Artesunate versus quinine for treating severe malaria (Review)

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ABSTRACT

Background
Severe malaria kills over a million people every year. We sought evidence of superiority of artesunate compared with the standard treatment quinine.

Objectives
To compare artesunate with quinine for treating severe malaria.

Search strategy
We searched the Cochrane Infectious Diseases Group Specialized Register (January 2007), CENTRAL (*The Cochrane Library* 2006, Issue 4), MEDLINE (1966 to January 2007), EMBASE (1974 to January 2007), LILACS (1982 to January 2007), ISI Web of Science (1945 to January 2007), the *meta*Register of Controlled trials (*m*RCT), conference proceedings, and reference lists of articles. We contacted researchers and the World Health Organization.

Selection criteria
Randomized controlled trials comparing intravenous, intramuscular, or rectal artesunate with intravenous or intramuscular quinine for treating adults and children with severe malaria who are unable to take medication by mouth.

Data collection and analysis
Two authors assessed the eligibility and methodological quality of trials, extracted and analysed data, and drafted the review. The third author contributed to the design and writing of the review. Death was the primary outcome. Dichotomous outcomes were summarized using relative risks and continuous outcomes by mean differences. Where appropriate, we combined data in meta-analyses. Heterogeneity was investigated for the primary outcome using subgroup analyses.

Main results
Six trials enrolling 1938 participants (1664 adults and 274 children) met our inclusion criteria. All six trials were conducted in Asia, and only one small trial enrolled only children. Five trials used intravenous artesunate and one trial intramuscular artesunate; all six used intravenous quinine. Treatment with artesunate significantly reduced the risk of death (RR 0.62, 95% CI 0.51 to 0.75; 1938 participants, 6 trials), reduced parasite clearance time (WMD 8.14 h, 95% CI 11.55 to 4.73; 292 participants, 3 trials), and hypoglycaemia detected by routine monitoring (RR 0.46, 95% CI 0.25 to 0.87; 185 participants, 2 trials). There was no evidence of a difference in neurological sequelae, coma recovery time, time to hospital discharge, fever clearance time, or adverse effects other than hypoglycaemia.

Authors' conclusions
Intravenous artesunate is the drug of choice for adults with severe malaria, particularly if acquired in Asia. This review did not identify sufficient data to make firm conclusions about the treatment of children or the effectiveness of intramuscular artesunate. There is an urgent need to compare the effects of artesunate with quinine in African children with severe malaria. The applicability of these results to Asian children and the ethics of further research are points of debate.

PLAIN LANGUAGE SUMMARY

Artesunate reduces death from severe malaria in adults in Asia, but there is not enough evidence to say how effective artesunate is in children, people in Africa, or on potential adverse effects

Severe malaria kills over a million people every year. The annual death toll can be as high as one in a 100 children under the age of five. Severe malaria occurs when infection with the malaria parasite is complicated by serious failure of the body's major organs. Sometimes it is associated with coma (known as cerebral malaria). Following cerebral malaria a small proportion of children suffer with long-term neurological disability.

Quinine, the standard treatment for severe malaria, often causes adverse effects. In most people symptoms are mild; less common but more serious adverse effects include low blood sugar and heart rhythm disturbances. Regular glucose measurement and a heart trace are therefore advised when quinine is given by injection. Lack of resources may not permit this monitoring in some settings.

Artesunate is generally well tolerated, safe, and does not require any monitoring. Artesunate comes from a family of drugs known as the artemisinin derivatives. Another drug from this group, artemether, has shown no reduction in death compared to quinine. Artemether absorption is erratic and unreliable. By contrast, artesunate levels peak reliably and predictably within an hour.

The review of trials assessed the effectiveness of artesunate versus quinine. Six trials involving 1938 people (1664 adults and 274 children) were identified, all undertaken in Asia. Treatment with artesunate significantly reduced the risk of death. It also reduced the time taken to clear parasites from the blood and reduced the number of people with low blood sugar during follow up in trials where this was routinely measured. There was no evidence to say if the drug is effective in children in Africa, in whom most deaths from severe malaria occur.

BACKGROUND

Severe malaria kills over a million people every year with annual death rates of up to one in a 100 children under the age of five (WHO 2000; Trape 2001). A small proportion of children may also suffer from long-term neurological disability as a consequence of severe malaria.

Severe malaria occurs when infection with the *Plasmodium falciparum* parasite is complicated by serious organ failure or metabolic abnormalities (Gilles 2000); cerebral malaria, unrousable coma not attributable to any other cause, is a specific type of severe malaria (Gilles 2000) that even with correct treatment can have a mortality rate approaching 20% (Jaffar 1997). A small proportion of survivors of cerebral malaria are left with persistent neurological sequelae. Severe malaria occurs most commonly in those with limited immunity to malaria. In highly endemic areas, young children are therefore at most risk of severe disease and death, whereas in areas of lower endemicity and travellers, both adults and children get severe disease (White 2003).

The standard treatment for severe malaria is an intravenous infusion of quinine (WHO 2000). Quinine may also be administered as an intramuscular injection. A loading dose of 20 mg/kg is recommended to reduce the time needed to reach effective concentrations in the blood (White 1982). A Cochrane Review found a significant reduction in fever clearance time and parasite clearance time with a loading dose compared with no loading dose but concluded that data were insufficient to demonstrate an impact on risk of death (Lesi 2004).

Adverse effects resulting from quinine therapy are common. Cinchonism (symptoms of quinine overdose) often occurs at conventional dose regimens. This usually mild and reversible symptom complex consists of tinnitus, deafness, dizziness, and vomiting, and may affect adherence. Hypoglycaemia is a less common but more serious adverse effect (White 1983). Some people are allergic to quinine and develop skin rashes and oedema even with small doses. Toxic levels of quinine can occur following rapid intravenous administration and can result in heart rhythm disturbances, blindness, coma, and even death (Sweetman 2005); hence the recommendation for routine cardiac monitoring during parenteral treatment (BNF 2007). In some parts of the world, such as South-East Asia, there is limited evidence of declining efficacy to quinine in severe malaria (Wongsrichanalai 2002).

Artesunate and other artemisinin derivatives offer an alternative to quinine for severe malaria. Artemisinin derivatives are produced from the leaves of the plant *Artemesia annua* and are less stage specific than quinine, killing young ring forms before sequestration has occurred (ter Kuile 1993). Drugs from this group clear malaria parasites faster than other agents, cure infections with multi-drug resistant *P. falciparum,* and reduce gametocyte carriage, and thus potentially the transmission (spread) of malaria (Adjuik 2004). In contrast to quinine, administration of artemisinins does not require cardiac monitoring and therefore may be a more practical option in resource-poor settings. Trials examining whether the artemisinin derivative artemether is more effective than quinine have not shown a reduction in mortality (AQMSG 2001). However, artemether, an oil-based intramuscular formulation, is prone

to erratic and partial absorption (Karbwang 1997; Murphy 1997; Mithwani 2003). In contrast, artesunate may be given by intramuscular or intravenous injection with peak concentrations reliably achieved within one hour of administration (Nealon 2002; Hien 2004).

Artemisinins are widely reported to be safe (Sweetman 2005). Animal studies using very high doses of artemisinins have demonstrated focal brain stem lesions particularly affecting the auditory pathways (Brewer 1994; Nontprasert 1998; Genovese 2000; Nontprasert 2000; Nontprasert 2002). Many studies of brain stem function in humans, including audiometry, have failed to show any abnormality following repeated courses of artemisinins (Ribeiro 1998; Kissinger 2000). To date, only one nested case-control study has demonstrated a significant audiometric hearing loss in factory workers treated with artemether-lumefantrine for uncomplicated malaria compared with workers with no history of exposure to malaria infection or artemether-lumefantrine (Toovey 2004). This result needs to be interpreted with caution due to a number of design limitations.

A Cochrane Review prepared in year 2000 assessed the effects of the artemisinin derivatives, including artesunate, for treating severe malaria (McIntosh 2000). This review has since been superseded by a series of Cochrane Reviews examining the different artemisinin derivatives, and our review concerns trials in artesunate for severe malaria.

OBJECTIVES

To compare artesunate with quinine for treating severe malaria.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials.

Types of participants

Adults and children with severe malaria who are unable to take medication by mouth.

Types of intervention

Intervention
Intravenous, intramuscular, or rectal artesunate.

Control
Intravenous or intramuscular quinine.

Types of outcome measures

Primary
Death.

Secondary

- Neurological sequelae.
- Coma recovery time.
- Time to hospital discharge.
- Fever clearance time.
- Parasite clearance time.

Adverse effects

- Serious adverse effects resulting in discontinuation of treatment (eg biochemical abnormalities, cardiac effects).
- Hypoglycaemia (symptomatic or asymptomatic).
- Other adverse events, including tinnitus, hearing impairment, nausea, and vomiting.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Infectious Diseases Group methods used in reviews.

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

Databases
We searched the following databases using the search terms and strategy described in Table 01: Cochrane Infectious Diseases Group Specialized Register (January 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2006, Issue 4); MEDLINE (1966 to January 2007); EMBASE (1974 to January 2007); LILACS (1982 to January 2007); ISI Web of Science (1945 to January 2007). We also searched the *meta*Register of Controlled trials (*m*RCT) using artesunate and quinine as search terms.

Conference proceedings
We searched the following conference proceedings for relevant abstracts: 4^{th} Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference, 13 to 18 November 2005, Yaoundé, Cameroon; 4^{th} European Congress on Tropical Medicine, 11 to 15 September 2005, Marseille, France; ACT NOW. An International Symposium on Malaria, 29 to 30 April 2004, Colombia, New York, USA; 2^{nd} International Malaria Research Conference, John Hopkins Malaria Research Institute, 25 to 26 March 2004, Maryland, USA; 3rd MIM Pan-African Conference, 18 to 22 November 2002, Arusha, Tanzania; and the 3rd European Congress on Tropical Medicine and International Health, 8 to 12 September 2002, Lisbon, Portugal.

Researchers, organizations, and pharmaceutical companies

We contacted individual researchers working in the field and the World Health Organization for unpublished and ongoing trials in January 2006.

Reference lists
We checked the reference lists of existing reviews and of all trials identified by the above methods.

METHODS OF THE REVIEW

Study selection
All trials identified by the search strategy were screened by Katharine Jones (KJ) and Sarah Donegan (SD) and full reports of potentially relevant trials were obtained. KJ and SD independently applied the inclusion criteria to the full reports using an eligibility form and scrutinized publications to ensure each trial was included in the review only once. Trial authors were contacted for clarification if necessary. Disagreement was resolved by discussion with David Lalloo (DL).

Assessment of methodological quality
KJ and SD independently evaluated the methodological quality of each trial and recorded the results in a table. The generation of the allocation sequence and allocation concealment were classified as adequate, inadequate, or unclear according to Juni 2001. Descriptive data were collected on whether participants, providers, and outcome assessors were blind to the treatment given. Inclusion of all randomized participants (proportion of participants included for which an efficacy endpoint is available) was classified as adequate (if > 90%), inadequate (if $\leq$ 90%), or unclear. Trial authors were contacted for clarification if necessary. Disagreement was resolved by discussion with the third author.

Data extraction
KJ and SD independently extracted data using a data extraction form. For each outcome we aimed to extract the number of participants randomized and the number analysed in each treatment group. For dichotomous outcomes, we recorded the number of participants experiencing the event and the number assessed in each treatment group. For continuous outcomes, we extracted arithmetic means and standard deviations for each treatment group, together with the numbers assessed in each group. If medians had been used we also extracted ranges whenever it was possible.

Data analysis
We analysed the data with Review Manager 4.2 (RevMan) using relative risk (RR) for dichotomous data, weighted mean difference (WMD) for continuous data, and 95% confidence intervals (CI). Medians and ranges were reported in a table. If arithmetic means were reported, normality of the data was checked by calculating the ratio of the mean over the standard deviation (Altman 1996). If this test suggested the data were skewed (ie if the ratio was less than 2), we commented on this in the text but still combined the results in a meta-analysis.

If there was discrepancy between the number randomized and the number analysed, we calculated the percentage loss to follow up for each treatment group and reported this information. Originally, we aimed to analyse data according to the intention-to-treat principle (all randomized participants should be analysed in the groups to which they were originally assigned). However, since for some trials it was unclear whether there was loss to follow up, we entered the number analysed into RevMan whenever these figures were available. By attempting to carry out a complete-case analysis in this way, we have tried to avoid making assumptions about the outcomes of participants that were lost to follow up.

We looked for statistical heterogeneity by inspecting the forest plots for overlapping confidence intervals, applying the chi-squared test (P-value < 0.10 considered statistically significant), and the I^2 test (I^2 value of 50% used to denote moderate levels of heterogeneity). If heterogeneity was detected but it was still considered clinically meaningful to combine studies, a random-effects model was used. The potential sources of heterogeneity explored for the primary outcome measure were prespecified in the protocol or post-hoc. The prespecified sources were allocation concealment, blinding, participant age (children versus adults), and drug regimen (loading dose versus no loading dose of quinine and use of any additional antimalarials). The post-hoc sources were presentation of severe malaria (severe versus cerebral malaria), method of diagnosing malaria (blood film versus rapid diagnostic test), route of artesunate administration (intravenous versus intramuscular), time since admission to hospital (before and after 48 hours since admission), and hyperparasitaemia.

As only one small trial used intramuscular artesunate we presented these results as a subgroup analysis rather than pooling data according to route of administration as stated in the protocol.

We constructed funnel plots to look for evidence of publication bias. The small number of trials included in the meta-analyses precluded meaningful use of these plots.

DESCRIPTION OF STUDIES

The six trials that met our inclusion criteria enrolled a total of 1938 participants of which 1664 were adults and 274 were children. Only one trial enrolled only children (Cao 1997); this small trial included 72 children. Results for children in the other trials could not be separated out for analysis (see 'Characteristics of included studies'). We identified one ongoing study, a large multicentre trial in African children (see 'Characteristics of ongoing studies'). Thirteen trials detected by the search specifications were excluded from the review (see 'Characteristics of excluded studies').

Location

Four trials took place in single centres in Vietnam. The other two were multicentred: Newton 2003 had two centres in Thailand; and Dondorp 2005 had 11 centres throughout Bangladesh, Myanmar, India, and Indonesia.

Source of funding
Three trials were funded by a medical research charity, one by international organizations including the World Health Organization, and one, Anh 1989, had contributions in the form of the study drugs from pharmaceutical companies. Funding was not specified for one trial (Hien 1992).

Participants
Anh 1989, Hien 1992, and Anh 1995 enrolled only adults with cerebral malaria; Cao 1997 included only children with cerebral malaria; Newton 2003 included only adults with severe malaria; and Dondorp 2005 included both adults and children with severe malaria. All trials except Dondorp 2005 used the presence of *P. falciparum* parasitaemia to confirm the diagnosis of malaria. Dondorp 2005 used a positive rapid diagnostic test. Although standardized clinical definitions for severe malaria exist, entry criteria were not consistent across trials

Interventions
All trials compared artesunate with quinine. Artesunate was given intravenously in five trials and intramuscularly in one trial (Cao 1997). Quinine was given intravenously in all six trials with an initial loading dose in four of these. Drug dosage and duration of treatment varied between the trials (see 'Characteristics of included studies' for details). Five trials gave an additional oral antimalarial to at least one of the treatment arms, which was unmatched between the treatment arms. Two trials, Hien 1992 and Cao 1997, included an additional rectal artemisinin arm that was not pertinent to this review.

Supportive care
All six trials reported measuring blood glucose on admission, but only four trials reported any subsequent monitoring for hypoglycaemia. Three trials reported routine measurement of blood glucose at variable time intervals; monitoring of all participants several times a day (Newton 2003); monitoring of all participants every four hours for the first 24 hours and then every six hours in any participants with coma, prostration, jaundice, or more than one complication (Cao 1997); monitoring in all participants on days 1, 3, 7, and 14 (Anh 1989). Blood glucose was only measured in those participants with clinical signs of hypoglycaemia in one trial (Dondorp 2005).

Outcome measures (defined in Table 02)
All six trials reported death as an outcome. Two trials reported neurological sequelae at discharge (Cao 1997; Dondorp 2005). Five trials reported coma recovery time (Anh 1989; Hien 1992; Anh 1995; Cao 1997; Newton 2003), and four trials reported fever clearance time (Hien 1992; Anh 1995; Cao 1997; Newton 2003). Reporting of parasite clearance time varied between trials and included parasite clearance times of 50%, 90%, 95%, and 100%. We chose to include data for parasite clearance time of 50% as this was most frequently reported in the trials (Anh 1989; Hien 1992; Anh 1995; Cao 1997; Newton 2003). Three trials reported time to hospital discharge (Cao 1997; Newton 2003; Dondorp 2005). Three trials reported adverse effects including hypoglycaemia (Cao 1997; Newton 2003; Dondorp 2005).

Length of follow up
Cao 1997 specified that participants were asked to return for a follow up visit three weeks after discharge from hospital. None of the other trials reported the length of follow up.

METHODOLOGICAL QUALITY

See Table 03 for a summary of the assessment of trial methodological quality. Further details are located in the 'Characteristics of included studies'.

The generation of the allocation sequence was adequate in all six trials. Allocation concealment was adequate in four trials; Anh 1989 and Newton 2003 reported that the randomization was open. In all six trials, investigators were aware of treatment allocation. Participants were blind to the intervention in Hien 1992, and microscopists and data analysts were blind to the intervention in Dondorp 2005. Newton 2003 and Dondorp 2005 clearly stated that no participants were lost to follow up. We were able to obtain individual patient data for one trial in which primary outcomes available for all included participants (Cao 1997). The number of participants randomized was used in the analysis for the remaining three trials (Anh 1989; Hien 1992; Anh 1995).

RESULTS

Death
Death was reported in all six trials. Treatment with artesunate significantly reduced the risk of death (RR 0.62, 95% CI 0.51 to 0.75; 1938 participants, 6 trials, Analysis 01.01) with a consistent reduction across trials. A subgroup analyses of trials reporting mortality before and after 48 hours since admission to hospital found no difference between the groups within 48 hours (1646 participants, 3 trials, Analysis 01.02).

In view of significant variation in trial design we explored potential sources of heterogeneity for mortality. We found that excluding trials with inadequate allocation concealment (Analysis 01.03), trials in which all participants had cerebral malaria (Analysis 01.04), and those with no loading dose of quinine (Analysis 01.05) did not alter the significance of the result. The one trial in which all participants were children found no evidence of a difference between the artesunate and quinine (72 participants, 1 trial, Analyses 01.06). This small trial was also the only trial to use an intramuscular formulation of artesunate (Analyses 01.07). Only one

trial looked at the effect of hyperparasitaemia on death (Dondorp 2005). It found that artesunate was more effective than quinine only in those participants with hyperparasitaemia (RR 0.26, 95% CI 0.14 to 0.49; 229 participants, 1 trial), with no evidence of a difference in those participants with no hyperparasitaemia (1153 participants, 1 trial). This result needs to be interpreted with caution as these subgroups may not be truly randomized.

Neurological sequelae at discharge
Two trials reported results for this outcome (Cao 1997; Dondorp 2005), and they found no evidence of a difference between the groups (1253 participants, 2 trials, Analysis 01.08).

Coma recovery time
The three trials that reported median coma recovery time had inconsistent results (see Table 04). Frequency of measuring this outcome varied between the trials (see Table 02). Two trials reported mean coma recovery time (Anh 1989; Anh 1995). There was no evidence of a difference between the groups, although the data were skewed and the results were inconsistent (231 participants, 2 trials, Analysis 01.09). One trial reported the mean, median, and mode for this outcome (Hien 1992), and the difference between these results suggest the data are skewed.

Time to hospital discharge
Two trials reported this outcome as a median (Cao 1997; Dondorp 2005). The results were consistent and showed no evidence of a difference between the groups (see Table 04). One trial reported this outcome as a mean (Newton 2003) with no evidence of a difference between the groups (113 participants, 1 trial, Analysis 01.10). The data appear skewed.

Fever clearance time
Two trials reported this outcome as a mean (Hien 1992; Anh 1995). There was no evidence of a difference between the groups, although the data appeared to be skewed and the results inconsistent (251 participants, 2 trials, Analysis 01.11). Two trials reported this outcome as a median (Cao 1997; Newton 2003), and the results were inconsistent (see Table 04). The frequency with which this outcome was measured differed between the trials (see Table 02).

Parasite clearance time
Three trials reported parasite clearance time of 50% as a mean (Anh 1989; Hien 1992; Anh 1995). Treatment with artesunate was associated with a reduction in parasite clearance time in all three trials (WMD 8.14 h, 95% CI 11.55 to 4.73; 292 participants, 3 trials, Analysis 01.12). Two trials reported median parasite clearance times of 50% (Newton 2003; Cao 1997), and the results were inconsistent (see Table 04). The frequency with which this outcome was measured differed between the trials (see Table 02).

Adverse effects
No trial reported discontinuation of medication. With the exception of hypoglycaemia, all adverse effects reported could be attributable to malaria. Artesunate was associated with less hypoglycaemia after admission, both in the two trials that measured blood glucose routinely (RR 0.46, 95% CI 0.25 to 0.87; 185 participants, 2 trials, Analysis 01.13.01) and in the one trial that only measured this outcome in participants with clinical signs of hypoglycaemia (RR 0.32, 95% CI 0.13 to 0.79; 1461 participants, 1 trial, Analysis 01.13.02).

DISCUSSION

Treatment with artesunate resulted in a significant reduction in mortality, parasite clearance time, and hypoglycaemia in people with severe malaria in Asia. There was no evidence of a difference in coma recovery time, time to hospital discharge, fever clearance time, or adverse effects other than hypoglycaemia. The number of participants with neurological sequelae is too small to draw any conclusions from these data. Subgroup analyses showed that the beneficial effect of artesunate was most marked in preventing death after 48 hours and occurred in cerebral malaria as well as all categories of severe malaria. One trial suggests that the benefit of artesunate is even greater in people with hyperparasitaemia.

Interpretation of these results is complicated by a number of different factors. The most important of these is that all of the trials were conducted in Asia and that most of the participants were adults. The biology and epidemiology of severe malaria is different in children who tend to present with a more severe spectrum of disease. It is therefore difficult to extrapolate these findings to African children who have the highest burden of severe disease. Differing quinine sensitivity patterns in South-East Asia may mean the magnitude of the beneficial effect of artesunate may not be as great in other parts of the world.

A wide variation in trial design also complicates interpretation of these results. Subgroup analyses showed that excluding poor quality trials, trials with no loading dose of quinine, and those in which all participants had cerebral malaria did not alter the reduction in mortality. Five out of six trials administered unmatched additional oral antimalarials to the intervention and control group, introducing a possible source of confounding factors. The trials also varied in their vigilance for hypoglycaemia, an important and reversible cause of death in patients with severe malaria, and which occurred with lower frequency in the artesunate arms. This could impair the ability of trials to quantify the benefits of artesunate as an antimalarial.

Despite these comments, the beneficial effect of intravenous artesunate upon mortality was considerable, and this is a very important intervention to improve the outcome in this major disease. Intramuscular artesunate would be particularly appropriate for resource-poor settings, but there were insufficient data for this review to establish the effectiveness of this formulation compared to quinine.

AUTHORS' CONCLUSIONS

Implications for practice

Intravenous artesunate is the drug of choice for adults with severe malaria, particularly if acquired in Asia. This review did not identify sufficient data to make firm conclusions about the treatment of children or the effectiveness of intramuscular artesunate. This review highlights the inadequate routine measurement of blood glucose, which ideally should be checked several times a day as advocated by recent World Health Organization guidelines (WHO 2006).

Implications for research

This review highlights a number of areas requiring further research. In particular, there is an urgent need to establish the comparative effectiveness of artesunate and quinine for severe malaria in African children. The ongoing study identified by this review has been designed to answer both this question as well as the relative effectiveness of intramuscular artesunate in this group. The applicability of these results to Asian children and the ethics of further research are points of debate. This review provides limited information regarding differences in hypoglycaemia and neurological sequelae between the two treatments, which impairs the ability to quantify the benefits of artesunate as an antimalarial. Both these outcomes are important in severe malaria, and future trials should include routine monitoring of blood glucose and prolonged neurological follow up for all participants.

POTENTIAL CONFLICT OF INTEREST

Dr David Lalloo was part of the data and safety monitoring committee for the Dondorp trial. This committee is independent, does not run or gain anything from the trial, and has a main role of protecting participants.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Anh 1989**
Methods	Generation of allocation sequence: random-number tables (personal communication from author) Allocation concealment: open Blinding: open label Inclusion of all randomized participants: not reported
Participants	Number: 41 enrolled Inclusion criteria: adults > 16 yr old with cerebral malaria (P. falciparum parasitaemia > 1000/mm3 and Glasgow Coma Scale of 14 or less not attributable to any cause other than malaria) Exclusions: not specified
Interventions	1. Artesunate: 60 mg IV at 0, 4, 24, and 48 h 2. Quinine: 20 mg/kg IV loading dose over 4 h at 0 h then 10 mg/kg IV every 8 h until able to swallow then 10 mg/kg PO every 8 h until day 7
Outcomes	1. Death 2. Coma recovery time 3. Parasite clearance time of 50% Not included in the review: 4. Parasite clearance time of 95%
Notes	Location: Vietnamese hospital Transmission: not specified Date: February to December 1989 Funding: Roche Asian Research Foundation supplied artesunate (personal communication from author) Additional antimalarials: none
Allocation concealment	B – Unclear

Study	**Anh 1995**
Methods	Generation of allocation sequence: central randomization (personal communication from author)

Characteristics of included studies (*Continued*)

	Allocation concealment: sealed envelopes (personal communication from author) Blinding: open label Inclusion of all randomized participants: not reported
Participants	Number: 190 enrolled Inclusion criteria: adults 15 to 65 yr with cerebral malaria (asexual P. falciparum parasitaemia and clinical signs of cerebral malaria alone or associated with other visceral complications) Exclusion criteria: associated P. vivax parasitaemia, pregnancy, and concomitant diseases such as diabetes mellitus, stroke, meningitis, head trauma, pulmonary tuberculosis, or AIDS
Interventions	1. Artesunate: 60 mg IV at 0, 4, 24, and 48 h 2. Quinine: 10 mg/kg IV over 4 h at 0 h then 10 mg/kg IV every 8 h until able to swallow then quinine PO at similar doses every 8 h until day 7
Outcomes	1. Death within 24 h 2. Death after 24 h 3. Coma recovery time 4. Fever clearance time 5. Parasite clearance time of 50% Not included in the review: 6. Parasite clearance time of 95% 7. Parasite clearance time of 100% 8. Time to sit 9. Time to take oral by self medication
Notes	Location: Vietnamese clinical research centre Transmission: not specified Date: July 1992 to May 1995 Funding: World Health Organization Additional antimalarials: artesunate given mefloquine PO 15 mg/kg at day 7; quinine none
Allocation concealment	A – Adequate

Study	**Cao 1997**
Methods	Generation of allocation sequence: computer generated (personal communication from author) Allocation concealment: sealed envelopes Blinding: open label Inclusion of all randomized participants: 100% (personal communication from author)
Participants	Number: 72 enrolled Inclusion criteria: children < 15 yr with severe malaria (asexual P. falciparum parasitaemia plus at least 1 of the following: coma (Blantyre Coma Scale less than or equal to 3), severe anaemia (capillary haematocrit < 15%) with parasitaemia (> 10,000/µL); hyperparasitaemia (> 10% parasitized red blood cells or parasitaemia > 500,000/µL); jaundice (obvious clinically or serum bilirubin > 48 µmol/L); hypoglycaemia (blood glucose < 2.2 mmol/L); spontaneous bleeding (eg gastrointestinal haemorrhage); shock (systolic blood pressure < 50 mmHg if aged < 6 yr, or < 70 mmHg if aged 6 to 14 yr); repeated generalized convulsions (3 or more in 24 h despite cooling); renal impairment (serum creatinine > 177 µmol/L, or urine output < 12 mL/kg/24 h that fails to improve despite rehydration) Exclusion criteria: severe diarrhoea, mixed infection with P. vivax, prior treatment with quinine > 60 mg/kg, artemisinin > 20 mg/kg, or artesunate > 2 mg/kg during the illness episode, or any antimalarial treatment continuing for > 48 h
Interventions	1. Artesunate: 3 mg/kg IM at 0 h then 2 mg/kg IM at 12, 24, 48, and 72 h 2. Quinine: 20 mg/kg IV loading dose over 4 h (omitted if pretreatment with quinine) then 10 mg/kg IV every 8 h up to day 7 3. [Not relevant to review: rectal artemisinin]

Characteristics of included studies (*Continued*)

Outcomes	1. Death 2. Number survived with neurological sequelae 3. Fever clearance time (all patients, excluding superinfections) 4. Coma resolution 5. Parasite clearance time of 50% 6. Period in hospital 7. Hypoglycaemia 8. Adverse effects Not included in this review: 9. Number survived well 10. Time to death from admission 11. Parasite clearance time of 90% 12. Parasite clearance time of 100% 13. Number with acute renal failure 14. Shock 15. Convulsions 16. Deterioration of coma score 17. Gastrointestinal bleeding 18. Anaemia 19. Chest infection 20. Urinary tract infection 21. Other infection 22. Reticulocyte count at admission, on day 5, at discharge 23. Haematocrit at admission, on day 5, at discharge
Notes	Location: Vietnamese hospital Transmission: not specified Date: August 1992 to March 1995 Funding: Wellcome Trust of Great Britain Additional antimalarials given: artesunate arm received mefloquine PO 15 mg/kg at 96 h; quinine arm given sulfadoxine-pyrimethamine 500 mg/25 mg on day 7
Allocation concealment	A – Adequate

Study	**Dondorp 2005**
Methods	Generation of allocation sequence: computer generated Allocation concealment: sealed envelopes Blinding: open label; the trial centre, microscopists assessing blood slides, and data analysts were blinded Inclusion of all randomized participants: 100%
Participants	Number: 1461 enrolled Inclusion criteria: adults and children > 2 yr with severe malaria (positive blood antigen stick test for P. falciparum and a diagnosis of severe malaria, according to the admitting physician) Exclusion criteria: convincing history of full treatment with quinine (40 mg/kg on the first day and 30 mg/kg on any subsequent day) or an artemisinin derivative for more than 24 h before admission, known allergy to 1 of the artemisinin derivatives or quinine
Interventions	1. Artesunate: 2.4 mg/kg IV at 0, 12, and 24 h then 2.4 mg/kg IV every 24 h until able to swallow then PO 2 mg/kg until day 7 2. Quinine: 20 mg/kg IV loading dose then 10 mg/kg every 8 h until able to swallow then PO 10 mg/kg every 8 h until day 7
Outcomes	1. In-hospital death 2. Death within 48 h of entry 3. Death after 48 h of entry

Characteristics of included studies (*Continued*)

	4. In-hospital death (blood-smear positive) 5. Neurological sequelae 6. Time to discharge (median, IQR, and range) 7. Hypoglycaemia after entry Not included in the review: 8. Combined outcome: in hospital death or neurological sequelae 9. Fetal death 10. Time to speak (median, IQR, and range) 11. Time to eat (median, IQR, and range) 12. Time to sit (median, IQR, and range) 13. Convulsions after entry 14. Shock developing after entry 15. Blackwater fever developing after entry 16. Dialysis after entry 17. Vasopressor treatment after entry 18. Mechanical ventilation after entry
Notes	Location: hospitals in Bangladesh, Myanmar, India, and Indonesia Transmission: not specified Date: June 2003 to May 2005 Funding: Wellcome Trust grant Additional antimalarials: both arms except in India and Bangladesh were given doxycycline (100 mg every 12 h for 7 d) once able to swallow
Allocation concealment	A – Adequate

Study	**Hien 1992**
Methods	Generation of allocation sequence: randomization tables (personal communication from author) Allocation concealment: sealed envelopes Blinding: participant blinded Inclusion of all randomized participants: not reported
Participants	Number: 61 enrolled Inclusion criteria: cerebral malaria (P. falciparum parasitaemia with clinical signs of malaria and a Glasgow Coma Scale < 10) Exclusion criteria: not specified
Interventions	1. Artesunate: 60 mg IV at 0, 4, 24, and 48 h 2. Quinine: 500 mg IV over 4 h then 500 mg IV every 8 h until able to swallow then 500 mg PO every 8 h until day 14 3. [Not relevant to review: rectal artemisinin]
Outcomes	1. Fever clearance time 2. Parasite clearance time of 50% 3. Time to regain full consciousness 4. Death Not included in the review: 5. Parasite clearance time of 90% 6. Parasite clearance time of 100%
Notes	Location: intensive care unit in Vietnam Transmission: not specified Date: 1989 to 1990 Funding: artesunate was provided by Professor Li Guo Qiao Additional antimalarials: artesunate arm had mefloquine (PO 500 mg) once able to swallow

Allocation concealment	A – Adequate

Study	**Newton 2003**
Methods	Generation of allocation sequence: computer generated Allocation concealment: open randomization Blinding: open label Inclusion of all randomized participants: 100%
Participants	Number: 113 enrolled, 100 analysed Inclusion criteria: adults aged 15 yr or above with severe malaria (single-species P. falciparum parasitaemia > 0.1% plus at least 1 of following: Glasgow Coma Scale < 11; haematocrit < 20% with asexual parasitaemia > 100,000/μL; total serum bilirubin > 50 μmol/L with asexual parasitaemia > 100,000/μL; serum creatinine > 264 mol/μL with urine output < 400 mL/24 h; systolic blood pressure < 80 mmHg with cool extremities; asexual parasitaemia > 10%; plasma lactate level > 4 mmol/L; plasma glucose level < 2.2 mmol/L; plasma venous bicarbonate level < 15 mmol/L Exclusion criteria: pregnancy, contraindications to study drugs, artesunate, mefloquine, or significant quinine (> 2 g) intake in the previous 24 h
Interventions	1. Artesunate: 2.4 mg/kg IV at 0 h then 1.2 mg/kg at 12 h then 1.2 mg/kg every 24 h until able to swallow then 12 mg/kg PO every 24 h over 7 days 2. Quinine: 20 mg/kg IV over 4 h loading dose then 10 mg/kg IV every 8 until able to swallow then 10 mg/kg PO until day 7
Outcomes	1. Fever clearance time 2. Parasite clearance time of 50% 3. Time to regain full consciousness 4. Death 5. Hypoglycaemia 6. Adverse effects Not included in the review: 7. Parasite clearance time of 90% 8. Parasite clearance time of 100%
Notes	Location: 2 hospitals in Thailand Transmission: seasonal low intensity Date: May to July 1994 and 1995 to 2001 Funding: Wellcome Trust of Great Britain Additional antimalarials: once able to swallow some participants in both arms were given additional antimalarials, but the drug given varied during the trial; AS: no additional antimalarial (n = 22), mefloquine 15 mg/kg (n = 1), mefloquine 25 mg/kg in 2 doses (n = 22), doxycycline 100 mg every 12 h for 7 d (n = 14); quinine: no additional antimalarial (n = 20), tetracycline 250 mg every 12 h for 7 d (n = 19), doxycycline 100 mg every 12 h for 7 days (n = 15)
Allocation concealment	C – Inadequate

IM: intramuscular; IQR: intraquartile range; IV: intravenous; n: number of participants; P.: Plasmodium; PO: by mouth

Characteristics of excluded studies

Study	**Reason for exclusion**
Awad 2003	Not a randomized controlled trial
Barnes 2004	Not severe malaria
Bounyasong 2001	Not severe malaria

Characteristics of excluded studies (*Continued*)

Haroon 2005	A quasi-randomized controlled trial in which the first patient was allocated a treatment at random and then future patients were allocated their treament using an alternating pattern
Krudsood 2003	Not a randomized controlled trial
Li 1990	Not severe malaria
McGready 2001a	Not severe malaria
McGready 2001b	Not a randomized controlled trial
Mohanty 2004	Not a randomized controlled trial (quasi-randomized)
Newton 2001	Treatment comparison is artesunate versus artesunate and quinine
Pukrittayakamee 2004	Not severe malaria
Win 1992	Not a randomized controlled trial
Zhao 2001	Not severe malaria

Characteristics of ongoing studies

Study	**AQUAMAT**
Trial name or title	"The AQUAMAT trial: An open label randomised comparison of injectable artesunate and quinine in children with severe falciparum malaria in Africa"
Participants	Inclusion criteria: OptiMal malaria rapid test positive; and treating physician considers patient to have severe malaria Exclusion criteria: patient has received more than or equal to 24 h of effective treatment with quinine or an artemisinin derivative; or patient has known allergy to quinine or an artemisinin derivative
Interventions	1. Intramuscular artesunate versus intramuscular quinine 2. Intravenous artesunate versus intravenous quinine
Outcomes	1. In-hospital mortality 2. Neurological sequelae 3. Recovery times
Starting date	18 July 2005
Contact information	Prof Nicholas White, Wellcome Unit, Faculty of Tropical Medicine, 420/6 Rajvithi Road, Bangkok, 10400, Thailand +66 23549172 +66 23549169 nickw@tropmedres.ac
Notes	ISRCTN: 50258054 Design: open, randomized, multicentre trial Location: Mozambique, Kenya, Gambia, Ghana Target recruitment number: 5300 End of recruitment date: 31 December 2005 End of follow-up date: 31 April 2009

ADDITIONAL TABLES

Table 01. Detailed search strategies

Search set	CIDG SR^	CENTRAL	MEDLINE^^	EMBASE^^	LILACS^^	ISI Web of Science
1	malaria	malaria	malaria	malaria	malaria	malaria
2	quinine	quinine	quinine	quinine	quinine	quinine
3	artesunate	quinimax	quinimax	quinimax	artesunate	artesunate
4	artemisinin*	CINCHONA ALKALOIDS	CINCHONA ALKALOIDS	CINCHONA-ALKALOID	artemisinin	arsumax
5	3 or 4	2 or 3 or 4	2 or 3 or 4	2 or 3 or 4	3 or 4	3 or 4
6	1 and 2 and 5	artesunate	artesunate	artesunate	1 and 2 and 5	1 and 2 and 5
7	-	arsumax	arsumax	arsumax	-	-
8	-	6 or 7	6 or 7	6 or 7	-	-
9	-	1 and 5 and 8	1 and 5 and 8	1 and 5 and 8	-	-
10	-	-	limit 9 to human	limit 9 to human	-	-
	^Cochrane Infectious Diseases Group Specialized Register		^^Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); upper case: MeSH or EMTREE heading; lower case: free text term			

Table 02. Definitions of outcome measures used in the review

Trial	Death	Neuro. sequelae^	Coma recovery time	Time to discharge	Fever clearance time	PCT 50%^^	Hypoglycaemia	Adverse effects
Anh 1989	Death	Not reported	Mean value (h) reported but not defined	Not reported	Not reported	Mean value (h) reported but not defined. Parasite counts every 8 h until 2 consecutive slides were negative and then every 24 h	Not reported	Not reported
Hien 1992	Death	Not reported	Mean, median, and mode values reported in hours. Defined as time to regain full consciousness (Glasgow Coma Scale of 15/15). Glasgow Coma Scale measured at 3-h intervals until full recovery of consciousness, and at 6-h intervals thereafter	Not reported	Mean value (h) reported. Defined as time (h) until "fever clearance". The axillary temperature was measured at 3-h intervals until "fever clearance", and at 6-h intervals thereafter	Mean value (h) reported but not defined. Parasite counts performed every 4 h for 12 h, then every 6 h until 3 consecutive films were negative	Not reported	None reported
Anh 1995	Death	Not reported	Mean value (h). Defined as time until consciousness regained. Glasgow Coma Scale measured every 12 h until regained consciousness	Not reported	Mean value (h) reported but not defined. Axillary temperature was recorded every 6 h until 4 consecutive temperatures were < 37.5 °C	Mean value (h) reported but not defined. Parasite count measured every 6 h until 3 consecutive blood smears were negative	Not reported	Not reported
Cao 1997	Death	Number survived with neurological	Median value (h) reported. Defined	Median value (d) reported	Median value (h) reported. Defined	Median value (h) reported but not	Blood glucose < 2.2 mmol/L.	Acute renal failure requiring

Table 02. Definitions of outcome measures used in the review (*Continued*)

Trial	Death	Neuro. sequelae^	Coma recovery time	Time to discharge	Fever clearance time	PCT 50%^^	Hypoglycaemia	Adverse effects
		sequelae. Case definition for neurological sequelae: abnormal neurological signs and/or symptoms at time of discharge from hospital that were not present before onset of the episode of malaria as reported by the child's parents. All children had a full neurological examination on admission and at discharge from hospital (personal communication from author)	as time (h) for Blantyre Coma Score to become 5/5. Coma score assessed every 4 h (or more frequently if critically ill) for the first 24 h, and then every 6 h until discharge		as time until temperature first dropped to 37.5 °C or below and remained below this level for at least 24 h. Axillary temperature measured every 4 h (or more frequently if critically ill) for the first 24 h, and then every 6 h until discharge	defined. Parasite count measured every 4 h (or more frequently if critically ill) for the first 24 h, and then every 6 h until discharge. Once 2 successive peripheral blood films had revealed no P. falciparum, no further blood film was made unless indicated clinically	Blood glucose measured every 4 h for first 24 h and then every 6 h until discharge from hospital if indicated (coma, prostration, jaundice, or > 1 complication - personal communication from author)	dialysis, shock, convulsions, deterioration of coma score, gastrointestinal bleeding, anaemia requiring blood transfusion, chest infection, urinary tract infection, other infections, derangement of biochemical markers
Newton 2003	Death	Not reported	Median value (h) reported. Defined as time to reach a Glasgow Coma Scale of 15 in those participants with a score < 11/15 on admission. Glasgow Coma Scale measured every 15 min for first h, at 2 h, and	Not reported	Median value (h) reported. Defined as time until the axillary temperature first dropped below 37.5 °C and remained below that level for 24 h. Axillary temperature measured every 15	Median value (h) reported. Defined as time to a 50% reduction in parasite density. Parasite counts were measured at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h, and then every 6 h until 6 h after parasite clearance	Plasma glucose less than or equal to 2.2 mmol/L. Plasma glucose measured at 0, 4, 8, 12, 16, 20, and 24 h and then every 6 h	Seizures, bleeding and sepsis after admission, pulmonary oedema, oliguria, time in intensive care unit

Table 02. Definitions of outcome measures used in the review (*Continued*)

Trial	Death	Neuro. sequelae^	Coma recovery time	Time to discharge	Fever clearance time	PCT 50%^^	Hypoglycaemia	Adverse effects
			then every 2 h until 12 h, every 4 h from 12 to 24 h, and every 6 h from 24 h until the score reached 15		min for the first h, at 2 h, and then every 2 h until 12 h, every 4 h from 12 to 24 h, and every 6 h from 24 h until fever cleared			
Dondorp 2005	Death	Neurological sequelae at discharge from hospital	Not reported	Median value (d) reported	Not reported	Not reported	Blood glucose < 2.2 mmol/L. Blood glucose checked in all patients on admission and then monitored on clinical indication	Not reported
		^Neurological sequelae at discharge				^^Parasite clearance time of 50%		

Table 03. Assessment of methodological quality

Trial	Randomization^	Concealment^	Blinding	Inclusion^
Anh 1989	Adequate	Inadequate	Open label	Unclear
Hien 1992	Adequate	Adequate	Participant blinded	Unclear
Anh 1995	Adequate	Adequate	Open label	Unclear
Cao 1997	Adequate	Adequate	Open label	Adequate (100%)
Newton 2003	Adequate	Inadequate	Open label	Adequate (100%)
Dondorp 2005	Adequate	Adequate	Open label (trial centre, microscopists assessing blood slides, and data analysts blinded until trial end)	Adequate (100%)

^Generation of allocation sequence, allocation concealment, and inclusion of all randomized participants

Table 04. Time-to-event data: medians, ranges, and modes

Outcome	Trial	Artesunate	Quinine
Coma recovery time (h): median (range), number	Hien 1992	35 (5 to 453); mode = 17; mean = 68.9	48 (7 to 144), mode = 43; mean = 58.1
	Cao 1997	42 (4 to 228), n = 10	31 (4 to 66), n = 2
	Newton 2003	17 (1 to 125), n = 16	18 (1 to 188), n = 16
Time to hospital discharge (d): median (range), number	Cao 1997	8 (5 to 20), n = 33	8 (5 to 24), n = 29
	Dondorp 2005	5 (0 to 54), n = 623	5 (0 to 45), n = 567
Fever clearance time (until first below 37.5 °C) (h): median (range), number	Cao 1997	4 (4 to 198), n = 35	8 (0 to 96), n = 35
	Newton 2003	11 (1 to 83), n = 42	13 (1 to 184), n = 42
Fever clearance time (until remains below 37.5 °C for 24 h) (h): median (range), number	Cao 1997	84 (4 to 198), n = 35	81 (0 to 246), n = 30
	Newton 2003	41 (3 to 138), n = 32	65 (12 to 383), n = 27
Time to parasite clearance of 50% (h): median (range), number	Cao 1997	5.7 (2.0 to 15.3), n = 35	13.2 (2.4 to 103.0), n = 32
	Newton 2003	9.1 (0.3 to 37.2), n = 56	8.0 (0.2 to 46.0), n = 49

ANALYSES

Comparison 01. Artesunate vs quinine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death	6	1938	Relative Risk (Fixed) 95% CI	0.62 [0.51, 0.75]
02 Death: time since admission to hospital [subgroup analysis]	6	3292	Relative Risk (Fixed) 95% CI	0.65 [0.52, 0.81]
03 Death: allocation concealment [subgroup analysis]	6	1938	Relative Risk (Fixed) 95% CI	0.62 [0.51, 0.75]
04 Death: cerebral malaria [subgroup analysis]	6	1938	Relative Risk (Fixed) 95% CI	0.62 [0.51, 0.75]
05 Death: loading dose vs no loading dose of quinine [subgroup analysis]	6	1938	Relative Risk (Fixed) 95% CI	0.62 [0.51, 0.75]
06 Death: participant age [subgroup analysis]	6	1938	Relative Risk (Fixed) 95% CI	0.62 [0.51, 0.75]
07 Death: intravenous vs intramuscular artesunate [subgroup analysis]	6	1938	Relative Risk (Fixed) 95% CI	0.62 [0.51, 0.75]
08 Neurological sequelae at discharge	2	1253	Relative Risk (Fixed) 95% CI	2.21 [0.64, 7.63]
09 Coma recovery time	2	231	Weighted Mean Difference (Random) 95% CI	2.11 [-19.17, 23.40]
10 Time to hospital discharge			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
11 Fever clearance time	2	251	Weighted Mean Difference (Random) 95% CI	-13.58 [-55.09, 27.92]
12 Parasite clearance time of 50%	3	292	Weighted Mean Difference (Random) 95% CI	-8.14 [-11.55, -4.73]
13 Hypoglycaemia			Relative Risk (Fixed) 95% CI	Subtotals only

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [administration & dosage; *therapeutic use]; Artemisinins [administration & dosage; *therapeutic use]; Injections, Intramuscular; Injections, Intravenous; Malaria [*drug therapy; mortality]; Quinine [administration & dosage; *therapeutic use]; Randomized Controlled Trials as Topic; Sesquiterpenes [administration & dosage; *therapeutic use]

MeSH check words

Adult; Child; Humans

COVER SHEET

Title	Artesunate versus quinine for treating severe malaria
Authors	Jones KL, Donegan S, Lalloo DG
Contribution of author(s)	Katharine Jones and Sarah Donegan assessed the eligibility and methodological quality of trials, extracted and analysed data, and drafted the review. David Lalloo contributed to the design and writing of the review.
Issue protocol first published	2006/2
Review first published	2007/4

Date of most recent amendment	17 August 2007
Date of most recent SUBSTANTIVE amendment	16 August 2007
What's New	2007, Issue 4 (deviations from protocol): We removed the requirement for all participants to fulfil the World Health Organization's definition for severe malaria (Gilles 2000) in view of the large number of participants this would have excluded from the review as the largest included trial used a clinical case definition. We changed the intervention from "parenteral quinine" to "intravenous, intramuscular, or rectal artesunate" to clarify that trials using artesunate suppositories were included in the review. We changed "neurological sequelae" to "neurological sequelae at discharge" to clarify the follow-up period for this outcome. We added the exploration of a number of post-hoc sources of heterogeneity for mortality after noting significant variation in study design across trials. We presented data for hypoglycaemia in a forest plot rather than a table as stated in the protocol to reflect the clinical importance of this outcome.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD005967.pub2
Cochrane Library number	CD005967
Editorial group	Cochrane Infectious Diseases Group
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Artesunate vs quinine, Outcome 01 Death

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 01 Death

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Anh 1989	2/19	7/22		3.0	0.33 [0.08, 1.41]
Anh 1995	8/99	18/91		8.7	0.41 [0.19, 0.89]
Cao 1997	4/37	5/35		2.4	0.76 [0.22, 2.59]
Dondorp 2005	107/730	164/731		76.3	0.65 [0.52, 0.81]
Hien 1992	5/31	8/30		3.8	0.60 [0.22, 1.64]
Newton 2003	7/59	12/54		5.8	0.53 [0.23, 1.26]
Total (95% CI)	975	963		100.0	0.62 [0.51, 0.75]
Total events: 133 (Artesunate), 214 (Quinine)					
Test for heterogeneity chi-square=2.26 df=5 p=0.81 I^2 =0.0%					
Test for overall effect z=4.82 p<0.00001					

Analysis 01.02. Comparison 01 Artesunate vs quinine, Outcome 02 Death: time since admission to hospital [subgroup analysis]

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 02 Death: time since admission to hospital [subgroup analysis]

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Death within 48 h					
Cao 1997	3/37	3/35		1.7	0.95 [0.20, 4.38]
Dondorp 2005	61/730	75/731		41.3	0.81 [0.59, 1.12]
Newton 2003	4/59	9/54		5.2	0.41 [0.13, 1.24]
Subtotal (95% CI)	826	820		48.2	0.78 [0.57, 1.05]
Total events: 68 (Artesunate), 87 (Quinine)					
Test for heterogeneity chi-square=1.43 df=2 p=0.49 I^2 =0.0%					
Test for overall effect z=1.65 p=0.1					
02 Death after 48 h					
Cao 1997	1/37	2/35		1.1	0.47 [0.04, 4.99]

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Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Dondorp 2005	46/730	89/731		49.0	0.52 [0.37, 0.73]
Newton 2003	3/59	3/54		1.7	0.92 [0.19, 4.34]
Subtotal (95% CI)	826	820		51.8	0.53 [0.38, 0.74]
Total events: 50 (Artesunate), 94 (Quinine)					
Test for heterogeneity chi-square=0.50 df=2 p=0.78 I^2 =0.0%					
Test for overall effect z=3.78 p=0.0002					
Total (95% CI)	1652	1640		100.0	0.65 [0.52, 0.81]
Total events: 118 (Artesunate), 181 (Quinine)					
Test for heterogeneity chi-square=4.76 df=5 p=0.45 I^2 =0.0%					
Test for overall effect z=3.84 p=0.0001					

Analysis 01.03. Comparison 01 Artesunate vs quinine, Outcome 03 Death: allocation concealment [subgroup analysis]

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 03 Death: allocation concealment [subgroup analysis]

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Adequate allocation concealment					
Anh 1995	8/99	18/91		8.7	0.41 [0.19, 0.89]
Cao 1997	4/37	5/35		2.4	0.76 [0.22, 2.59]
Dondorp 2005	107/730	164/731		76.3	0.65 [0.52, 0.81]
Hien 1992	5/31	8/30		3.8	0.60 [0.22, 1.64]
Subtotal (95% CI)	897	887		91.2	0.63 [0.51, 0.77]
Total events: 124 (Artesunate), 195 (Quinine)					
Test for heterogeneity chi-square=1.37 df=3 p=0.71 I^2 =0.0%					
Test for overall effect z=4.41 p=0.00001					
02 Inadequate allocation concealment					
Anh 1989	2/19	7/22		3.0	0.33 [0.08, 1.41]
Newton 2003	7/59	12/54		5.8	0.53 [0.23, 1.26]
Subtotal (95% CI)	78	76		8.8	0.46 [0.22, 0.97]
Total events: 9 (Artesunate), 19 (Quinine)					
Test for heterogeneity chi-square=0.31 df=1 p=0.58 I^2 =0.0%					

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Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=2.05 p=0.04					
Total (95% CI)	975	963	◆	100.0	0.62 [0.51, 0.75]
Total events: 133 (Artesunate), 214 (Quinine)					
Test for heterogeneity chi-square=2.26 df=5 p=0.81 I^2 =0.0%					
Test for overall effect z=4.82 p<0.00001					

Analysis 01.04. Comparison 01 Artesunate vs quinine, Outcome 04 Death: cerebral malaria [subgroup analysis]

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 04 Death: cerebral malaria [subgroup analysis]

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 All participants have cerebral malaria					
Anh 1989	2/19	7/22		3.0	0.33 [0.08, 1.41]
Anh 1995	8/99	18/91		8.7	0.41 [0.19, 0.89]
Hien 1992	5/31	8/30		3.8	0.60 [0.22, 1.64]
Subtotal (95% CI)	149	143	◆	15.5	0.44 [0.25, 0.78]
Total events: 15 (Artesunate), 33 (Quinine)					
Test for heterogeneity chi-square=0.57 df=2 p=0.75 I^2 =0.0%					
Test for overall effect z=2.84 p=0.005					
02 Severe malaria					
Cao 1997	4/37	5/35		2.4	0.76 [0.22, 2.59]
Dondorp 2005	107/730	164/731		76.3	0.65 [0.52, 0.81]
Newton 2003	7/59	12/54		5.8	0.53 [0.23, 1.26]
Subtotal (95% CI)	826	820	◆	84.5	0.65 [0.52, 0.80]
Total events: 118 (Artesunate), 181 (Quinine)					
Test for heterogeneity chi-square=0.26 df=2 p=0.88 I^2 =0.0%					
Test for overall effect z=4.04 p=0.00005					
Total (95% CI)	975	963	◆	100.0	0.62 [0.51, 0.75]
Total events: 133 (Artesunate), 214 (Quinine)					
Test for heterogeneity chi-square=2.26 df=5 p=0.81 I^2 =0.0%					
Test for overall effect z=4.82 p<0.00001					

Analysis 01.05. Comparison 01 Artesunate vs quinine, Outcome 05 Death: loading dose vs no loading dose of quinine [subgroup analysis]

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 05 Death: loading dose vs no loading dose of quinine [subgroup analysis]

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 No loading dose					
Anh 1995	8/99	18/91		8.7	0.41 [0.19, 0.89]
Hien 1992	5/31	8/30		3.8	0.60 [0.22, 1.64]
Subtotal (95% CI)	130	121		12.5	0.47 [0.25, 0.87]
Total events: 13 (Artesunate), 26 (Quinine)					
Test for heterogeneity chi-square=0.37 df=1 p=0.54 I^2 =0.0%					
Test for overall effect z=2.42 p=0.02					
02 Loading dose					
Anh 1989	2/19	7/22		3.0	0.33 [0.08, 1.41]
Cao 1997	4/37	5/35		2.4	0.76 [0.22, 2.59]
Dondorp 2005	107/730	164/731		76.3	0.65 [0.52, 0.81]
Newton 2003	7/59	12/54		5.8	0.53 [0.23, 1.26]
Subtotal (95% CI)	845	842		87.5	0.64 [0.52, 0.78]
Total events: 120 (Artesunate), 188 (Quinine)					
Test for heterogeneity chi-square=1.08 df=3 p=0.78 I^2 =0.0%					
Test for overall effect z=4.24 p=0.00002					
Total (95% CI)	975	963		100.0	0.62 [0.51, 0.75]
Total events: 133 (Artesunate), 214 (Quinine)					
Test for heterogeneity chi-square=2.26 df=5 p=0.81 I^2 =0.0%					
Test for overall effect z=4.82 p<0.00001					

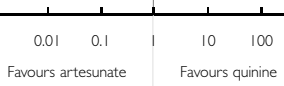
Analysis 01.06. Comparison 01 Artesunate vs quinine, Outcome 06 Death: participant age [subgroup analysis]

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 06 Death: participant age [subgroup analysis]

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Adults (15/16 years +)					
Anh 1989	2/19	7/22		3.0	0.33 [0.08, 1.41]
Anh 1995	8/99	18/91		8.7	0.41 [0.19, 0.89]
Hien 1992	5/31	8/30		3.8	0.60 [0.22, 1.64]
Newton 2003	7/59	12/54		5.8	0.53 [0.23, 1.26]
Subtotal (95% CI)	208	197		21.4	0.47 [0.29, 0.75]
Total events: 22 (Artesunate), 45 (Quinine)					
Test for heterogeneity chi-square=0.68 df=3 p=0.88 I^2 =0.0%					
Test for overall effect z=3.17 p=0.002					
02 Children 2 to 15 years					
Cao 1997	4/37	5/35		2.4	0.76 [0.22, 2.59]
Subtotal (95% CI)	37	35		2.4	0.76 [0.22, 2.59]
Total events: 4 (Artesunate), 5 (Quinine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.44 p=0.7					
03 All ages					
Dondorp 2005	107/730	164/731		76.3	0.65 [0.52, 0.81]
Subtotal (95% CI)	730	731		76.3	0.65 [0.52, 0.81]
Total events: 107 (Artesunate), 164 (Quinine)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.78 p=0.0002					
Total (95% CI)	975	963		100.0	0.62 [0.51, 0.75]
Total events: 133 (Artesunate), 214 (Quinine)					
Test for heterogeneity chi-square=2.26 df=5 p=0.81 I^2 =0.0%					
Test for overall effect z=4.82 p<0.00001					



Analysis 01.07. Comparison 01 Artesunate vs quinine, Outcome 07 Death: intravenous vs intramuscular artesunate [subgroup analysis]

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 07 Death: intravenous vs intramuscular artesunate [subgroup analysis]

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Intravenous artesunate					
Anh 1989	2/19	7/22		3.0	0.33 [0.08, 1.41]
Anh 1995	8/99	18/91		8.7	0.41 [0.19, 0.89]
Dondorp 2005	107/730	164/731		76.3	0.65 [0.52, 0.81]
Hien 1992	5/31	8/30		3.8	0.60 [0.22, 1.64]
Newton 2003	7/59	12/54		5.8	0.53 [0.23, 1.26]
Subtotal (95% CI)	938	928		97.6	0.61 [0.50, 0.75]
Total events: 129 (Artesunate), 209 (Quinine)					
Test for heterogeneity chi-square=2.15 df=4 p=0.71 I² =0.0%					
Test for overall effect z=4.81 p<0.00001					
02 Intramuscular artesunate					
Cao 1997	4/37	5/35		2.4	0.76 [0.22, 2.59]
Subtotal (95% CI)	37	35		2.4	0.76 [0.22, 2.59]
Total events: 4 (Artesunate), 5 (Quinine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.44 p=0.7					
Total (95% CI)	975	963		100.0	0.62 [0.51, 0.75]
Total events: 133 (Artesunate), 214 (Quinine)					
Test for heterogeneity chi-square=2.26 df=5 p=0.81 I² =0.0%					
Test for overall effect z=4.82 p<0.00001					

Analysis 01.08. Comparison 01 Artesunate vs quinine, Outcome 08 Neurological sequelae at discharge

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 08 Neurological sequelae at discharge

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cao 1997	1/33	0/30		14.3	2.74 [0.12, 64.69]
Dondorp 2005	7/623	3/567		85.7	2.12 [0.55, 8.17]
Total (95% CI)	656	597		100.0	2.21 [0.64, 7.63]

Total events: 8 (Artesunate), 3 (Quinine)

Test for heterogeneity chi-square=0.02 df=1 p=0.89 I^2 =0.0%

Test for overall effect z=1.26 p=0.2

Analysis 01.09. Comparison 01 Artesunate vs quinine, Outcome 09 Coma recovery time

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 09 Coma recovery time

Study	Artesunate N	Mean(SD)	Quinine N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Anh 1989	19	45.17 (30.29)	22	53.60 (25.87)		51.5	-8.43 [-25.82, 8.96]
Anh 1995	99	71.30 (81.00)	91	58.00 (49.00)		48.5	13.30 [-5.57, 32.17]
Total (95% CI)	118		113			100.0	2.11 [-19.17, 23.40]

Test for heterogeneity chi-square=2.76 df=1 p=0.10 I^2 =63.7%

Test for overall effect z=0.19 p=0.8

Analysis 01.10. Comparison 01 Artesunate vs quinine, Outcome 10 Time to hospital discharge

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 10 Time to hospital discharge

Study	Artesunate N	Mean(SD)	Quinine N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
Newton 2003	59	5.10 (3.14)	54	5.00 (4.50)		0.10 [-1.34, 1.54]

Analysis 01.11. Comparison 01 Artesunate vs quinine, Outcome 11 Fever clearance time

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 11 Fever clearance time

Study	Artesunate N	Mean(SD)	Quinine N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Anh 1995	99	67.36 (41.40)	91	63.30 (46.50)		59.0	4.06 [-8.50, 16.62]
Hien 1992	31	39.00 (30.00)	30	78.00 (102.00)		41.0	-39.00 [-77.00, -1.00]
Total (95% CI)	130		121			100.0	-13.58 [-55.09, 27.92]

Test for heterogeneity chi-square=4.45 df=1 p=0.03 I^2 =77.5%

Test for overall effect z=0.64 p=0.5

Analysis 01.12. Comparison 01 Artesunate vs quinine, Outcome 12 Parasite clearance time of 50%

Review: Artesunate versus quinine for treating severe malaria

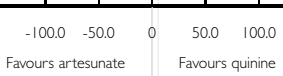
Comparison: 01 Artesunate vs quinine

Outcome: 12 Parasite clearance time of 50%

Study	Artesunate N	Mean(SD)	Quinine N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Anh 1989	19	7.58 (3.32)	22	15.73 (9.78)		30.0	-8.15 [-12.50, -3.80]
Anh 1995	99	10.64 (8.24)	91	16.12 (14.25)		37.5	-5.48 [-8.83, -2.13]
Hien 1992	31	5.40 (3.20)	30	16.60 (10.70)		32.5	-11.20 [-15.19, -7.21]
Total (95% CI)	149		143			100.0	-8.14 [-11.55, -4.73]

Test for heterogeneity chi-square=4.65 df=2 p=0.10 I^2 =57.0%

Test for overall effect z=4.68 p<0.00001



Analysis 01.13. Comparison 01 Artesunate vs quinine, Outcome 13 Hypoglycaemia

Review: Artesunate versus quinine for treating severe malaria

Comparison: 01 Artesunate vs quinine

Outcome: 13 Hypoglycaemia

Study	Artesunate n/N	Quinine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Routine monitoring					
Cao 1997	6/37	9/35		37.1	0.63 [0.25, 1.59]
Newton 2003	6/59	15/54		62.9	0.37 [0.15, 0.88]
Subtotal (95% CI)	96	89		100.0	0.46 [0.25, 0.87]
Total events: 12 (Artesunate), 24 (Quinine)					
Test for heterogeneity chi-square=0.71 df=1 p=0.40 I^2 =0.0%					
Test for overall effect z=2.39 p=0.02					
02 Clinical monitoring					
Dondorp 2005	6/730	19/731		100.0	0.32 [0.13, 0.79]
Subtotal (95% CI)	730	731		100.0	0.32 [0.13, 0.79]
Total events: 6 (Artesunate), 19 (Quinine)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.47 p=0.01