We calculated risk ratio with 95% confidence intervals for comparisons of discrete variables, and calculated the mean difference for continuous data. We performed statistical tests to ascertain the homogeneity of the effects of compared interventions. Where we observed heterogeneity of effects, we attempted to explain this, including sensitivity analyses of indicators of study quality. We also considered publication bias.

RESULTS

Description of studies

We identified 91 publications relevant to the review question and we formally applied the eligibility criteria to these. Twelve studies were included while 79 were excluded. The most frequent reasons for exclusion were non-randomization of participants, failure to assess or give data on relevant outcome measures, failure to compare drug with placebo or other methods stipulated in the Protocol for this review, and inclusion of adult participants (see 'Characteristics of excluded studies').

The 12 trials that met the inclusion critieria had a total of 1509 children aged between 3 months and 15 years (see 'Characteristics of included studies'). Seven trials included only participants aged 6 years or less. Temperature was measured using digital electronic (six trials) and mercury thermometer (two trials); the method used was not mentioned in four trials. The sites at which temperature was measured were rectum (six trials), axilla (two trials), oral (two trials), or not mentioned (two trials).

Seven trials compared paracetamol with placebo (Brewer 1968, Steele 1970, Doran 1989, Walson 1989, Kramer 1991, Wilson 1991, Kauffman 1992a). Six trials compared paracetamol with physical methods (Steele 1970, Friedman 1990, Kinmonth 1992, Agbolosu 1997, Aksoylar 1997, Brandts 1997).

Both single doses (nine trials) and multiple doses (three trials) of paracetamol were evaluated. The dosage of paracetamol varied across the trials, ranging between 8 and 15 mg/kg per dose. One trial (Brandts 1997) administered paracetamol rectally, the others used the oral route.

Tepid sponging was the main physical method (five trials); one trial included warm sponging along with unwrapping the children (Kinmonth 1992). One trial (Brandts 1997) combined tepid sponging with using a wet blanket and fanning. Sponging was intermittent for 20 minutes or longer each time in all the trials except one in which the children were sponged continuously (Brandts 1997). The temperature of water used for warm sponging was described as being just below each participant's body temperature (32 to 41.7 °C) while the duration of warm sponging varied (range of 1 to 82 minutes; median of 9 minutes). The water temperature ranged between 28 and 34 ° C.

Outcome measures

The outcome measures varied widely between the included trials (see 'Characteristics of excluded studies'). The observation period also varied from 1 to 2 hours (3 trials); 3 to 6 hours (3 trials); 7 to 24 hours (3 trials); and 2 to 7 days (3 trials).

Some notable results unsuitable for meta-analysis have been included in Appendix 1 and Appendix 2.

See the 'Characteristics of included studies' for further information on the included studies.

Risk of bias in included studies

The allocation sequence was adequately concealed only in 7 (Doran 1989, Kauffman 1992a, Kinmonth 1992, Kramer 1991, Steele 1970, Walson 1989, Wilson 1991) of the 12 included trials. 10 trials described satisfactory methods of generation of allocation sequence while 2 used a quasi-randomization approach. Observers were blinded in six trials (Brewer 1968, Doran 1989, Kauffman 1992a, Kramer 1991, Walson 1989, Wilson 1991) partially blinded in one (Steele 1970), and unblinded in five trials. Dropout or exclusion rates were generally low in the trials (0 to 10.3%). The only trial with a relatively high dropout rate (Kramer 1991) performed an intention-to-treat analysis thereby minimizing the attrition bias associated with high losses to follow up. Since none of the other trials provided a detailed trial profile it is difficult to ascertain the actual magnitude of losses to follow up. All the trials stated the frequency of observation. We made no further exclusions on the basis of poor methodological quality.

Effects of interventions

1. Paracetamol compared to placebo

Seven trials compared paracetamol and placebo (Brewer 1968, Steele 1970, Doran 1989, Walson 1989, Kramer 1991, Kauffman 1992a, Wilson 1991).

Primary outcomes

Fever clearance time

Only one trial (Kramer 1991) involving 225 children reported this outcome over 2 to 6 days of observation. In the paracetamol group this was 34.7 hours (n = 123) and in the placebo group it was 36.1 hours (n = 102). The authors report that this was not statistically significantly different, using student t-test and the Mann-Whitney U test (standard deviation not given).

Febrile convulsion

Kramer 1991 reported that no febrile convulsion occurred in either the paracetamol or placebo group; participants were aged 6 months to 6 years. The other trials made no specific mention of the occurence of seizures.

Secondary outcomes

One trial (Steele 1970) reported on the proportion of children with fever by the second hour of observation while three trials (Brewer 1968, Steele 1970, Walson 1989) reported on adverse events. None of the trials reported on the rate of temperature fall or proportion in whom associated symptoms were resolved.

Without fever by two hours

One trial (Steele 1970) showed that significantly more children in the paracetamol group (17/25) than placebo (0/15) were without fever by the second hour of starting treatment (risk ratio (RR) 21.54; 95% confidence intervals (CI) 1.39 to 333.99; Analysis 1.1). No data were available for fever resolution at one and six hours.

Symptom resolution

Although none of the trials provided relevant data on this outcome, two trials showed that the mean time to resolution of symptoms or healing did not differ significantly between children who received paracetamol (multiple doses) and who were given placebo over two to six days of observation (see Appendix 1) (Doran 1989, Kramer 1991).

Adverse events

Meta-analysis of data from three trials (Brewer 1968, Steele 1970, Walson 1989) involving a total of 254 participants showed that the incidence of adverse events in the paracetamol (9/130) and placebo (4/124) groups did not differ significantly (RR 1.84, 95% CI 0.65 to 5.18; Analysis 1.2). Adverse events were mild in all cases and included drowsiness and mild gastrointestinal symptoms.

2. Paracetamol compared to physical methods

Six trials (Steele 1970, Friedman 1990, Kinmonth 1992, Agbolosu 1997, Aksoylar 1997, Brandts 1997) compared paracetamol with physical methods (sponging with or without fanning or unwrapping). Data were adequate for meta-analysis in two trials (Agbolosu 1997, Steele 1970).

Primary outcomes

Fever clearance time

Brandts 1997 showed no difference in fever clearance time following treatment with paracetamol or physical methods (sponging, fanning, and wet blanket) in a study of 50 children, but this could not confirmed by re-analysis because the full data set was not available. This trial used multiple doses of paracetamol and followed the children (with respect to this outcome measure) for up to four days.

Febrile convulsion

One trial (Agbolosu 1997) reported one case of febrile convulsion among the sponging group (1/40) and none among the paracetamol group (0/40), but the difference was not statistically significant (RR 0.33; 95% CI 0.01 to 7.95; see Appendix 2). Five other trials (Steele 1970, Friedman 1990, Kinmonth 1992, Aksoylar 1997, Brandts 1997) made no specific reference to this outcome measure.

Secondary outcomes

Without fever by one and two hours

This outcome was assessed by two trials (Steele 1970, Agbolosu 1997). At one hour, there was no statistically significant difference in the number of children without fever in either the paracetamol or placebo group (fever free: paracetamol group 28/65; sponging group 18/55; RR 1.49; 95% CI 0.98 to 2.25; Analysis 2.1). At two hours, one trial (Agbolosu 1997) showed a statistically significant difference (RR 2.53; 95% CI 1.69 to 3.80), and the other trial (Steele 1970) did not (RR 1.27; 95% CI -0.74 to 2.20). The test for heterogeneity was statistically significant, and a combined analysis using a random effects model provides further uncertainty about the consistency of this effect (RR 1.84; 95% CI 0.94 to 3.61, random effects model).

Adverse events

The occurrence of adverse events as reported in the two trials (Steele 1970, Agbolosu 1997) was not statistically significantly different between the paracetamol (2/65) and sponging (6/55) groups (RR 0.26; 95% CI 0.07 to 1.01; Analysis 2.3). The other trials (Friedman 1990, Kinmonth 1992, Aksoylar 1997, Brandts 1997) did not report adverse events in either of the intervention groups. The adverse events reported were shivering, goose pimples, discomfort, and in one sponged participant, convulsion.

Other outcome measures

No data were available for meta-analysis of other measures of antipyretic efficacy as stipulated in the Protocol for this review. Details of other additional outcomes are presented in Appendix 1 and Appendix 2. No trial assessed the attitude of caregivers to 'no intervention' compared with physical methods of treating fever.

DISCUSSION

We found a small number of trials that tested paracetamol against placebo or physical methods for treating fever. Some of these studies were carefully conducted, while in others a lack of detail in the methods made it difficult to evaluate them.

Most studies were small, none identified primary outcomes in their research design, and the outcomes varied considerably between studies. In addition, data were often incomplete, with few providing standard deviation on mean measures or details of the statistical tests used by the authors.

We have not systematically assessed observational data of paracetamol efficacy, as we aimed to focus on more reliable comparisons between paracetamol and mechanical methods or placebo from randomized controlled trials. The comparative data were surprisingly sparse, and it is not clear whether paracetamol is effective when compared to placebo or physical methods in (1) reducing fever reduction and (2) reducing risk of febrile convulsions.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review shows that inconsistent and weak evidence supports the use of paracetamol to reduce fever in children. This does not mean that paracetamol is ineffective, but simply that the number of reliable studies evaluating it against placebo or physical methods are too few to be sure it has a therapeutic effect.

In the absence of any obvious harms, a campaign to alter practice is not justifiable. Caregivers and doctors have faith in paracetamol, but its continued use needs to be justified in terms of benefit through future research or the outcome of the related Cochrane Reviews (see description in the 'Background') of the effects of other antipyretic drugs in the management of fever.

Implications for research

We have not demonstrated any convincing direct evidence that paracetamol is effective in reducing fever or preventing febrile convulsions in children. This has the following research implications.

1. Further research in this area warrants larger studies measuring a few simple pragmatic outcomes, such as febrile convulsions; mean time to resolution of fever; and number of participants without fever by one hour.

2. A systematic review of the effects of paracetamol in adults could provide some evidence that clinicians may generalize for all age groups in the interim. Trials including only adults will however not provide any useful information on febrile convulsion since this is a childhood problem.

3. Further reviews of antipyretic drugs need to compare, in the first instance, the drug against placebo. Head to head comparisons against paracetamol presume that paracetamol is the standard treatment.

4. Monitoring of common adverse events and occasional rare events needs to be considered in all evaluations of antipyretic drugs in children.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agbolosu 1997

Methods	Randomized (using block randomization), parallel, open trial Followed up for 2 hours
Participants	80 children aged 6 to 60 months, axillary temperature 38.5 to 40 °C with urinary tract infection and/or malaria Exclusion criteria: received antipyretic 2 hours prior to study entry; requiring admission; urgent investigation; or emergency treatment
Interventions	Paracetamol: 15mg/kg given as single dose Sponging: from head to toe (except scalp) until temperature is <38 °C, using tepid water (temperature range 28 to 34 °C) at ambient temperature 21 to 32 °C
Outcomes	Mean temperature over time Mean fall in temperature by group Proportion of children whose temperature fell to <38.5 °C at different time intervals
Notes	Study location: Malawi A thin layer of water left on the body of the children receiving tepid sponging until temperature fell below 38.5 °Cs C No losses to follow up or withdrawals recorded

Aksoylar 1997

Methods	Randomized (method not specified), open parallel trial. Followed up for 3 hours
Participants	224 children aged 6 months to 5 years, rectal temperature 39 °C, with viral and bacterial infections

Aksoylar 1997 *(Continued)*

	Exclusion criteria: received antipyretic 6 hours prior to study entry; allergy to study medications; renal, gastrointestinal, haematologic, cardiopulmonary, malignant, and central nervous system diseases; dehydration
Interventions	Paracetamol: 15mg/kg Ibuprofen: 8mg/kg Aspirin: 15mg/kg given as single dose Sponging: for 20 minutes with tepid water (feels neutral in temperature to a nurse's elbow)
Outcomes	Mean temperature over time Time of maximum fall in temperature Rate of fall of temperature Adverse events
Notes	Study location: Turkey 23 (10.3%) children withdrawn or lost to follow up

Brandts 1997

Methods	Randomized, from random numbers table; no blinding; 3/50 (6%) children withdrawn; no intention-to-treat analysis; allocation concealment unclear
Participants	50 children with uncomplicated *Plasmodium falciparum* (parasite density: 25,000 to 200,000/uL); aged 2 to 7 years Exclusion criteria: complicated malaria; haemoglobin <8.0 g/dL (PCV<24%); glucose <2.8 mmol/L; lactate >3.5 mmol/L; schizontaemia >50/uL; platelets <50,000/uL; pigment containing neutrophils >2%
Interventions	1. Mechanical antipyretic treatment (continuous electric fanning, tepid sponging, and cool blankets) plus paracetamol suppositories (50mg/kg/day at 10 to 15mg/kg 4 to 6 hourly); expelled suppositories replaced immediately 2. (Control): mechanical antipyretic therapy (as above) without paracetamol Similar antimalarials in both groups: intravenous quinine 15mg/kg 12 hourly x 4 days; then oral quinine 15mg/kg 12 hourly x 3 days
Outcomes	Fever clearance time Parasite clearance time Cure rate Tumour necrosis factor (TNF) PHA-TNF Interleukin-6 (IL-6), (PHA-IL6), and oxygen radicals
Notes	Study location: Gabon 3 (6.0%) children withdrawn or lost to follow up

Brewer 1968

Methods	Randomized (using random code), parallel, placebo (double blind) controlled trial Followed up for 3 hours
Participants	223 children aged <14 years, rectal temperature >38.3 °C (101 °F), with viral and bacterial infection Exclusion criteria: vomiting
Interventions	Paracetamol: 3mg/kg Indomethacin: 1mg/kg; placebo; given as single dose
Outcomes	Mean changes in temperature over time Proportion of children showing specified temperature reduction Proportion and mean temperature reduction in those with temperature >39.4 °C (103 °F) Adverse events
Notes	Study location: USA No losses to follow up or withdrawals recorded

Doran 1989

Methods	Randomized (using table of random numbers), parallel, double blind, placebo controlled study Followed up for 6 days
Participants	68 children aged 1 to 12 years with varicella exanthema Exclusion criteria: received any medication within 48 hours prior to study entry; history of seizure or other neurologic disorder; receiving long term medication; immunosuppressed
Interventions	Paracetamol: 10mg/kg Placebo Given as multiple dose at 4 hourly interval for 4 days
Outcomes	Time to total scabbing Itching on day 4 Activity score of the children on day 2 Time to last new vesicle Time to total healing
Notes	Study location: USA 6 (8.8%) children withdrawn or lost to follow up

Friedman 1990

Methods	Randomized (using table of random numbers), parallel, open trial Followed up for 1 hour
Participants	73 children aged 6 weeks to 4 years, rectal temperature 38.9 °C (102 °F), with viral and bacterial infection Exclusion criteria: received antipyretic 4 hours prior to study entry; and/or antibiotic in the past 72 hours; history of febrile convulsions; allergy to paracetamol
Interventions	Paracetamol: 10 to 15 mg/kg as single dose Sponging: with tepid water of about 37.8 °C (100 °F) for 20 minutes Paracetamol and tepid sponging
Outcomes	Mean temperature over time
Notes	Study location: USA No losses to follow up or withdrawals recorded

Kauffman 1992a

Methods	Randomized, double blind placebo controlled Follow up: antipyretic effect for 8 hours; adverse events for 24 hours
Participants	37 children aged 2 to 12 years with intercurrent febrile illness, oral temperature at ≥ 38.3 °C at least one hour before enrollment
Interventions	Paracetamol: 10mg/kg Ibuprofen: 7.5 or 10mg/kg; placebo
Outcomes	Percentage decrease in temperature from baseline Area under the curve of percentage decrease in temperature against time Treatment failures and adverse events
Notes	Study location: USA Treatment failures were treated with 10mg/kg of paracetamol regardless of original treatment group

Kinmonth 1992

Methods	Randomized (method not stated), parallel, open trial Followed up for 4 hours
Participants	52 children aged 3 months to 5 years, axillary temperature 37.8 to 39.9 °C, with mainly viral infection Exclusion criteria: received antipyretic 4 hours prior to study entry; temperature >40 °C; serious concomitant disease; history of febrile convulsions; contraindication to paracetamol

Kinmonth 1992 *(Continued)*

Interventions	Paracetamol: 120mg for 1 year or less and 240mg for more than 1 year as single dose Unwrapping Sponging: with warm water (mean temperature 37.1 °C) Paracetamol and warm sponging
Outcomes	Mean change in temperature over time Acceptability of treatment to child and parents Mean time of temperature below 37.2 °C
Notes	Study location: UK No losses to follow up or withdrawals recorded

Kramer 1991

Methods	Randomized (table of random numbers), parallel, double blind, placebo controlled Follow up: until fever free for at least 24 hours
Participants	304 children aged 6 months to 6 years, rectal temperature ≥ 38 °C with viral infection Exclusion criteria: onset >4 days; bacterial infection; history of convulsion; fever ≥ 41 °C
Interventions	Paracetamol: 10 to 15mg/kg given 4 hourly versus placebo
Outcomes	Mean duration of fever Mean duration of other symptoms Improvement in comfort/ behaviour
Notes	Study location: Canada 79 (26%) children randomized participants dropped

Steele 1970

Methods	Quasi-randomized (using serially numbered envelopes), parallel, placebo controlled, partially blinded (physical method arm not blinded) Followed up for 2 hours
Participants	130 children aged 6 months to 5 years, rectal temperature 39.4 °C or more, lasting more than 3 days, of viral and bacterial origin Exclusion criteria: received antipyretic 4 hours before study entry
Interventions	Paracetamol (alone or with sponging): 80mg, 160mg, 240mg, and 320mg for ages 6 to 18, 18 to 30, 30 to 48, and 48 to 60 months respectively

Steele 1970 *(Continued)*

	Mechanical: sponging with tepid water (excluding face and head); 2 other mechanical interventions: sponging with ice water or alcohol plus water were also applied
Outcomes	Percentage with temperature ≤ 38.3 °C at 1 and 2 hours; percentage with comfort rated as good, fair, or poor
Notes	Study location: Hawaii No losses to follow up or withdrawals recorded

Walson 1989

Methods	Randomized (using block randomization), parallel, double blind, placebo controlled trial Followed p for 8 hours
Participants	127 children aged 2 to 11 years, oral temperature 38.3 to 40 °C, (diagnosis not specified) Exclusion criteria: received antipyretic 8 hours before study entry; had prestudy salicylate or paracetamol of >50mg/L or >5mg/L respectively; hypersensitivity to medications; history of gastrointestinal tract, renal, liver, cardiopulmonary diseases; convulsive disorders; vomiting within 24 hours before study entry; dehydration
Interventions	Paracetamol:10mg/kg Ibuprofen: 5mg/kg and 10mg/kg; placebo; given as single dose.
Outcomes	Mean temperature over time Mean percent reduction in temperature Area under percent reduction-time curve Adverse events
Notes	Study location: USA 9 (7.1%) children withdrawn or lost to follow up Antibiotics allowed to participants that required them

Wilson 1991

Methods	Randomized (method not stated), parallel, modified double-blind, placebo controlled trial Followed up for 6 to 12 hours
Participants	178 children aged 3 months to 12 years, rectal temperature 38.3 to 40.5 °C, with clinically stable condition Exclusion criteria: received antipyretic 2 hours before study entry; or antibiotics 12 hours before study entry; history of febrile seizures within 6 months; cancer; hypersensitivity to study or related drugs; severe illness
Interventions	Paracetamol: 12.5mg/kg Ibuprofen: 5 and 10mg/kg

Wilson 1991 *(Continued)*

	Placebo: 0.5ml/kg (single dose)
Outcomes	Rate of temperature fall Time to maximum antipyresis Mean change in temperature over time Area under the curve of antipyresis Adverse events
Notes	Study location: USA No losses to follow up or withdrawals recorded

C: Centigrade; F: Fahrenheit; PCV: packed cell volume; PHA-IL6: phytohaemagglutinin-interleukin-6; PHA-TNF: phytohaemagglutinin-tumor necrosis factor.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adam 1994	Not a clinical trial; review (not systematic).
Amdekar 1985	Not compared with physical methods or placebo or no intervention.
Autret 1994	Not compared with physical methods or placebo or no intervention.
Autret 1997	Not compared with physical methods or placebo or no intervention.
Baker 1987	Not compared with physical methods or placebo or no intervention.
Brown 1992	No relevant outcome compared between paracetamol and placebo.
Carley 1999	Review article; not randomized controlled trial.
Catti 1990	No physical methods or placebo group.
Colgan 1957	Not compared with physical methods or placebo or no intervention.
Cullen 1989	Not compared with physical methods or placebo or no intervention.
D'Apuzzo 1992	Not compared with physical methods or placebo or no intervention.
Duhamel 1993	Not compared with physical methods or placebo or no intervention.
Eden 1967	Not compared with physical methods or placebo or no intervention.
Eskerud 1991	Not randomized controlled trial; a survey.
Fasan 1980	Not compared with physical methods or placebo or no intervention; drug combined with chloroquine.
Fruthaler 1964	Review article (not systematic); not a trial.
Fusi 1991	Paracetamol in both arms of trial.

Study	Reason for exclusion
Gianiorio 1993	Not compared with physical methods or placebo or no intervention.
Goyal 1998	Not compared with physical methods or placebo or no intervention.
Houry 1999	Not compared with physical methods or placebo or no intervention.
Ismail 1995	Not compared with physical methods or placebo or no intervention; adults included.
Joshi 1990	Not compared with physical methods or placebo or no intervention.
Keinanen 1977	Not compared with physical methods or placebo or no intervention; not randomized.
Krishna 1995a	Not compared with physical methods or placebo or no intervention; adults included.
Krishna 1995b	Not compared with physical methods or placebo or no intervention; adults included.
Lal 2000	Not compared with physical methods or placebo or no intervention.
Lesko 1995	Not compared with physical methods or placebo or no intervention.
Lesko 1997	Not compared with physical methods or placebo or no intervention.
Lewis 1988	Participants not febrile at onset; prophylactic use.
Mahar 1994	Not compared with placebo or no intervention; paracetamol in both arms of trial.
Maison 1998	Not randomized controlled trial.
McIntyre 1996	Not compared with physical methods or placebo or no intervention.
Moreno Martinez 1995	Not compared with physical methods or placebo or no intervention.
Nahata 1984	Not compared with physical methods or placebo or no intervention.
Newman 1985	Participants in the same arm of study received either aspirin or paracetamol; not analysed in sub-groups of types of drugs received.
Nwanyanwu 1999	Not compared with physical methods or placebo or no intervention.
Pasquale 1993	Not compared with physical methods or placebo or no intervention.
Polidori 1993	Not compared with physical methods or placebo or no intervention.
Purssell 2000	Review (not systematic); not a trial.
Schnaiderman 1993	No placebo or physical methods arm; paracetamol in both arms.
Sharber 1997	Paracetamol given to participants in both arms of trial.
Sheth 1980	Not compared with physical methods or placebo or no intervention.
Sidler 1990	Not compared with physical methods or placebo or no intervention.
Simila 1976	Not compared with physical methods or placebo or no intervention.

Study	Reason for exclusion
Steele 1972	Not compared with physical methods or placebo or no intervention.
Sugimura 1994	Not randomized controlled trial, not compared with physical methods or placebo.
Ugazio 1993	Not compared with physical methods or placebo or no intervention.
Uhari 1995	Paracetamol combined with another drug or placebo.
Ulukol 1999	Not compared with physical methods or placebo or no intervention.
Van Esch 1995	Not compared with physical methods or placebo or no intervention.
Vauzelle-Kervroedan	Not compared with physical methods or placebo or no intervention.
Vernon 1979	Not compared with physical methods or placebo or no intervention.
Walker 1993	Not compared with physical methods or placebo or no intervention.
Walson 1990	Not compared with physical methods or placebo or no intervention.
Walson 1992	Not compared with physical methods or placebo or no intervention.
Weippl 1985	Not compared with physical methods or placebo or no intervention.
Wessie 1987	Not compared with physical methods or placebo or no intervention.
Wilson 2000	Paracetamol used in both arms of trial.
Yaffe 1981	Review (not systematic); not a trial.

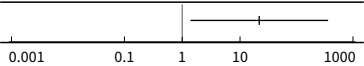
DATA AND ANALYSES

Comparison 1. Paracetamol compared to a placebo

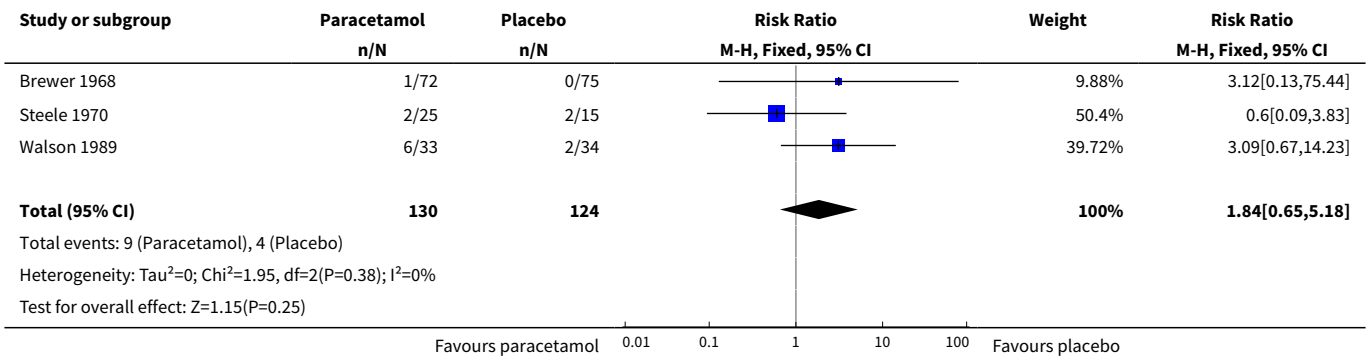
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Without fever by 2nd hour	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse events	3	254	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.65, 5.18]

Analysis 1.1. Comparison 1 Paracetamol compared to a placebo, Outcome 1 Without fever by 2nd hour.

Study or subgroup	Paracetamol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Steele 1970	17/25	0/15		21.54[1.39,333.99]



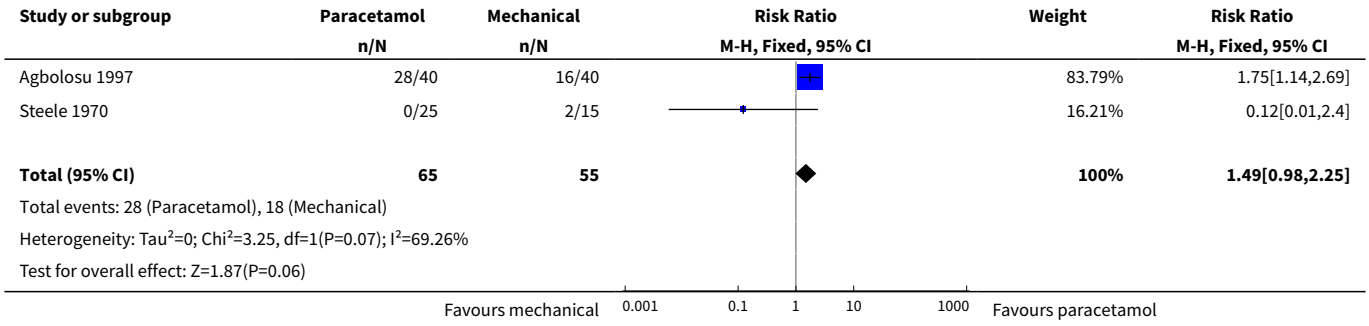
Analysis 1.2. Comparison 1 Paracetamol compared to a placebo, Outcome 2 Adverse events.



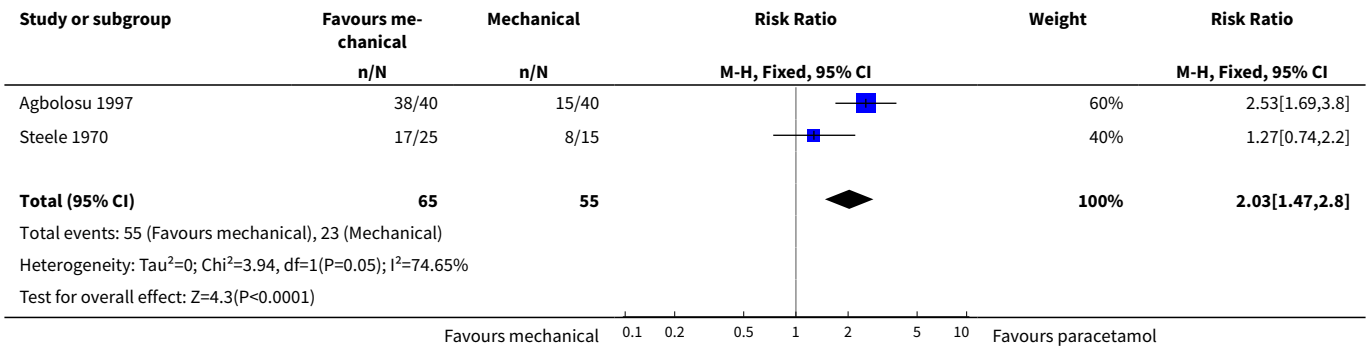
Comparison 2. Paracetamol compared to physical cooling methods

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Without fever by 1st hour	2	120	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.98, 2.25]
2 Without fever by 2nd hour	2	120	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.47, 2.80]
3 Adverse events	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.07, 1.01]

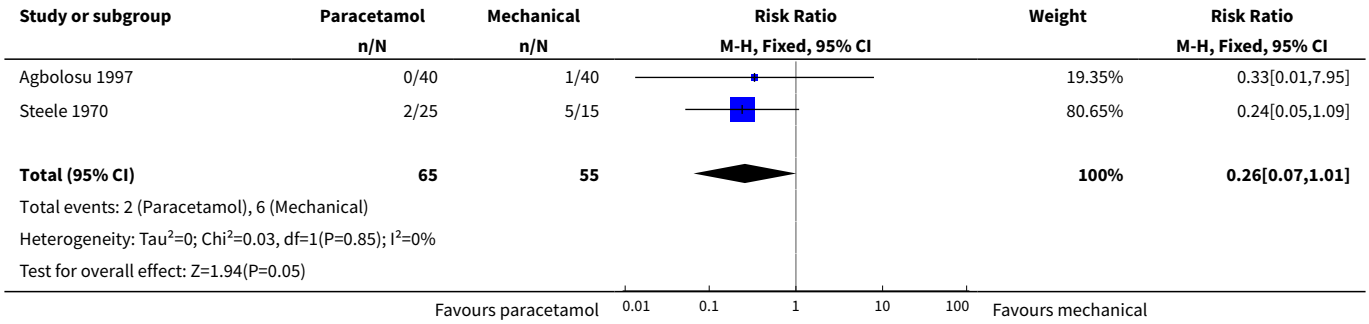
Analysis 2.1. Comparison 2 Paracetamol compared to physical cooling methods, Outcome 1 Without fever by 1st hour.



Analysis 2.2. Comparison 2 Paracetamol compared to physical cooling methods, Outcome 2 Without fever by 2nd hour.



Analysis 2.3. Comparison 2 Paracetamol compared to physical cooling methods, Outcome 3 Adverse events.



APPENDICES

Appendix 1. Paracetamol compared to placebo

Trial	Outcome compared	Paracetamol (result)	Placebo (result)	Summary of effects	Source of data
Kramer 1991	Fever clearance time (mean duration of fever)	34.7 hours	36.1 hours	No statistically significant difference.	Figure/Text
Kramer 1991	Mean duration of other symptoms	72.9 hours	71.7 hours	No statistically significant difference.	Figure/Text
Walson 1989	Mean percentage reduction in temperature at 1 hour, 2 hours, and 4 hours respectively	34.2%, 57.5%, 59.0% respectively	6.2%, 15.0%, 21.3% respectively	Statistically significant difference in all cases.	Tables/Text
Wilson 1991	Mean (standard deviation) percentage efficacy at maximal effect	76.80 (44.92%)	14.88 (54.44%)	Statistically significantly different.	Table

(Continued)

Kauffman 1992a	Adverse events	None observed	None observed	No statistically significant difference.	Text
Kauffman 1992a	Mean temperature at 3 to 5 hours post-treatment	Approximately 37.7 to 38.0 °C	Approximately 39.1 to 39.3 °C	Statistically significantly lower in paracetamol group.	Table/Text
Doran 1989	Mean (standard deviation) time to total healing of children with chicken pox	16.20 (5.80) days	16.10 (5.60) days	No statistically significant difference.	Table
Doran 1989	Mean (standard deviation) activity score on day 2	3.13 (0.23)	2.82 (0.24)	Statistically significantly better in paracetamol group.	Text

Appendix 2. Paracetamol compared to physical methods

Trial	Outcome measure	Paracetamol (Result)	Mechanical (Result)	Summary of effects	Source of data
Aksoylar 1997	Mean drop in temperature at 30 minutes	0.3 °C	0.7 °C	p<0.001	Graph/Text
Aksoylar 1997	Mean drop in temperature at 2 hours	0.6 °C	1.3 °C	p<0.001	Graph/Text
Brandts 1997	Fever clearance time	32 hours	43 hours	No statistically significant difference	Text
Friedman 1990	Mean drop in temperature at 30 minutes	0.9 °F	0.5 °F	No statistically significant difference	Table
Friedman 1990	Mean drop in temperature at 60 minutes	1.7 °F	1.0 °F	p=0.03	Table
Kinmonth 1992	Time below 37.2 °C (period of antipyresis)	129 minutes	54 minutes	Paracetamol had longer period of antipyresis	Table
Kinmonth 1992	Intervention well tolerated by child	8 (n=26)	12 (n=26)	Risk ratio 0.67; 95% confidence interval 0.33 to 1.36	Table/Text (reanalysis with Metaview)
Agbolosu 1997	Number with febrile seizure	0 (n=40)	1 (n=40)	Risk ratio 0.33; 95% confidence interval 0.01 to 7.95; fixed effect model	Table (reanalysis with Metaview)

WHAT'S NEW

Date	Event	Description
18 February 2009	Amended	Title changed from *Paracetamol for treating fever in children* to *Paracetamol versus placebo or physical methods for treating fever in children*, in order to reflect the content of the review.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 2, 2002

Date	Event	Description
1 October 2008	Amended	Converted to new review format with minor editing (risk ratio used for all dichotomous outcomes).
21 May 2004	Amended	New studies found but not yet included or excluded.

CONTRIBUTIONS OF AUTHORS

Both reviewers prepared the protocol, selected trials, and extracted data. Martin Meremikwu performed data analysis and wrote the full review. Angela Oyo-Ita checked it for accuracy and provided advice.

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (eg, employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- University of Calabar, Calabar, Nigeria.

External sources

- Cochrane Child Health Field, Canada.
- Effective Health Care Alliance Programme, funded by the Department for International Development (DFID), UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [*therapeutic use]; Analgesics, Non-Narcotic [*therapeutic use]; Fever [*drug therapy]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant