High first dose quinine regimen for treating severe malaria (Review)

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[Intervention Review]

High first dose quinine regimen for treating severe malaria

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ABSTRACT

Background

Quinine is used for treating severe malaria. There are arguments for giving an initial high dose. We examined the evidence for and against this policy.

Objectives

To assess the clinical outcomes and adverse events of a high first (loading) dose regimen of quinine compared with a uniform (no loading) dose regimen in people with severe malaria.

Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (February 2009), CENTRAL (*The Cochrane Library* Issue 1, 2009), MEDLINE (1966 to February 2009), EMBASE (1974 to February 2009), LILACS (1982 to February 2009), and conference proceedings for relevant abstracts. We also contacted researchers working in the field and checked the reference lists of all studies.

Selection criteria

Randomized controlled trials comparing a high first (loading) dose of intravenous quinine with a uniform (no loading) dose of intravenous quinine in people with severe malaria.

Data collection and analysis

Two reviewers independently assessed the risk of bias in the trials and extracted data (including adverse event data). We used Review Manager 5.0 to analyse the data: risk ratio (RR) for binary data and mean difference (MD) for continuous data with 95% confidence intervals (CI). We contacted study authors for additional information.

Main results

Four trials (n = 144) met the inclusion criteria. Loading dose was associated with fewer deaths, but this was not statistically significant (RR 0.62, 95% CI 0.19 to 2.04; 3 trials). Loading dose was associated with faster clearance of parasites (WMD -7.44 hours, 95% CI -13.24 to -1.64 hours; 2 trials), resolution of fever (WMD -11.11 hours, 95% CI -20.04 to -2.18 hours; 2 trials). No statistically significant difference was detected for recovery of consciousness, neurological sequelae, or convulsions, but the numbers were small.

Authors' conclusions

Quinine loading dose reduced fever clearance time and parasite clearance time. Data are insufficient to directly demonstrate an impact of loading dose on risk of death.

PLAIN LANGUAGE SUMMARY

Initial high dose of quinine to treat severe malaria

People with severe malaria are unconscious, have difficulty breathing, may convulse, and have low blood sugar. They need treating quickly.

Quinine given intravenously or intramuscularly has been used for some years to treat severe malaria. It is particularly helpful as it works against parasites resistant to chloroquine, which used to be an effective and commonly used drug.

The World Health Organization recommends that doctors give people with severe malaria an initial high dose (loading dose) of intravenous quinine followed by lower quinine maintenance doses. This is to get an effective drug concentration in the blood. Several different quinine loading doses, maintenance doses, and dose intervals have been examined. There are some concerns about adverse effects in children.

The authors of this review wanted to summarize the benefits and harms of different quinine dosing regimens. They identified four relevant trials with 144 participants. A high initial dose of quinine reduced fever clearance time and parasite clearance time, but there were too few data to describe the impact on death. No difference was detected for recovery of consciousness and other neurological symptoms, but there were probably too few participants to detect differences.

BACKGROUND

Each year an estimated 500,000 to 2 million people die from the effects of malaria (WHO 1990a). The majority of these deaths occur in children under five years old that live in areas of intense malaria transmission, notably in sub-Saharan Africa (WHO 1996; Schellenberg 1999). Severe malaria syndromes have been described and summarized by the World Health Organization (WHO) (WHO 2000). They include the presence of asexual parasitaemia associated with clinical or laboratory findings such as impaired consciousness, respiratory distress, convulsions, severe anaemia, and hypoglycaemia (low blood sugar).

Healthcare workers treating malaria know that it is important for people with severe malaria to receive the correct doses of an effective antimalarial drug given by an appropriate route promptly; the aim of this initial stage of treatment is resuscitation. Later, when the person's condition has stabilized and drugs can be taken orally, it is sometimes convenient to change the drug in order to eradicate circulating asexual parasite forms. Drugs currently in use for initial resuscitation include chloroquine (although resistance to this compound is restricting its utility), quinine, and the artemisinin derivatives (mainly artemether, artesunate, and dihydroartemisinin). Mefloquine and sulfadoxine-pyrimethamine are often used for subsequent treatment, but they are not employed for resuscitation. The choice of drug is governed by the availability, cost, and pattern of drug resistance in the community (Phillips 1996). For many years chloroquine was the preferred drug for treating severe malaria. Resistance of the malaria parasite to chloroquine was first observed in South-East Asia and South America (Bjorkman 1990). This has reduced the effectiveness of chloroquine as an antimalarial and has led to a rise in deaths from malaria (Trape 1998). In many areas of chloroquine resistance, quinine has returned as the first-line drug for severe forms of malaria (White 1982; WHO 1986). The escalating problem of drug resistance continues to challenge health workers involved in managing severe forms of malaria (Nuwaha 2001).

The WHO recommends that people with severe malaria be given an initial high dose of intravenous quinine, also referred to as the loading dose (WHO 1986). This is followed by quinine maintenance doses (Chongsuphajaisiddhi 1981; White 1982; WHO

1986; WHO 1990b). The rationale for the loading dose is the urgent need to achieve an effective quinine concentration in the blood (Allen 1996). Death in severe malaria often occurs in the first 12 to 48 hours of admission (Allen 1996; van der Torn 1998). Pharmacokinetic studies have clearly demonstrated that drug therapy needs to exceed the parasite minimum inhibitory concentration as soon as possible and thereafter maintain therapeutic drug levels for the remainder of the treatment (White 1983). The high first dose is also used in the managing children with severe malaria (Waller 1990; Winstanley 1994; van Hensbroek 1996). A variety of quinine loading doses, maintenance doses, and dose intervals have been examined over the last 15 years. The 'WHO standard' is now 20 mg/kg of the dihydrochloride salt infused at constant rate over 4 hours, followed by 10 mg/kg of the salt infused over 2 hours, and repeated every 8 hours. All people with cerebral malaria, and the majority with other severe malaria syndromes, are incapable of taking oral medications: thus the parenteral routes are obligatory. In those people with severe malaria who are able to take medicines orally, parenteral routes are still preferred for reasons such as the possibility of ileus (obstruction of the intestines) causing gastroparesis (paralysis of the stomach); oral dosing carries the risk of vomiting and aspiration, and the assurance with parenteral dosing is that the drug is in the body.

The Type A (dose related) adverse reactions of quinine include hypoglycaemia (Phillips 1984), renal failure (Sharma 1989), and an abnormal heartbeat (cardiac arrhythmias) (Jacqz-Aigrain 1994). The Type B (not classically dose related) adverse reactions include haemolysis (the breakdown of red blood cells) and thrombocytopenia (low platelet count) (Jacqz-Aigrain 1994). Cinchonism, characterized by ringing in the ears, headache, and deafness (Dorland 2000), is a common symptomatic and dose-related adverse reaction to quinine. However, in routine clinical practice, this is rarely considered a problem in severe malaria as a large proportion of patients have perturbed consciousness, and for this reason cinchonism is not viewed as a reason to reduce quinine doses in patients. There are concerns about an increased risk of adverse effects in children given a high first dose of quinine (van Hensbroek 1996). Very rarely, death may be associated with intravenous quinine (Hall 1977; White 1989).

Before the WHO recommendation in 1986 to treat severe malaria with a high first dose regimen, a uniform dose regimen (no loading dose) of quinine of 10 mg/kg every 8 hours was used (Hall 1977). This uniform dose regimen has been considered to have fewer adverse effects than the high first dose regimen (Davis 1988; Kawo 1991). While the new drugs suitable for treating chloroquine resistant malaria remain expensive, quinine will continue to be an important drug in the battle to reduce mortality from the severe forms of malaria in low-income and middle-income countries. Consequently, quinine must be used in the most effective way possible.

The purpose of this review is to summarize the benefits and harms of different quinine dosing regimens with a view to improving policy and practice.

OBJECTIVES

To assess the clinical outcomes and adverse events of a high first (loading) dose regimen of quinine compared with a uniform (no loading) dose regimen in people with severe malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and quasi-randomized controlled trials.

Types of participants

People (adults and children) with any form of severe malaria (as defined by trial authors) treated with intravenous quinine.

Types of interventions

Intervention

Loading (high first) dose of intravenous quinine (20 mg/kg salt equivalent to 16 mg/kg base, as the first dose).

Control

No loading (uniform) dose of intravenous quinine (10 mg/kg salt equivalent to 8 mg/kg base, as the first dose).
After the first dose, people in both groups will be given 10 mg/kg salt or 8 mg/kg base every 8 or 12 hours.

Types of outcome measures

Primary

Death.

Secondary

- Coma recovery time (time between the onset of coma and its resolution or as defined by the trial authors).
- Convulsions (as defined by the trial authors).
- Fever clearance time (time between start of treatment and return of body temperature to normal or as defined by the trial authors).
- Parasite clearance time (time between start of treatment and the first negative blood test or as defined by the trial authors).
- Number of participants with asexual parasitaemia at 24 and 48 hours.
- Neurological sequelae.

Adverse events

- Hypoglycaemia (blood glucose < 2.2 mmol/litre) during hospitalization.
- Anaemia (haemoglobin < 10 g/litre at follow-up visit).
- Any other.

Search methods for identification of studies

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

Databases

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (February 2009); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 1, 2009); MEDLINE (1966 to February 2009); EMBASE (1974 to February 2009); and LILACS (1982 to February 2009).

Table 1. Search strategies for databases

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	quinine	quinine	QUININE	quinine	quinine
2	malaria	loading dose	quinine	quinimax	malaria
3	-	high dose	1 or 2	1 or 2	1 and 2
4	-	malaria	loading dose	loading dose	-
5	-	2 or 3	high dose	high dose	-

Table 1. Search strategies for databases (*Continued*)

6	-	1 and 4 and 5	load*	4 or 5	-
7	-	-	4 or 5 or 6	3 and 6	-
8	-	-	3 and 7	exp MALARIA	-
9	-	-	exp MALARIA	malaria	-
10	-	-	malaria	8 or 9	-
11	-	-	9 or 10	7 and 10	-
12	-	-	8 and 11	limit 11 to human	-
13	-	-	limit 12 to human	-	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Alderson 2004); upper case: MeSH or EMTREE heading; lower case: textword.

Conference proceedings

We searched the conference proceeding of The Third MIM Pan-African Malaria Conference (Arusha, Tanzania November 17 to 22, 2002) for relevant abstracts.

Researchers

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

Reference lists

We checked the citations of all studies identified by the search strategy.

Data collection and analysis

Selection of studies

We independently screened the results of the search to select potentially relevant studies. We then independently applied eligibility criteria to the potentially relevant studies. These criteria were based on the type of participant, study design, intervention, comparisons, and outcomes. We resolved differences in opinion through discussion. Where there was ambiguity, we sought clarification from the trial authors. We excluded studies that did not meet these criteria and stated the reason in the 'Characteristics of excluded studies'.

Data extraction and management

Afolabi Lesi extracted data on methods, participants, interventions, and outcomes from the trials, and Martin Meremikwu independently cross checked these data. Where there were differences, we referred to the original paper. We entered the data into Review Manager 5. Where possible, we scrutinized the data sources for multiple publications from the same data sets.

Assessment of risk of bias in included studies

We independently assessed the risk of bias in the trials to be included with regard to the allocation sequence, concealment of allocation, blinding, and completeness of the trial. We classified generation of the allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Jüni 2001. We classified blinding as open (all parties are aware of the treatment given), single (participant or care provider or assessor is unaware of the treatment given), or double blind (through the use of a placebo – either the participant and the care provider, or the participant

and assessor are unaware of the treatment given). We considered loss to follow up to be adequate if it is less than 10%. Wherever necessary, we contacted trial authors for clarification.

Data synthesis

We combined binary data using risk ratio (RR) and combined continuous data using the mean difference (MD). We used 95% confidence intervals (CI). If there was evidence of skewed data, or data were presented using medians and ranges, we presented the data in tables only.

Where trials presented results using time-to-event or censored data analysis, we intended to extract estimates of log hazards ratio and variance using methods proposed by Parmar 1998.

We assessed heterogeneity by visually examining the forest plot and using the chi-squared test for heterogeneity with a 10% level of statistical significance. In the absence of homogeneity of treatment effects, we intended to use a random-effects model, and if the number of studies permitted, to investigate the heterogeneity using the following subgroups: children compared with adults; and high compared with low transmission of malaria.

We examined funnel plots for asymmetry, which could be caused by publication bias, differences in methodological quality, or heterogeneity of results.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Eligibility

We identified 11 potentially relevant publications, of which four met the inclusion criteria (Fargier 1991; Pasvol 1991; Tombe 1992; Assimadi 2002). We have provided the reasons for excluding studies in the 'Characteristics of excluded studies'. The included trials are described in the 'Characteristics of included studies' and are summarized below.

Participants

The trials included a total of 164 participants, but only 144 were available for analysis because 20 children (out of 59) in Pasvol 1991 had been randomized to receive intramuscular quinine. Tombe 1992 and Pasvol 1991 studied people with severe malaria: Tombe 1992 studied 33 people aged 14 years or older, and Pasvol 1991 studied 59 children. Fargier 1991 and Assimadi 2002 studied people with cerebral malaria: Fargier 1991 studied 20 people aged 15 years or older, and Assimadi 2002 studied 72 children between 8 months and 15 years old. Fargier 1991 provided medians and ranges that were not adequate for meta-analysis. We contacted trial authors for further information, but none responded.

Interventions

Tombe 1992, Pasvol 1991, and Assimadi 2002 used a quinine loading dose of 20 mg/kg (salt), while Fargier 1991 used 16 mg/kg (base). Quinine was given by both intramuscular and intravenous route in the Pasvol 1991 trial, while the other three trials used only intravenous infusion. We did not include the participants (n = 20) in treatment arm of Pasvol 1991 that received intramuscular quinine.

Outcome measures

Three trials reported on the primary outcome of death, two reported on coma recovery time, fever clearance time and parasite clearance time, and one trial reported on convulsions and the number with asexual parasitaemia at 24 and 48 hours. Three trials reported on adverse events (but not anaemia), and two of these also reported neurological sequelae. Fargier 1991 reported duration of coma and the parasite clearance time, but did not provide adequate data for meta-analysis (*see* Table 2 for details).

Table 2. Comparison of treatment groups given intravenous quinine (Fargier 1991)[a]

Outcome	Loading dose	No loading dose	P value
Mean age (years)	24.2	22.1	Not statistically significant
Glasgow coma score on admission	8.6 (6 to 11)	8.8 (8 to 11)	Not statistically significant
Duration of coma before admission (h)	10.0	10.2	Not statistically significant

Table 2. Comparison of treatment groups given intravenous quinine (Fargier 1991)[a] (*Continued*)

Duration of coma after start of treatment (h)	6.8 (3 to 14)	13.0 (8 to 24)	0.003
Parasite clearance time (h)	40.8	52.2	0.05

[a] Non-parametric Mann-Whitney U test corrected for ties; figures presented are median (range) except where otherwise stated.

Risk of bias in included studies

The methodological quality of the trials is summarized in Table 3.

Table 3. Risk of bias assessment

Trial	Sequence	Concealment	Blinding	Loss to follow up
Assimadi 2002	Unclear	Unclear	None	Unclear[a]
Fargier 1991	Adequate (using random-number tables)	Unclear	None	Unclear[a]
Pasvol 1991	Adequate (using computers)	Adequate (sealed envelopes)	None	Inadequate (loading dose group: 21 randomized, 1 excluded, 2 had another severe diagnosis (meningitis), 18 analysed; uniform dose group: 22 randomized, 1 excluded, 1 withdrew, 20 analysed)
Tombe 1992	Adequate (using random-number tables)	Unclear	None	Unclear[a]

[a] No information in the published trial, and the trial authors did not respond to our request for clarification.

Generation of allocation sequence

All the trials were reported by the trial authors to be randomized, but none stated the method used to generate allocation sequence. Two trialists, G Pasvol and M Tombe, responded to our request for further information and clarified that the allocation sequence in their studies was generated using computers and random-number tables respectively.

Allocation concealment

Allocation concealment was unclear in three trials. We were able to determine that Pasvol 1991 used an adequate method for concealing treatment allocation (sealed envelopes) from his correspondence, but M Tombe did not provide explicit clarification.

Blinding

It was also unclear whether the trials were blinded; from correspondence with G Pasvol and M Tombe, we were able to determine that there was no attempt to mask treatment from the participants or the investigators.

Loss to follow up

The loss to follow up was unclear in three trials and was inadequate in Pasvol 1991, which reported over 10% loss to follow up (80.4% of randomized participants available for analysis).

Effects of interventions

Death

Three trials reported deaths (Pasvol 1991; Tombe 1992; Assimadi 2002). Eleven deaths were recorded among 144 participants in both groups. The difference was not statistically significant (RR 0.62, 95% CI 0.19 to 2.04; Analysis 1.1). We did not detect statistically significant heterogeneity between these data sets.

Coma recovery time

Pasvol 1991 and Assimadi 2002 did not report a statistically significant difference between both groups (WMD 5.17 hours, 95% CI -1.14 to 11.47; Analysis 1.2).

Convulsions

Pasvol 1991 reported convulsions in 13 out of 39 participants in both groups (RR 0.73, 95% CI 0.29 to 1.84; Analysis 1.3).

Fever clearance time and parasite clearance time

Pasvol 1991 and Tombe 1992 reported on both outcomes. Those participants that received a loading dose had both a statistically significantly shorter fever clearance time (WMD -11.11 hours, 95% CI -20.04 to -2.18; Analysis 1.4) and parasite clearance time (WMD -7.44 hours, 95% CI -13.24 to -1.64; Analysis 1.5) than those that did not. The test for heterogeneity for both outcomes was not statistically significant.

Number with asexual parasitaemia at 24 hours and 48 hours

Assimadi 2002 reported no statistically significant difference between both groups of participants with asexual parasitaemia at 24 hours (RR 1.27, 95% CI 0.87 to 1.84; Analysis 1.6) and 48 hours (RR 0.08, 95% CI 0.00 to 1.39; Analysis 1.7).

Neurological sequelae

Pasvol 1991 and Assimadi 2002 identified neurological sequelae in both the loading dose group (2/53) and no loading dose group (4/58) (RR 0.56, 95% CI 0.11 to 2.90; Analysis 1.8).

Adverse events

See Analysis 1.9. Pasvol 1991 and Tombe 1992 reported hypoglycaemia in 7 out of 72 participants across both groups (RR 1.39, 95% CI 0.32 to 6.00). Tombe 1992 also reported tinnitus, hearing loss, hypotension (low diastolic blood pressure), vomiting, abdominal pain, blurred vision, urticarial rash, and phlebitis. Only hearing loss differed statistically significantly between the two study groups. There was a statistically significant difference in the number of participants receiving the quinine loading dose that had partial hearing loss (10/17) compared with the number receiving no quinine loading dose (3/16) (RR 3.14, CI 1.05 to 9.38). The trial authors reported that all the participants "regained their hearing" by day 15 at follow up (Tombe 1992). Assimadi 2002 reported that only one participant in the loading dose group had any abnormalities of heartbeat (prolonged QT interval) (RR 3.17, 95% CI 0.13 to 75.24). None of the trials reported any cinchonism.

DISCUSSION

The allocation sequence was adequately generated in two of the four trials included in this review (Pasvol 1991; Tombe 1992). Allocation concealment was adequate (using sealed envelopes) in only one trial (Pasvol 1991). We note that there was no attempt to mask the treatment from the participants or the investigators. We recognize the difficulty of completely blinding treatment in trials of this nature where the volume of the loading dose obviously differs, and that in almost all cases involving children the doses to be given have to be worked out on the field after estimating the child's weight. Nevertheless, we consider that these methodological issues have not been uniformly handled in the trials. Failing to conceal allocation or blind clinical trials or even failure to do an intention-to-treat analysis increases the risk of bias and brings the internal validity of the results to question (Schulz 1995).

As a result of the small number of participants and deaths in each trial, there might be some uncertainty surrounding the estimate of risk ratio and any inferences could be misleading. Overall there were not enough trials to investigate the role of the age of the participants with severe malaria, the differences in pattern of illness, and the local endemicity pattern. About a third of the participants in the included trials were adults (Fargier 1991; Tombe 1992), and the remainder were children (Pasvol 1991; Assimadi 2002). The pattern of severe malaria in the trials varied. Two trials included people only with cerebral malaria (Fargier 1991; Assimadi 2002), the other two included people with different disorders recognized in the syndrome of severe malaria (WHO 2000).

From the results it appears that there is insufficient evidence to determine whether using a high first (loading) dose of quinine reduces deaths from severe malaria. The presence of convulsion

and the duration of coma are of prognostic significance (Jaffar 1997). There is also insufficient evidence to determine whether giving a loading dose is associated with fewer convulsions or a shorter recovery of consciousness.

With regard to fever and parasite clearance times, the loading dose regimen offers an advantage over the no loading dose regimen. However, this conclusion is based on the results of two small trials.

Concerning adverse events with quinine, the results show that the loading dose had a statistically significant association with partial hearing loss. Although the trialist who reported this outcome effect described it as transient, disappearing by day 15 at follow up (Tombe 1992), we note that the effect can be distressing for the patient.

The principal goal of treatment in severe malaria is to prevent people from dying. The limited data available from this review shows that there is insufficient evidence to determine whether giving a quinine loading dose to people with severe malaria offers any additional benefit with regards to preventing death. These results need to be interpreted with caution given the small size of the trials, the wide confidence intervals for all the outcome measures studied, and the mostly varied and sometimes uncertain methodological quality of the individual trials.

AUTHORS' CONCLUSIONS

Implications for practice

High first dose quinine reduced fever clearance time and parasite clearance time in severe malaria. There is insufficient evidence to demonstrate directly an effect on death, convulsions, hypoglycaemia, or coma recovery time

Implications for research

Larger, better quality trials evaluating the benefits or harm of quinine loading dose in cerebral malaria are warranted. Researchers conducting trials in severe malaria should use pragmatic outcomes, including death and number of convulsions, as primary outcome measures for benefit rather than depend on parasite or fever clearance times.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Assimadi 2002

Methods	Randomized controlled trial
Participants	Number of participants: 72 Inclusion criteria: children between 8 months to 15 years with cerebral malaria
Interventions	1. Loading dose: 17.5 mg/kg intravenous quinine base followed 8 h later by 8.7 mg/kg and then every 12 h 2. Uniform dose: 13.1 mg/kg intravenous quinine base every 12 h
Outcomes	1. Death 2. Duration of coma 3. Parasite clearance time 4. Adverse events
Notes	Study location: Lome, Republic of Benin Parasite counts and clinical assessments done every 6 h

Fargier 1991

Methods	Randomized controlled trial
Participants	Number of participants: 20 Inclusion criteria: 15 years and above with cerebral malaria
Interventions	1. Loading dose: 16 mg/kg intravenous quinine base followed by 8 mg/kg every 8 h 2. Uniform dose: 8 mg/kg intravenous quinine base every 8 h
Outcomes	1. Duration of coma 2. Parasite clearance time
Notes	Study location: Yaounde, Cameroon (Central Africa)

Pasvol 1991

Methods	Randomized controlled trial
Participants	Number of participants: 59; 20 not included in the final analysis as they had been randomized to a group that received intramuscular quinine Inclusion criteria: children with severe malaria
Interventions	1. High initial dose: 20 mg/kg intravenous or intramuscular quinine salt followed by 10 mg/kg every 12 h 2. Uniform dose: 5 to 10 mg/kg intravenous quinine salt every 12 h

Pasvol 1991 (*Continued*)

Outcomes	1. Death 2. Convulsion 3. Fever clearance time 4. Parasite clearance time 5. Coma recovery time 6. Adverse events
Notes	Study location: Kilifi, Kenya Parasite counts and clinical parameters every 6 h

Tombe 1992

Methods	Randomized controlled trial
Participants	Number of participants: 33 Inclusion criteria: aged 14 years and above with severe malaria
Interventions	1. Loading dose: 20 mg/kg intravenous quinine salt followed by 10 mg/kg every 8 h 2. Uniform dose: 10 mg/kg quinine salt every 8 h
Outcomes	1. Death 2. Fever clearance time 3. Parasite clearance time 4. Adverse events
Notes	Study location: Nairobi, Kenya Parasite counts every 6 h

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

Davis 1988	Clinical trial; not a randomized controlled trial
Davis 1990	Clinical trial; not a randomized controlled trial
Mehta 1994	Case control study; participants matched for age and sex; not a randomized controlled trial
van der Torn 1998	Not a randomized controlled trial
White 1983	Some participants did not have severe malaria
Winstanley 1994	Clinical trial; not a randomized controlled trial

DATA AND ANALYSES

Comparison 1. High first (loading) dose compared with no loading dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3	144	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.19, 2.04]
2 Coma recovery time	2	99	Mean Difference (IV, Fixed, 95% CI)	5.17 [-1.14, 11.47]
3 Convulsions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Fever clearance time	2	68	Mean Difference (IV, Fixed, 95% CI)	-11.11 [-20.04, -2.18]
5 Parasite clearance time	2	67	Mean Difference (IV, Fixed, 95% CI)	-7.44 [-13.24, -1.64]
6 Number with asexual parasitaemia at 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Number with asexual parasitaemia at 48 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Neurological sequelae	2	111	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.11, 2.90]
9 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Hypoglycaemia	2	72	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.32, 6.00]
9.2 Tinnitus	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.33, 24.43]
9.3 Hearing loss	1	33	Risk Ratio (M-H, Fixed, 95% CI)	3.14 [1.05, 9.38]
9.4 Cinchonism	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.5 Hypotension (diastolic blood pressure < 60 mm mercury)	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.19]
9.6 Arrhythmia (prolonged QT interval)	1	72	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [0.13, 75.24]

Analysis 1.1. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 1 Death.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

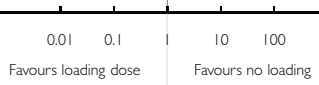
Outcome: 1 Death

Study or subgroup	Loading dose n/N	No loading dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Assimadi 2002	2/35	2/37		29.2 %	1.06 [0.16, 7.10]
Pasvol 1991	1/18	4/21		55.4 %	0.29 [0.04, 2.38]
Tombe 1992	1/17	1/16		15.5 %	0.94 [0.06, 13.82]
Total (95% CI)	**70**	**74**		**100.0 %**	**0.62 [0.19, 2.04]**

Total events: 4 (Loading dose), 7 (No loading dose)

Heterogeneity: Chi^2 = 0.89, df = 2 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 0.79 (P = 0.43)



Analysis 1.2. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 2 Coma recovery time.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

Outcome: 2 Coma recovery time

Study or subgroup	Loading dose N	Mean(SD)	No loading dose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Assimadi 2002	35	35.5 (17.8)	37	28.6 (14.4)		70.6 %	6.90 [-0.60, 14.40]
Pasvol 1991	13	14 (18)	14	13 (12)		29.4 %	1.00 [-10.63, 12.63]
Total (95% CI)	**48**		**51**			**100.0 %**	**5.17 [-1.14, 11.47]**

Heterogeneity: Chi^2 = 0.70, df = 1 (P = 0.40); I^2 =0.0%

Test for overall effect: Z = 1.61 (P = 0.11)

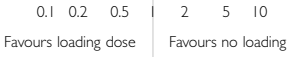
Analysis 1.3. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 3 Convulsions.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

Outcome: 3 Convulsions

Study or subgroup	Loading dose n/N	No loading dose n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Pasvol 1991	5/18	8/21		0.73 [0.29, 1.84]



Analysis 1.4. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 4 Fever clearance time.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

Outcome: 4 Fever clearance time

Study or subgroup	Loading dose N	Mean(SD)	No loading dose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pasvol 1991	18	15 (12)	21	30 (27)		48.6 %	-15.00 [-27.81, -2.19]
Tombe 1992	15	44 (13.92)	14	51.43 (19.62)		51.4 %	-7.43 [-19.89, 5.03]
Total (95% CI)	**33**		**35**			**100.0 %**	**-11.11 [-20.04, -2.18]**

Heterogeneity: $Chi^2 = 0.69$, df = 1 (P = 0.41); $I^2 = 0.0\%$

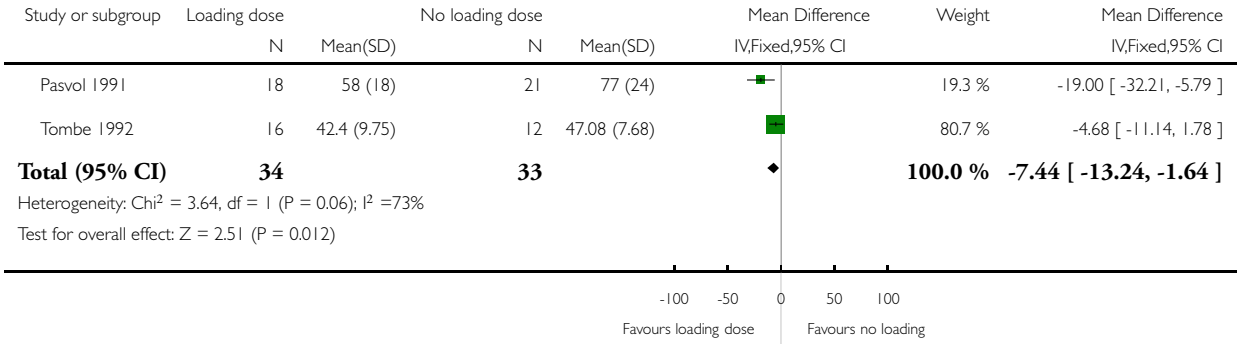
Test for overall effect: Z = 2.44 (P = 0.015)

Analysis 1.5. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 5 Parasite clearance time.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

Outcome: 5 Parasite clearance time

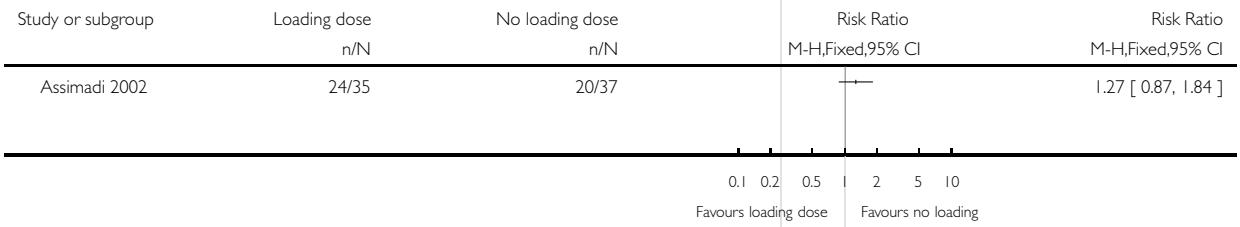


Analysis 1.6. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 6 Number with asexual parasitaemia at 24 hours.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

Outcome: 6 Number with asexual parasitaemia at 24 hours



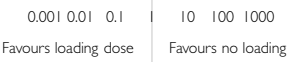
Analysis 1.7. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 7 Number with asexual parasitaemia at 48 hours.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

Outcome: 7 Number with asexual parasitaemia at 48 hours

Study or subgroup	Loading dose n/N	No loading dose n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Assimadi 2002	0/35	6/37		0.08 [0.00, 1.39]



Analysis 1.8. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 8 Neurological sequelae.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

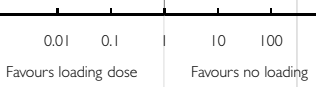
Outcome: 8 Neurological sequelae

Study or subgroup	Loading dose n/N	No loading dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Assimadi 2002	1/35	2/37		51.3 %	0.53 [0.05, 5.57]
Pasvol 1991	1/18	2/21		48.7 %	0.58 [0.06, 5.91]
Total (95% CI)	**53**	**58**		**100.0 %**	**0.56 [0.11, 2.90]**

Total events: 2 (Loading dose), 4 (No loading dose)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%

Test for overall effect: Z = 0.70 (P = 0.48)



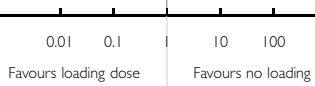
Analysis 1.9. Comparison 1 High first (loading) dose compared with no loading dose, Outcome 9 Adverse events.

Review: High first dose quinine regimen for treating severe malaria

Comparison: 1 High first (loading) dose compared with no loading dose

Outcome: 9 Adverse events

Study or subgroup	Loading dose n/N	No loading dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Hypoglycaemia					
Pasvol 1991	1/18	2/21		64.2 %	0.58 [0.06, 5.91]
Tombe 1992	3/17	1/16		35.8 %	2.82 [0.33, 24.43]
Subtotal (95% CI)	**35**	**37**		**100.0 %**	**1.39 [0.32, 6.00]**
Total events: 4 (Loading dose), 3 (No loading dose)					
Heterogeneity: Chi^2 = 0.95, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
2 Tinnitus					
Tombe 1992	3/17	1/16		100.0 %	2.82 [0.33, 24.43]
Subtotal (95% CI)	**17**	**16**		**100.0 %**	**2.82 [0.33, 24.43]**
Total events: 3 (Loading dose), 1 (No loading dose)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.94 (P = 0.35)					
3 Hearing loss					
Tombe 1992	10/17	3/16		100.0 %	3.14 [1.05, 9.38]
Subtotal (95% CI)	**17**	**16**		**100.0 %**	**3.14 [1.05, 9.38]**
Total events: 10 (Loading dose), 3 (No loading dose)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.041)					
4 Cinchonism					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Loading dose), 0 (No loading dose)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 Hypotension (diastolic blood pressure < 60 mm mercury)					
Tombe 1992	16/17	15/16		100.0 %	1.00 [0.84, 1.19]
Subtotal (95% CI)	**17**	**16**		**100.0 %**	**1.00 [0.84, 1.19]**
Total events: 16 (Loading dose), 15 (No loading dose)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.96)					
6 Arrhythmia (prolonged QT interval)					
Assimadi 2002	1/35	0/37		100.0 %	3.17 [0.13, 75.24]
Subtotal (95% CI)	**35**	**37**		**100.0 %**	**3.17 [0.13, 75.24]**



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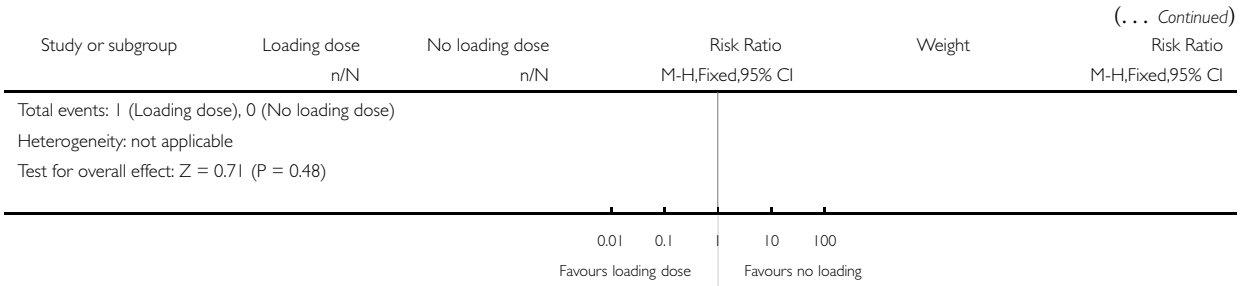

WHAT'S NEW

Last assessed as up-to-date: 18 February 2009.

19 February 2009	New search has been performed	Search updated. No new studies found

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 3, 2002

13 August 2008	Amended	Converted to new review format with minor editing. Plain language summary added to review.
31 July 2006	New search has been performed	New studies sought but none found; search dates updated.
30 March 2004	New citation required and conclusions have changed	Issue 3, 2004: We included a trial published that studied 72 children with cerebral malaria. We added neurological sequelae to the list of outcome measures.

CONTRIBUTIONS OF AUTHORS

Afolabi Lesi (AL) and Martin Meremikwu (MM) identified the topic. AL wrote the protocol, designed the eligibility and validity criteria, and the data extraction forms. AL and MM extracted the data. AL wrote the results and the discussion and MM revised them.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- College of Medicine, University of Lagos, Nigeria.

External sources

- Department for International Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*administration & dosage]; Injections, Intravenous; Malaria [*drug therapy]; Quinine [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans