

# Antipyretic measures for treating fever in malaria (Review)

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[Intervention Review]

# Antipyretic measures for treating fever in malaria

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## ABSTRACT

### Background

Fever control measures are commonly used in treating malaria. Some researchers have suggested that fever reduction may prolong malaria illness.

### Objectives

We aim to assess whether antipyretic measures in malaria influences outcome, measured by length of illness, parasitaemia, and occurrence of convulsions.

### Search strategy

We searched the Cochrane Infectious Diseases Group Trial Register (December 2002), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 4, 2002), MEDLINE (1966 to December 2002); EMBASE (1980 to December 2002), LILACS (December 2002). We contacted researchers and organisations working in the field.

### Selection criteria

Randomised or pseudo-randomised trials which compared antipyretic drugs with mechanical or no antipyretic measures in patients with slide-confirmed malaria.

### Data collection and analysis

Inclusion criteria were independently applied by two reviewers. We extracted data from selected trials using a standard form. Mean difference with 95% confidence interval was calculated for continuous data.

### Main results

Three randomised trials with pooled 128 adults and children with falciparum malaria; all unblinded; allocation concealment unclear in two. Inconsistent pattern of fever clearance between trials, but malaria cure rate reported to be similar between intervention and control in all trials. Mean parasite clearance time reported to be similar in one trial but longer in paracetamol group in two trials: sample size in one trial was too small to conclude anything (n=7), while the other trial was difficult to evaluate.

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## Authors' conclusions

There is insufficient data to confirm or refute an impact of antipyretic measures on parasitaemia or malarial illness.

## PLAIN LANGUAGE SUMMARY

### Antipyretic measures for treating fever in malaria

Plain language summary pending.

## BACKGROUND

Malaria is a major cause of morbidity in the tropics, and causes an estimated one million deaths every year (WHO 1997). Fever is the commonest symptom of malaria and is often associated with malaise, vomiting and, in children, febrile convulsions. Measures to treat fever include sponging with tepid water, or fanning, and these are thought to make the patients feel better and prevent febrile convulsion (Millichap 1960).

Some authorities are raising questions over the value of these traditional practices for fever in children (Kramer 1991), and in malaria in particular (Brandts 1997). A recent study of African children showed that 54% of febrile convulsions occurred at rectal temperature below 38 degrees centigrade (Waruiru 1996), raising questions over the potential benefit of fever control in preventing malaria-related convulsions.

There are also indications that fever and cytokines associated with it are beneficial. Some animal studies have shown that cytokines have specific anti-infective actions and tend to enhance the chance of survival (Hanson 1983, Bernheim 1976). More recently a study in people with malaria concluded that paracetamol prolonged malaria parasitaemia (Brandts 1997).

Despite widespread use of paracetamol in fever management and the prevailing controversies over its safety and effectiveness, we found no systematic review on the subject (Hayward 1999). As a follow-up to this observation and recently reported controversies over its effects in treatment of malaria, we undertook a systematic review to test the null hypothesis that paracetamol and other fever control measures do not prolong malaria illness. We aim to explore the topic of the benefits and harms of fever control in children at a later date.

## OBJECTIVES

Antipyretic measures for treating fever in malaria (Review)

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To assess the effects of antipyretic measures in malaria on length of fever, parasitaemia, occurrence of convulsions or other adverse effects.

## Hypotheses

1. Antipyretic drugs prolong the duration of malaria illness.
2. Antipyretic drugs prolong malaria parasitaemia.
3. Antipyretic drugs increase the risk of convulsion.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised and quasi-randomised controlled trials.

#### Types of participants

Children or adults with malarial illness confirmed by malaria blood slides.

#### Types of interventions

1. Antipyretic drugs (aspirin, paracetamol).
2. Mechanical methods such as tepid sponging or fanning.

## Types of outcome measures

### Primary outcomes

- Fever clearance time (time between onset of treatment and return of temperature to normal).
- Parasite clearance time.
- Occurrence of convulsions.

### Other outcomes

#### Clinical

- Proportion still feverish six and twelve hours after treatment started.
- Mean drop in temperature within first 6 hours of starting treatment.
- Vomiting episodes after treatment

#### Parasitic

- Parasite clearance time (time between onset of treatment and clearance of malaria parasites from peripheral blood film).
- Presence of parasites at 3, 7 and 14 days after treatment started.
- Cure rate (percentage of patients without symptoms and parasitaemia by day 14).

## Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

We used the following search terms for all trial registers and databases: pyrexia, fever, antipyretic and malaria

We searched the Cochrane Infectious Diseases Group specialized trials register for relevant trials up to December 2002. Full details of the Cochrane Infectious Diseases Group 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, published in *The Cochrane Library* (Issue 4, 2002). This contains mainly reference information to randomized controlled trials and controlled clinical trials in health care.

We searched the following electronic databases using the search terms in combination with the search strategy developed by the Cochrane Collaboration and detailed in appendix 5c of the Cochrane Reviewers' Handbook (Clarke 2002): MEDLINE

(1966 to December 2002); African Index Medicus (1998); EMBASE (1980 to December 2002); LILACS (La Literatura Latinoamericana y del Caribe de Informacion en Ciencias de Salud) www.bireme.br; accessed December 2002; and Science Citation Index (1981 to December 2002).

We also checked the reference lists of all trials identified by the above methods.

We contacted researchers and organisations working in the field for information on unpublished and ongoing trials.

## Data collection and analysis

Two reviewers (MM, KL) applied the inclusion criteria to all potential trials. Where there was any doubt, the third reviewer (PG) was consulted.

We extracted data using a standard form. We wrote to authors for additional data where required.

We assessed the study quality using the standard methods of the Cochrane Infectious Diseases Group (see editorial group details).

## Anticipated comparisons

- Antipyretic drugs (aspirin, paracetamol) compared with no intervention.
- Mechanical methods (tepid sponging, fanning). compared with no intervention.
- Antipyretic drugs compared with mechanical method.
- Potential sources of heterogeneity were the method of reducing fever, and whether study participants were adults or children.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

Fifteen clinical studies were identified, 11 were excluded and one is awaiting assessment. The main reasons for exclusion were lack of controls (see '[Characteristics of excluded studies](#)'). Some trials included antipyretic drugs on both arms of the trials. As the inclusion criteria specified malarial illness, two trials were excluded because they included only non-malarial cases while one which included a greater proportion non-malarial cases was also excluded. Only one study (Brandts 1997) included children of an age susceptible to febrile convulsion.

Three trials met the criteria for inclusion (see '[Characteristics of included studies](#)'). There were a total of 168 participants in the

three trials but only 128 were eligible for inclusion in meta-analysis; 33 and 7 were excluded from Hemmer 1991 and Krishna 1995a respectively.

Brandts 1997 compared a combination of mechanical methods (fanning and sponging) and rectal paracetamol with mechanical methods alone in 50 slide-confirmed cases of uncomplicated falciparum malaria (aged 2-7 years) in Gabon. Three were withdrawn. Hemmer 1991 in Germany, studied three groups with malaria who either received a) intravenous acetylsalicylic acid (aspirin; n=31); b) intravenous heparin (n=33) or; c) neither of these drugs (n=33). All had confirmed falciparum malaria (19 were complicated), and were aged > 14 years. The heparin group was excluded from this review leaving a total of 64 participants in the aspirin (n=31) and control (n=33) groups.

Krishna 1995a in Thailand studied a total of 21 adult cases of uncomplicated falciparum malaria in three groups of 7 each but only two groups were analysed for this review. The group which received quinine followed by paracetamol after 2 hours was excluded from the review, while the group that received paracetamol followed by quinine and the control group (which had no antipyretic) were included. The group that received delayed paracetamol was excluded from data synthesis because most participants (3/7; 42.9%) were withdrawn. The data provided by Krishna 1995a which were suitable for meta-analysis were temperature changes within first 6 hours, fever clearance time (FCT) and parasite clearance time (PCT).

Other trials did not fully report their data in a form that could be used in meta-analysis, with no statistical measure of variance for FCT or PCT provided in either Brandts 1997, or Hemmer 1991. Where information for inclusion in meta-analysis was not available, the results have been summarised in "other data" table.

### Risk of bias in included studies

All trials were described as randomised. Allocation concealment was adequate in Hemmer 1991, unclear in Brandts 1997 and Krishna 1995a was an open trial. The method of generating the numbers was specified in one (Brandts 1997), the other two were unclear.

Reported losses to follow-up or withdrawal were 0% (Hemmer 1991), 6% (Brandts 1997). Krishna 1995a was a small study, with high level of attrition (24%). Small sample size and high attrition rate recorded by Krishna 1995a grossly limits the power of the trial and reliability of meta-analysis.

All the trials were unblinded. None of the trials used an intention to treat analysis.

### Effects of interventions

#### Fever clearance time

Fever clearance time was reported in two studies, but the results showed no consistent pattern. In Brandts 1997, mean fever clearance time was shorter in the paracetamol group, and reported as not significant. In Krishna 1995a, fever clearance time was longer in the paracetamol group, but the difference was not significant (60 vs 44 hrs; mean difference (MD) 16.0, 95% confidence interval (CI) -24.10 to 56.10). Hemmer 1991 reported that the FCT was not significantly different between the aspirin group and control.

Krishna 1995a reported the mean fall in temperature within 6 hours of treatment. The average fall was greater in the paracetamol group, but again this was not significant (MD 1.20 °C, 95% CI 0.20 to 2.20).

#### Parasite clearance time

Brandts 1997 reported a longer parasite clearance time (PCT) in the paracetamol group than mechanical group (75 hours versus 59 hours); they reported this as significant, but the method of analysis is not given (difference=16 hours, 95% CI 8 to 24); as data on variance in the two arms were not given, we could not repeat this analysis.

Hemmer 1991 provided no data but reported that PCT did not differ between the aspirin group and controls.

In Krishna 1995a, parasite clearance time was longer in the paracetamol group than the controls (72 vs 53 hr; MD 19.00, 95% CI 1.38 to 36.62).

#### Antimalarial cure rate

The three trials reported that cure rates were not different between paracetamol or aspirin groups and controls. None supplied data.

#### Alleviation of other symptoms

One trial reported that paracetamol alleviated headache but gave no data or comparative analysis (Krishna 1995a). Nausea, vomiting and myalgia which were also monitored half-hourly by Krishna 1995a did not differ between the study groups.

#### Adverse events

No severe adverse events were reported.

#### Cytokines

Although cytokines was not specified in the review protocol, two of the reviewed trials provided information on cytokines and we have summarised this data. Cytokines are chemical substances produced by leucocytes in the process of combating disease; tumour necrosis factor (TNF) and interleukins (IL) are common types.

Brandts 1997 and Hemmer 1991 reported that TNF did not differ significantly between paracetamol or aspirin groups and controls. Brandts 1997 however, reported that phytohaemagglutinin induced TNF was significantly lower in the paracetamol group on day 1 but not on days 0, 2 and 4. Interleukin-6 did not differ between the paracetamol and mechanical groups (Brandts 1997). Other outcomes prespecified in the original protocol included convulsions and vomiting. These were not reported on in any of the studies.

## DISCUSSION

The major objective of this review was to ascertain from reliable research whether antipyretic measures impact on the treatment of malaria. Biological theory led researchers to ask if fever control could prolong parasitaemia and do harm in patients with malaria.

The review identified only three trials related to fever control in malaria. These trials were small and therefore lack statistical power to draw reliable conclusions. This also limits their ability to detect impact on substantive outcomes. For example, no febrile convulsions were recorded in the studies. In addition, most of the study participants were outside the age range during which febrile convulsion is common, indicating that we have no evidence for or against a protective effect on this outcome.

The studies reported no adverse effects of anti-pyretic drugs on clinical outcomes (malaria fever). Two studies showed a tendency for parasite clearance time to be longer in patients treated with paracetamol (Brandts 1997, Krishna 1995a). The trials were not blinded and did not appear to have adequately concealed allocation. Health staff are likely to influence treatment, and there is the potential for bias in the results (Schulz 1995). In addition, data provided in one trial (Brandts 1997) were not complete to allow us to statistically re-evaluate the evidence while the sample size of the second trial (Krishna 1995a) was too small (n=7). The small

size of these trials and the risk of bias within them make it difficult to draw a reliable conclusion.

## AUTHORS' CONCLUSIONS

### Implications for practice

Fever management in malaria remains a common practice in both mild and severe disease. There is currently insufficient evidence to recommend a change in the practice.

### Implications for research

There are some data which suggest that antipyretic drugs prolong malaria parasitaemia, but additional research evidence will be needed to draw a reliable conclusion. The effects of fever control methods in general on clinical outcomes (especially convulsions in children) need to be evaluated by a systematic review as a prelude to further research on fever control. We have started this protocol. In the light of summaries around benefits and harms of fever reduction in all febrile illnesses, researchers can make more informed decisions about whether to conduct trials around fever control confined only to malaria.

An alternative approach to a trial confined to malaria is to examine fever control in all patients with fever living in a malarious area regardless of the aetiology and explore malaria infection as a potential source of heterogeneity in the effect estimates.

## ACKNOWLEDGEMENTS

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Brandts CH, Ndjave M, Graninger W, Kremsner PG. Effects of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. *Lancet* 1997;**350**:704–709.

#### Hemmer 1991 *{published data only}*

Hemmer CJ, Kern P, Holst FG, Nawroth PP, Dietrich M. Neither heparin nor acetylsalicylic acid influence the clinical course in human *Plasmodium falciparum* malaria: a prospective randomised study. *Am J Trop Med Hyg* 1991;**45**:608–612.

#### Krishna 1995a *{published data only}*

Krishna S, Supanaranond W, Pukrittayakamee S, et al. Fever in uncomplicated *Plasmodium falciparum* infection: effects of quinine and paracetamol. *Trans R Soc Trop Med Hyg* 1995;**89**:197–199.

### References to studies excluded from this review

#### Agbolosu 1997 *{published data only}*

Agbolosu NB, Cuevas LE, Milligan P, Broadhead RL, Brewster D, Graham SM. Efficacy of tepid sponging versus paracetamol in reducing temperature in febrile children. *Ann Trop Paediatr* 1997;**17**:283–288.

**Fasan 1980** *{published data only}*

Fasan PO, Mabadeje AFB. A controlled trial of a combination of Chloroquine with Paracetamol in the treatment of acute malaria in a semi-immune population. *J Trop Med Hyg* 1980;**83**:191–193.

**Ismail 1995** *{published data only}*

Ismail S, Na Bangchang K, Karbwang J, Back DJ, Edwards G. Paracetamol disposition in Thai patients during and after treatment of falciparum malaria. *Eur J Clin Pharmacol* 1995;**48**:65–69.

**Kramer 1991** *{published data only}*

Kramer MS, Naimark LE, Roberts-Brauer R, McDougall A, Leduc DG. Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin. *Lancet* 1991;**337**:591–594.

**Krishna 1995b** *{published data only}*

Krishna S, Pukrittayakamee S, Supanaranond W, et al. Fever in uncomplicated Plasmodium falciparum malaria: randomized double-blind comparison of ibuprofen and paracetamol treatment. *Trans R Soc Trop Med Hyg* 1995;**89**:507–509.

**Mahar 1994** *{published data only}*

Mahar, et al. Tepid sponging to reduce temperature in febrile children in a tropical climate. *Clin Pediatr* 1994;**33**:227–231.

**Newman 1985** *{published data only}*

Newman J. Evaluation of sponging to reduce body temperature in febrile children. *Can Med Assoc J* 1985;**132**:641–642.

**Nwanyanwu 1999** *{published data only}*

Nwanyanwu OC, Ziba C, Kazembe PN. Paracetamol and ibuprofen for treatment of fever in Malawian children aged less than five years. *Trans R Soc Trop Med Hyg* 1999;**93**:84.

**Sharber 1997** *{published data only}*

Sharber J. The efficacy of tepid sponge bathing to reduce fever in young children. *Am J Emerg Med* 1997;**15**:188–192.

**Steel 1970** *{published data only}*

Steel RW, Tanaka PT, Lara RP, Bass JW. Evaluation of sponging and oral antipyretic therapy to reduce fever. *J Pediatr* 1970;**77**:824–829.

**Walker 1993** *{published data only}*

Walker O, Salako LA, Sowumi A, Olupitan SB, Oyewo EA. Parenteral piroxicam in the management of fever, arthralgia and musculoskeletal conditions of acute malaria: an open randomised comparison with oral acetylsalicylic acid and paracetamol. *Nig Med Pract* 1993;**25**:39–42.

## References to studies awaiting assessment

**Aksoylar 1997** *{published data only}*

Aksoylar S, et al. Evaluation of sponging and antipyretic medication to reduce body temperature in febrile children. *Acta Paediatr Japonica* 1997;**39**:215–217.

**Lell 2001** *{published data only}*

Lell B, Sovric M, Schmid D, Luckner D, Herbich K, Long HY, et al. Effect of antipyretic drugs in children with malaria. *Clinical Infectious Diseases* 2001;**32**(5):838–41.

**Tarimo 2002** *{published data only}*

Tarimo DS, Minjas JN, Bygberg IC. Sulfadoxine-pyrimethamine monotherapy in Tanzanian children gives rapid parasite clearance but slower fever clearance that is improved by chloroquine in combination therapy. *Tropical Medicine & International Health* 2002;**7**(7):592–8.

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Bernheim HA, Kluger MJ. Effects of drug-induced antipyresis on survival. *Science* 1976;**193**:237–239.

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**Hanson 1983**

Hanson DF, Murphy PA, Silicano R, Shin HS. The effects of temperature on the activation of thymocytes by interleukins I and II. *J Immunol* 1983;**130**:216–221.

**Hayward 1999**

Hayward J, Veale B. Paracetamol for fever in children: high time for systematic reviews of the evidence. *Australian Family Physician* 1999;**28**:105.

**Millichap 1960**

Millichap JG. A critical evaluation of therapy of febrile seizures. *J Pediatr* 1960;**56**:364–368.

**Schulz 1995**

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

**Waruiru 1996**

Waruiru CM, Newton CR, Foster D, et al. Epileptic seizures and malaria in Kenyan children. *Trans R Soc Trop Med Hyg* 1996;**90**:152–155.

**WHO 1997**

World Health Organization. World malaria situation in 1994. *Wkly Epid Rec* 1997;**72**:269–274.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Brandts 1997

Methods	Randomised from random numbers table, unblinded 3/50 (6%) withdrawn No intention to treat analysis Allocation concealment unclear
Participants	50 children with uncomplicated <i>Plasmodium falciparum</i> (parasite density: 25,000 to 200,000/ $\mu$ L) Aged 2-7 years Gabon, West Africa Exclusion criteria: complicated malaria, Hb < 8.0 g/dL (PCV < 24%), glucose < 2.8 mmol/L, lactate > 3.5 mmol/L, schizontaemia > 50/ $\mu$ L, platelets < 50,000/ $\mu$ L, pigment-containing neutrophils > 2%
Interventions	A: mechanical antipyretic treatment (continuous electric fanning, tepid sponging and cool blankets) plus paracetamol suppositories (50 mg/kg/day at 10 to 15 mg/kg, 4 to 6 hourly); expelled suppositories replaced immediately B (Control): mechanical antipyretic therapy (as above) without paracetamol Similar antimalarials in both groups: intravenous quinine 15 mg/kg, 12 hourly for 4 days; then oral quinine at 15 mg/kg, 12 hourly, for 3 days
Outcomes	1. Fever clearance time (FCT) 2. Parasite clearance time (PCT) 3. Cure rate 4. Tumour necrosis factor (TNF) 5. Phytohaemagglutinin-induced TNF (PHA-TNF) 6. Interleukin-6 (IL-6) 7. IL-6 (phytohaemagglutinin-induced IL-6 (PHA-IL6)) 8. Oxygen radicals
Notes	-

#### Hemmer 1991

Methods	Randomised, unblinded, method of randomisation not specified, separate randomization for complicated and uncomplicated Allocation adequately concealed in sealed envelopes by another department None lost to follow-up No intention to treat analysis
Participants	64 patients were included in the meta-analysis out of 97 patients, aged > 14 years Heparin group excluded All were treated in Hamburg, Germany (18 African, 79 European) All had history of fever (1-30 days) 78 were uncomplicated 19 complicated (impaired cerebral function = 14; clotting disorder = 4; impaired renal function = 4; others = 3)

**Hemmer 1991** (Continued)

Interventions	Antipyretics: Control: No antipyretic Intervention 1: Intravenous (IV) acetylsalicylic acid (ASA: 500 mg; days 0, 2, 4) Intervention 2: subcutaneous heparin 70 units/kg, 3/day for 5 days, with no ASA Anti-malarials: Uncomplicated: randomised to oral quinine (20-25 mg/kg/day) plus doxycycline (100mg/day) or mefloquine 20mg/kg in 3 doses, 6 hours apart Complicated: standard therapy with intravenous quinine
Outcomes	1. Fever clearance time (FCT) 2. Parasite clearance time 3. Length of hospital stay 4. Platelets 5. Prothrombin time (PT) 6. Partial thromboplastin time (PTT) 7. Fibrinogen levels 8. Tumour necrosis factor-alpha (TNFa) levels
Notes	-

**Krishna 1995a**

Methods	Randomised, unblinded, method of randomisation not stated Concealment of allocation unclear Losses to follow-up not clearly stated but calculated to be 5 (23.8%), since final report of FCT and PCT indicated that n=16 out of 21 No intention to treat analysis
Participants	14 patients were included out of 21 adults (7 per group) All had uncomplicated falciparum malaria Kanchanaburi, Thailand Oral temperature > 38 °C Range of parasitaemia: 1130 to 24,9600/μL Exclusion criteria: age < 14 years, pregnancy, paracetamol taken < 6 hours before
Interventions	Group A: Quinine (10 mg/kg, oral) followed 2 hours later by paracetamol (15 mg/kg, oral) Group B: Paracetamol (15 mg/kg) followed 2 hours later by quinine (10 mg/kg) Group C: Quinine (10 mg/kg) with no paracetamol Group A was excluded from review
Outcomes	1. Mean maximal fall in temp in 6 hours 2. Time taken for temp to drop to < 38 °C 3. Fever clearance time (FCT) 4. Parasite clearance time (PCT) 5. Cure rate 6. Blood levels of paracetamol

**Krishna 1995a** (Continued)

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

Agbolosu 1997	Randomised trial of paracetamol vs tepid sponging but participant but 56.2% of participants did not have malaria
Fasan 1980	Clinical trial of combination of paracetamol and chloroquine; included no placebo or mechanical antipyretic group
Ismail 1995	Randomised trial of paracetamol in regimens of artemisinin derivatives; did not compare paracetamol with placebo or mechanical antipyretic group
Kramer 1991	Randomised, placebo-controlled trial of febrile children but participants did not have malaria
Krishna 1995b	Randomised trial but compared two antipyretic drugs; no placebo or mechanical antipyretic group
Mahar 1994	Open randomised comparison of paracetamol and tepid sponging; participants had fever of presumed viral origin and not malaria
Newman 1985	Not confirmed malaria patients
Nwanyanwu 1999	Mechanical measure or non-treated controls not included
Sharber 1997	Randomised trial but both arms received paracetamol alone or with tepid sponging
Steel 1970	Not confirmed malaria patients
Walker 1993	Clinical trial of antipyretic drugs in malaria patients but does not include a placebo or mechanical antipyretic group

**Characteristics of studies awaiting assessment** [ordered by study ID]**Aksoylar 1997**

Methods	-
Participants	-
Interventions	-

**Aksoylar 1997** (Continued)

Outcomes	-
Notes	-

**Lell 2001**

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Tarimo 2002**

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

## DATA AND ANALYSES

### Comparison 1. Antipyretic drugs vs mechanical/no antipyretic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever clearance			Other data	No numeric data
2 Maximum temperature fall in 6 hrs	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Parasite clearance			Other data	No numeric data
4 Antimalarial cure rate			Other data	No numeric data
5 TNF Day 0 to 4			Other data	No numeric data
6 IL-6 Day 0 to 4			Other data	No numeric data
7 PHA-TNF day 0-4			Other data	No numeric data
8 PHA-IL-6			Other data	No numeric data
9 Length of hospital stay			Other data	No numeric data
10 Fever clearance time	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Parasite clearance time	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

#### Analysis 1.1. Comparison 1 Antipyretic drugs vs mechanical/no antipyretic, Outcome 1 Fever clearance.

##### Fever clearance

Brandts 1997	Fever clearance time (FCT) was 32 hr in paracetamol treated group and 43 hr in group that had only mechanical antipyretic treatment; difference 11 hour not statistically significant (95% CI -2 to 24).
Hemmer 1991	Fever clearance time = 96hr (range: 48-216 hr) in ASA group and 72 (range: 48-144) in controls; not statistically different.
Krishna 1995a	Fever clearance time = 60 (sd=44) hours in patients who had paracetamol at onset of treatment; 60 (sd=36) hours in those that paracetamol 2hrs after quinine and 44 (sd=24) hours in controls.

#### Analysis 1.2. Comparison 1 Antipyretic drugs vs mechanical/no antipyretic, Outcome 2 Maximum temperature fall in 6 hrs.

Review: Antipyretic measures for treating fever in malaria

Comparison: 1 Antipyretic drugs vs mechanical/no antipyretic

Outcome: 2 Maximum temperature fall in 6 hrs

Study or subgroup	Treatment		Control		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
Krishna 1995a	7	2.1 (0.79)	7	0.9 (1.1)		1.20 [ 0.20, 2.20 ]

-4 -2 0 2 4  
Favours Treatment Favours Control

**Analysis 1.3. Comparison 1 Antipyretic drugs vs mechanical/no antipyretic, Outcome 3 Parasite clearance.****Parasite clearance**

Brandts 1997	Parasite clearance time(PCT) = 75 hrs in paracetamol group and 59 hrs in mechanical antipyretic group (95% CI 8 to 24; p = 0.004).
Hemmer 1991	No significant difference between ASA group and control (actual data not provided).
Krishna 1995a	Parasite clearance time = 72 (sd = 17) hr in group given paracetamol at onset of treatment; 71 (sd=29) hr in those given paracetamol after 2hr; and 53 (sd=14) in controls.

**Analysis 1.4. Comparison 1 Antipyretic drugs vs mechanical/no antipyretic, Outcome 4 Antimalarial cure rate.****Antimalarial cure rate**

Brandts 1997	No treatment failure, difference in cure rate.
Hemmer 1991	No difference in cure rate.
Krishna 1995a	No treatment failure, no difference in cure rate.

**Analysis 1.5. Comparison 1 Antipyretic drugs vs mechanical/no antipyretic, Outcome 5 TNF Day 0 to 4.****TNF Day 0 to 4**

Brandts 1997	No significant difference blood levels of tumour necrosis factor on days 0,1, 2 and 4.
Hemmer 1991	TNF levels elevated before treatment (30.4pg/ml, range <15-896 pg/ml) but decreased during antimalarial therapy (p < 0.001). Levels did not differ between ASA and control group.

**Analysis 1.6. Comparison 1 Antipyretic drugs vs mechanical/no antipyretic, Outcome 6 IL-6 Day 0 to 4.****IL-6 Day 0 to 4**

Brandts 1997	Interleukin-6 (IL-6) did not differ significantly between paracetamol and mechanical antipyretic group on days 0, 1, 2 and 4.
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**Analysis 1.7. Comparison 1 Antipyretic drugs vs mechanical/no antipyretic, Outcome 7 PHA-TNF day 0-4.****PHA-TNF day 0-4**

Brandts 1997	Blood levels of phytohaemagglutinin-induced TNF was significantly lower in paracetamol group on day 1 but not different on days 0, 2 and 4.
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**Analysis I.8. Comparison I Antipyretic drugs vs mechanical/no antipyretic, Outcome 8 PHA-IL-6.**

**PHA-IL-6**

Brandts 1997	Levels of phytohaemagglutinin-induced interleukin-6 (PHA-IL6) did not differ between paracetamol and mechanical antipyretic groups on days 0, 1, 2 and 4.
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**Analysis I.9. Comparison I Antipyretic drugs vs mechanical/no antipyretic, Outcome 9 Length of hospital stay.**

**Length of hospital stay**

Hemmer 1991	Length of hospital stay was similar: 8 (4-27)days and 8 (4-31) in ASA and control groups respectively.
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**Analysis I.10. Comparison I Antipyretic drugs vs mechanical/no antipyretic, Outcome 10 Fever clearance time.**

Review: Antipyretic measures for treating fever in malaria

Comparison: I Antipyretic drugs vs mechanical/no antipyretic

Outcome: 10 Fever clearance time

Study or subgroup	Treatment		Control		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
Krishna 1995a	6	60 (44)	6	44 (24)		16.00 [ -24.10, 56.10 ]

**Analysis I.11. Comparison I Antipyretic drugs vs mechanical/no antipyretic, Outcome 11 Parasite clearance time.**

Review: Antipyretic measures for treating fever in malaria

Comparison: I Antipyretic drugs vs mechanical/no antipyretic

Outcome: 11 Parasite clearance time

Study or subgroup	Treatment		Control		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
Krishna 1995a	6	72 (17)	6	53 (14)		19.00 [ 1.38, 36.62 ]

## WHAT'S NEW

Last assessed as up-to-date: 15 January 2000.

29 July 2008	Amended	Converted to new review format with minor editing.
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## HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 2, 2000

30 October 2004	Amended	New studies found but not yet included or excluded.
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11 December 2002	Amended	Abstract and search strategy edited.
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## CONTRIBUTIONS OF AUTHORS

Paul Garner wrote the protocol, assisted with applying inclusion criteria, data interpretation and writing the review; Karl Logan and Martin Meremikwu conducted the data analysis and wrote the review.

Bernard Brabin and Bernard Coulter commented on the protocol; John Heyward and James Bunn commented on the final review.

## DECLARATIONS OF INTEREST

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

## SOURCES OF SUPPORT

### Internal sources

- Liverpool School of Tropical Medicine, UK.

## **External sources**

- Department for International Development, UK.
- European Commission (Development Directorate XII), Belgium.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Analgesics, Non-Narcotic [\*therapeutic use]; Fever [\*drug therapy; etiology]; Malaria [complications; \*drug therapy]

### **MeSH check words**

Humans