Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial

*South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group**

Summary

Background **In the treatment of severe malaria, intravenous artesunate is more rapidly acting than intravenous quinine in terms of parasite clearance, is safer, and is simpler to administer, but whether it can reduce mortality is uncertain.**

Methods **We did an open-label randomised controlled trial in patients admitted to hospital with severe falciparum malaria in Bangladesh, India, Indonesia, and Myanmar. We assigned individuals intravenous artesunate 2·4 mg/kg bodyweight given as a bolus (n=730) at 0, 12, and 24 h, and then daily, or intravenous quinine (20 mg salt per kg loading dose infused over 4 h then 10 mg/kg infused over 2–8 h three times a day; n=731). Oral medication was substituted when possible to complete treatment. Our primary endpoint was death from severe malaria, and analysis was by intention to treat.**

Findings **We assessed all patients randomised for the primary endpoint. Mortality in artesunate recipients was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34·7% (95% CI 18·5–47·6%; p=0·0002). Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk 3·2, 1·3–7·8; p=0·009).**

Interpretation **Artesunate should become the treatment of choice for severe falciparum malaria in adults.**

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Introduction

Quinine has been the mainstay of treatment of severe malaria since the introduction of Cinchona Bark to European medicine in the 1630s. There is evidence of a decline in the efficacy of the drug in southeast Asia, in terms of parasite and fever clearance in uncomplicated malaria and coma recovery times in severe malaria, but there is no indication of a corresponding rise in mortality.[1,2] There have been occasional case reports[3–5] of treatment not curing severe malaria, but these reports are limited by the absence of measurements of plasma quinine concentrations.[6] Quinine, because it can be relied on, is the only drug recommended for the treatment of severe malaria throughout Africa, South America, and most of Asia. But even with prompt administration of quinine in maximum doses the mortality of severe malaria remains high. Cerebral malaria, the most prominent manifestation of severe malaria, has a treated mortality rate of 15–20%. With multiple vital organ dysfunction, the mortality rate can rise above 30%.[7,8] Despite many treatment trials, no intervention has been shown conclusively to reduce these high figures. Indeed, no randomised controlled trial on severe malaria has shown a convincing benefit for any intervention over standard treatment with parenteral quinine alone, and many adjuvant treatments have proved harmful. Quinine has a narrow therapeutic ratio.[8] In the treatment of severe malaria, parenteral quinine is given either by intramuscular injection or as slow rate-controlled intravenous infusions,[7–9] since rapid injection results in potentially lethal hypotension. Intramuscular administration is painful, and can cause sterile abscesses, sciatic nerve damage, and predispose to lethal tetanus.[10] Blindness and deafness can follow self poisoning, but these adverse effects are rare in severe malaria, whereas quinine induced hyperinsulinaemic hypoglycaemia is a common and serious complication.[7,8,11]

The rediscovery of qinghaosu (artemisinin) in China in 1972[12] and the subsequent synthesis of artemether and artesunate have provided highly effective alternatives to quinine.[13] The artemisinin derivatives are the most rapidly acting and potent of all the antimalarial drugs. They can be given once daily and are safer and easier to administer than quinine. Artesunate or artemether given orally are an essential component of the combination treatment of uncomplicated falciparum malaria, which is now accepted as the treatment of choice.[14] In several southeast Asian countries, parenteral artemisinin derivatives are used in preference to quinine for severe malaria, but quinine is still the drug of choice in most of the malaria-affected regions of the world.[7,8]

The largest clinical trials done on severe malaria have been randomised comparisons of artemether and quinine.[15] When these trials began 14 years ago in Vietnam, the UNICEF-UNDP-World Bank-WHO Tropical Disease Research Special Programme for Research and Training in Tropical Diseases (WHO-TDR) favoured parenteral artemether, and the closely related compound artemotil, over artesunate. The results of these trials[15,16] showed that although artemether was safer and easier to use than quinine, overall survival was not significantly different. In

prospectively defined subgroup analyses, artemether did reduce mortality significantly in adults from southeast Asia, but not in children from Africa. Findings of studies on the pharmacokinetics of the artemisinin derivatives suggest that artesunate would have been a better choice than artemether; artemether is an oil-based formulation that releases the drug slowly and erratically from the injection site,[17–20] whereas artesunate can be given intravenously and is absorbed reliably and rapidly after intramuscular injection with peak concentrations arising within 1 h.[20–22] Artesunate and its main active metabolite dihydroartemisinin have relative in-vitro potency, by comparison with artemether, of 2·9 and 4·0, respectively.[23] Results of a pilot randomised comparison[24] of intravenous artesunate and intravenous quinine in patients with severe malaria (n=113) on the north-western border of Thailand showed that mortality was 22% in the quinine group and 12% in the artesunate group. Our aim was, therefore, to establish conclusively which, of parenteral artesunate or parenteral quinine, is the more effective drug for the treatment of severe malaria.

Methods

Participants

See http://www.sequamat.info

See Lancet Online for webtable

Between June, 2003, and May, 2005, we did a multicentre, open-label, randomised comparison of parenteral artesunate and parenteral quinine in patients admitted to hospital with severe falciparum malaria. The participating centres (webtable) were located in Bangladesh, Myanmar (Burma), India, and Indonesia. Our inclusion criteria were patients' age older than 2 years, a positive blood antigen stick test for *Plasmodium falciparum* histidine rich protein 2 (HRP2; Paracheck, Orchid Biosystems, Goa, India), and a diagnosis of severe malaria, according to the admitting physician. We did not include patients if there was a 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, or if there was known allergy to one of the artemisinin derivatives or quinine.

All patients, or their attendant relative or guardian, provided written informed consent, and the study was approved by every participating institution's local or national ethics committee and the Oxford tropical research ethics committee.

Procedures

Patients with suspected severe malaria were admitted and examined. We confirmed their diagnosis of malaria with an HRP2-antigen based rapid test (Paracheck), and kept an independent sequential record of all patients assessed. We randomised patients to intravenous artesunate or quinine. The two-step randomisation was produced with a computer generated randomisation list. After informed consent was obtained, we signed and dated a numbered sealed envelope across the seal, then opened it to reveal a unique study number. This number did not indicate the treatment allocation, but referred to a separate sealed hardcover box, containing the study drug, case record form, and all disposables needed for drug administration and blood sampling. Hence, local investigators were unaware of the allocated treatment until after the patients had been randomised. The trial centre, microscopists assessing blood slides, and data analysts remained unaware of treatment allocation until the end of the study. We retained all envelopes, boxes, and records for subsequent inspection by the study monitors.

A peripheral blood smear was stored for later quantitative parasite counting, and blood was taken for immediate haematocrit and biochemical analysis with the EC8+ card for a handheld battery-operated biochemical analyser (i-STAT; Abbott, East Windsor, NJ, USA). This machine provided an immediate hardcopy readout of biochemical results with time and date. Treatment was started immediately. All other aspects of supportive treatment, based on WHO guidelines,[7,8] were unaffected by the trial.

If assigned, artesunate 2·4 mg/kg bodyweight (Guilin Pharmaceutical Factory, Guangxi, People's Republic of China) was given on admission, then at 12 h, 24 h, and thereafter once daily until oral medication could be taken reliably. Every 60 mg vial contained anhydrous artesunic acid, which we dissolved in 1 mL 5% sodium bicarbonate and then mixed with 5 mL of 5% dextrose before injecting as a bolus into an indwelling intravenous cannula. When the patient had recovered sufficiently to take tablets, we administered oral artesunate 2 mg salt per kg per day to complete a total course (including parenteral treatment) of 7 days, providing a total cumulative dose of 17–18 mg/kg.

Alternatively, quinine dihydrochloride (Government Pharmaceutical Organisation, Bangkok, Thailand) was given in a 20 mg/kg loading dose infused over 4 h (in 500 mL 5% dextrose water or 0·9% saline), followed by 10 mg/kg infused over 2–8 h three times a day until starting oral therapy. When the patient had recovered sufficiently to take tablets, we administered oral quinine 10 mg/kg every 8 h to provide a total quinine course of 7 days.

We combined both regimens, except in children younger than age 8 years or pregnant women, with oral doxycycline 100 mg twice a day for 7 days once the patient could take oral medication. The hospitals in Chittagong, Bangladesh, and in Orissa, India, did not give doxycycline with either study drug.

External monitors regularly inspected the trial sites. We checked drug content and quality in random ampoules taken from the purchase lots. The data safety and monitoring committee chairman also made periodic checks of clinical and laboratory variables and

other aspects of management to ascertain whether randomisation was adequate. We replaced any study centre that enrolled a predominance of non-severe patients with another centre in the same country. We entered all data in duplicate into a purpose-designed database. All malaria slides were read in the reference laboratories in the Shoklo Malaria Research Unit in Mae Sot, Thailand, or in the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Our primary endpoint was death from severe malaria—ie, in-hospital mortality—and secondary outcome measures were incidence of neurological sequelae, combined death or neurological sequelae, recovery times (times to eat, speak, sit, and discharge), and development of severe complications.

Statistical analysis

Our aim was to include 2000 patients with severe malaria, to be able to show a 33% reduction in mortality from 12% to 8% with a power of 80% and a confidence of 95%, allowing a drop out (ineligibility) rate of 5%. This estimate was based on about half of the enrolled patients subsequently fulfilling modified WHO criteria for severe malaria (panel),[25] and these patients having a 24% mortality (based on local figures). We gave all patients' data and outcomes to an independent data and safety monitoring committee whose remit included advising us to stop the trial if there was evidence beyond reasonable doubt that the results would change clinical practice. The trial was stopped on May 11, 2005.

We did the analysis according to a prespecified analytical plan. The primary analysis was by intention to treat. We also did a per-protocol analysis of the primary outcome and certain subgroup analyses (those related to prognostic factors: confirmed falciparum malaria; severe malaria and less severe malaria; age [children and adults]; sex; pregnancy [including fetal outcome]; pretreatment with an antimalarial; and with and without specified complications of severe malaria—ie, cerebral malaria, renal failure, jaundice, severe anaemia, acidosis, haemodynamic shock, and hyperparasitaemia [defined as >10% parasitaemia]). For the purposes of the per-protocol analysis, we based the diagnosis of falciparum malaria on the presence of asexual *P falciparum* parasites on the peripheral blood smear. An analysis of treatment effect in high-mortality and low-mortality study sites was also prespecified. For the severity subgroup analysis, we stratified patients retrospectively into two groups: those who fulfilled the criteria for severe malaria with a modification of definitions used by Hien and colleagues (panel),[25] and those who did not fulfil these criteria (ie, less severe malaria). Since we captured all mortality endpoints and there were no patients lost to follow up, a comparison of proportions rather than person-time rates was used in the analyses. Furthermore, because mortality from severe malaria is probably dependent on the quality of care across the different sites, we stratified comparisons between proportions by site.

We did analyses with Stata 9 software package (Statacorp, College Station, TX, USA). We stratified all main analyses by study site, and applied tests of homogeneity of treatment effects. Proportions were analysed with a stratified Mantel-Haenszel approach. We analysed time-to-event variables with Cox regression analysis.

Panel: Prospectively specified criteria used to define severe malaria

All measurements and assessments done on entry to study. A single criterion, in addition to asexual P falciparum *parasites on the peripheral blood film, was sufficient.*

- Glasgow coma scale <11/15 in adults, or Blantyre coma scale ⩽3/5 in children
- Shock, as assessed by admitting physician (low blood pressure and cool peripheries)
- Blood bicarbonate <15 mmol/L
- Haematocrit <20% and *P falciparum* parasitaemia >100 000/μL
- Visible jaundice and *P falciparum* parasitaemia >100 000/μL
- Blood urea nitrogen >17 mmol/L
- Asexual *P falciparum* parasitaemia >10%.
- Plasma glucose <2·2 mmol/L
- Respiratory distress (>32 breaths per min)

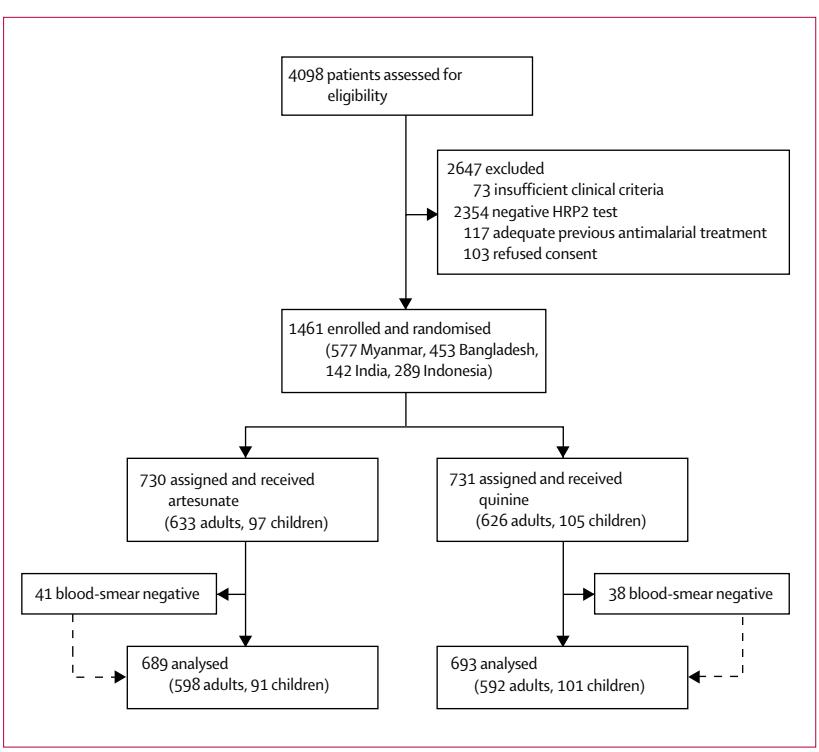

Figure 1: **Trial profile**

	Artesunate (n=730)	Quinine (n=731)
Sex		
Male	546 (75%)	529 (72%)
Female	184 (25%)	202 (28%)
Child (age <15 years)	97 (13%)	105 (14%)
Pregnant	23 of 133 (17%)	26 of 143 (18%)
Pretreatment with antimalarial drug	167 (23%)	142 (19%)
Pretreatment with quinine	103 (14%)	84 (11%)
Pretreatment with artemisinin derivative	25 (3%)	42 (6%)
Pretreatment with chloroquine	43 (6%)	21 (3%)
Pretreatment with sulphadoxine-pyrimethamine	9 (1%)	10 (1%)
Pretreatment with mefloquine	0	5 (1%)
Pretreatment with an effective antimalarial*	125 (17%)	118 (16%)
Severe malaria†	509 (70%)	541 (74%)
Malaria parasites on blood film	708 (97%)	716 (98%)
Hyperparasitaemia (>10%)	121 (17%)	108 (15%)
Complications on admission		
Coma (Glasgow coma scale <11 or Blantyre coma scale <3)	284 (39%)	304 (42%)
Convulsions	89 (12%)	87 (12%)
Jaundice (clinical)	355 (49%)	349 (48%)
Severe anaemia (haemoglobin <50 g/L)	40/683 (6%)	54/675 (8%)
Shock (clinical)	78 (11%)	92 (13%)
Acidosis (base excess less than −3·3 mmol/L)	308/662 (47%)	334/648 (52%)
Hypoglycaemia (blood glucose <2·2 mmol/L)	8/701 (1%)	17/693 (3%)
Respiratory distress	79 (11%)	96 (13%)
Blackwater fever	20 (3%)	16 (2%)
History of anuria	99 (14%)	135 (18%)

Data are number (%). *Pretreatment with quinine, an artemisinin derivative, or mefloquine. Excludes chloroquine and sulphadoxine-pyrimethamine, which are ineffective throughout this region. †See panel for definition.

Table 1: **Categorical baseline characteristics**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We randomised 1461 (730 assigned artesunate, 731 assigned quinine) of 4098 patients assessed for eligibility. Diagnosis of falciparum malaria was not confirmed by the presence of parasites on the blood smear in 79 (5%) of these patients. Patients with unconfirmed malaria were included in the main intention-to-treat analysis, but were excluded from the per-protocol analysis. Table 1 shows the baseline characteristics of all individuals randomised. In the artesunate group, 509 (70%) individuals had severe disease compared with 541 (74%) in the quinine group. Baseline characteristics and predictors of severity did not differ greatly between the groups (table 1 and table 2), except for history of anuria (an excess in the quinine group) and pretreatment with chloroquine (more in the artesunate group). History of anuria was subjective, depending on the recollection of patients or attendant relatives. There were no differences between the study groups in concentrations of blood urea nitrogen or levels of acidosis at admission. Antimalarial pretreatment was not associated with a difference in the overall severity of disease. The treatment effects on the main outcomes were not significantly affected by adjustment

	Artesunate (n=730)	Quinine (n=731)
Age (years); mean (95% CI)	27·9 (26·8–29·0)	27·9 (26·8–29·0)
Days of fever	5 (3–7, 0–120)	5 (3–7, 0–120)
Days of coma	0 (0–0·75, 0–4)	0·1 (0–1, 1–7)
Physical examination		
Weight (kg)	50 (43–55, 9–85)	50 (43–60, 9–100)
Temperature (°C)	38 (37·2–38·9, 35–41·5)	37·9 (37–38·9, 33·8–41·5)
Adult respiratory rate per min	24 (20–32, 12–103)	26 (20–32, 12–68)
Systolic blood pressure (mm Hg)	100 (90–115, 30–200)	100 (90–110, 30–180)
Diastolic blood pressure (mm Hg)	60 (60–70, 0–120)	60 (54–70, 0–100)
Glasgow coma scale (n=1425)	12 (9–15, 3–15)	12 (8–15, 3–15)
Blantyre coma scale (n=36)	4 (3–5, 1–5)	4 (3–5, 0–5)
Investigation		
Parasite count (per μL); geometric mean (95% CI)	39 850 (33 300–47 700)	31 050 (25 800–37 450)
Sodium (mmol/L)	134 (130–137, 108–159)	134 (130–138, 100–165)
Potassium (mmol/L)	3·9 (3·4–4·3, 2–8·8)	3·8 (3·4–4·3, 2–7·4)
Chloride (mmol/L)	101 (98–104, 77–130)	101 (98–105, 71–128)
Blood urea nitrogen (mmol/L of urea)	9·2 (5·4–17·8, 1·1–104)	10·4 (5·7–21·4, 1·1–86·8)
Haematocrit (%)	30 (22–36, 9–60)	29 (21–36, 5–62)
Haemoglobin (g/L)	100 (71–120, 26–200)	100 (70–120, 80–200)
pH	7·407 (7·352–7·448, 6·5–7·696)	7·4 (7·347–7·45, 6·542–7·582)
$paCO_2$ (mm Hg)	33 (28–38, 6–68)	32 (27–37, 7–83)
Total CO_2 (mmol/L)	22 (18–25, 2–45)	22 (17–25, 3–42)
Base excess (mmol/L)	−3 (−8 to 0, −30 to 22)	−4 (−9 to 0, −30 to 12)
Anion gap (mmol/L)	12·5 (0 to 16, −30 to 38)	13 (−1 to 16, −28 to 58)

Data are median (IQR, range) unless otherwise stated.

Table 2: **Continuous baseline characteristics**

	Artesunate (n=730)	Quinine (n=731)	Mantel-Haenszel stratified OR/hazard ratio [hr] (95% CI)	p (stratified)	p for homogeneity
In-hospital death	107 (15%)	164 (22%)	0·60 (0·45–0·79)	0·0002	0·39
Death within 48 h of entry	61 (8%)	75 (10%)	0·81 (0·57–1·16)	0·25	0·67
Death after 48 h of entry	46 (6%)	89 (12%)	0·48 (0·33–0·70)*	0·0001	0·73
In-hospital death (blood-smear positive)	105 of 689 (15%)	157 of 693 (23%)	0·62 (0·47–0·82)	0·0007	0·29
Neurological sequelae	7 (1%)	3 (<1%)	2·3 (0·59–8·8)	0·22	0·34
Combined outcome: in hospital death or neurological sequelae	114 (16%)	167 (23%)	0·63 (0·48–0·82)	0·0007	0·36
Fetal death	5 of 23 (22%)	5 of 26 (19%)	1·33 (0·28–6·18)	0·72	0·34
Time to discharge (days); median (IQR, range)	5 (4–8, 0–54)	5 (4–8, 0–45)	hr 0·93 (0·83–1·04)	0·20	0·77
Time to speak (days); median (IQR, range)	1 (0–2, 0–35)	1 (0–2, 0–21)	hr 0·97 (0·84–1·13)	0·73	0·82
Time to eat (days); median (IQR, range)	2 (0–3, 0–21)	2 (0–4, 0–47)	hr 0·91 (0·79–1·04)	0·17	0·69
Time to sit (days); median (IQR, range)	2 (0–3, 0–30)	2 (0–3, 0–45)	hr 0·91 (0·80–1·05)	0·19	0·82
Convulsions after entry	31 (4%)	43 (6%)	0·70 (0·44–1·12)	0·14	0·09
Shock developing after entry	26 (4%)	36 (5%)	0·72 (0·43–1·21)	0·22	0·59
Hypoglycaemia after entry	6 (<1%)	19 (3%)	0·31 (0·12–0·78)	0·009	0·94
Blackwater fever developing after entry	49 (7%)	33 (5%)	1·58 (0·94–2·65)	0·08	0·54
Dialysis after entry	60 (8%)	48 (7%)	1·25 (0·85–1·85)	0·25	0·011
Vasopressor treatment after entry	23 (3%)	24 (3%)	0·92 (0·52–1·64)	0·78	0·28
Mechanical ventilation after entry	26 (4%)	39 (5%)	0·65 (0·39–1·1)	0·11	0·40

Data are number (%) unless otherwise stated. Analysis by intention to treat unless otherwise indicated. Results stratified by study site. *Excludes patients who died within 48 h.

***Table* 3: Results by treatment group**

for either history of anuria or antimalarial pretreatment. Overall the two treatment groups were well balanced.

Mortality was 19% (271 of 1461) overall. Mortality in the artesunate group was 15% compared with 22% in the quinine group (relative risk 0·69, 95% CI 0·54–0·83; table 3). The result of the analysis on confirmed malaria (smear positive) cases only was similar (relative risk 0·69, 0·55–0·85; table 3). Of the 332 smear-positive patients who did not fulfil the criteria for severe malaria on admission, nine died (3%). Mortality in the patients who fulfilled the criteria for severe malaria was 24% (253 of 1050). 23 and 29 patients in the artesunate and quinine groups, respectively, died on the day of admission (OR 0·78, 0·45–1·36; p=0·38). Most of the treatment effect resulted from reduction in mortality after the first 24–48 h after entry to the study (table 3, figure 2). Overall mortality varied significantly between countries (from 9·3% in Indonesia to 28% in Bangladesh), but there was no significant heterogeneity in treatment effect (figure 3). The absolute risk reduction associated with artesunate treatment was fairly consistent, ranging from 5% to 9%. Thus the numbers needed to treat to save one life ranged from 11·1 to 20·2 between the countries.

Ten patients were discharged from hospital with residual neurological sequelae; seven in the artesunate group and three in the quinine group (p=0·23). Five individuals had psychiatric sequelae, four had persisting problems with balance (one of whom had both psychiatric sequelae and a tremor), and two had a hemiparesis. When we combined deaths and neurological sequelae, there were 114 (16%) adverse effects in the artesunate group and 167 (23%) in the quinine group (relative risk 0·70, 0·57–0·86; table 4). With the exception of hypoglycaemia there were no serious adverse effects that could be attributed to either treatment.

Among those who survived, there were no significant differences between the treatment groups for times to speak, eat, sit, and be discharged (table 3). There was a significant excess of hypoglycaemia after study entry in the quinine group compared with the artesunate group (RR 3·2, 95% CI 1·3–7·8; table 3). There were no differences between the study groups in the incidence of haemodynamic shock, convulsions, and blackwater fever, or in the use of supportive therapies (mechanical

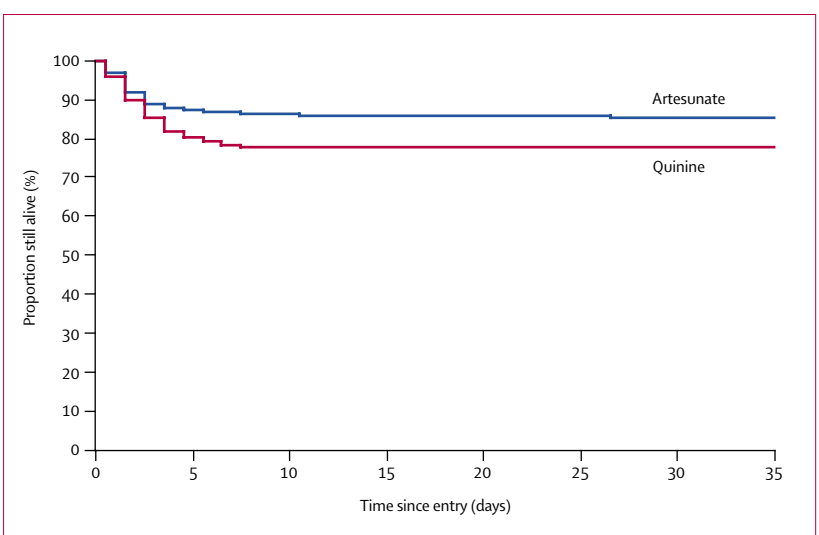

***Figure 2*: Survival curve of in-hospital mortality**
Patients either died in hospital or were discharged well, so all deaths included. To construct plot survival time of all discharged patients was set to 35 days.

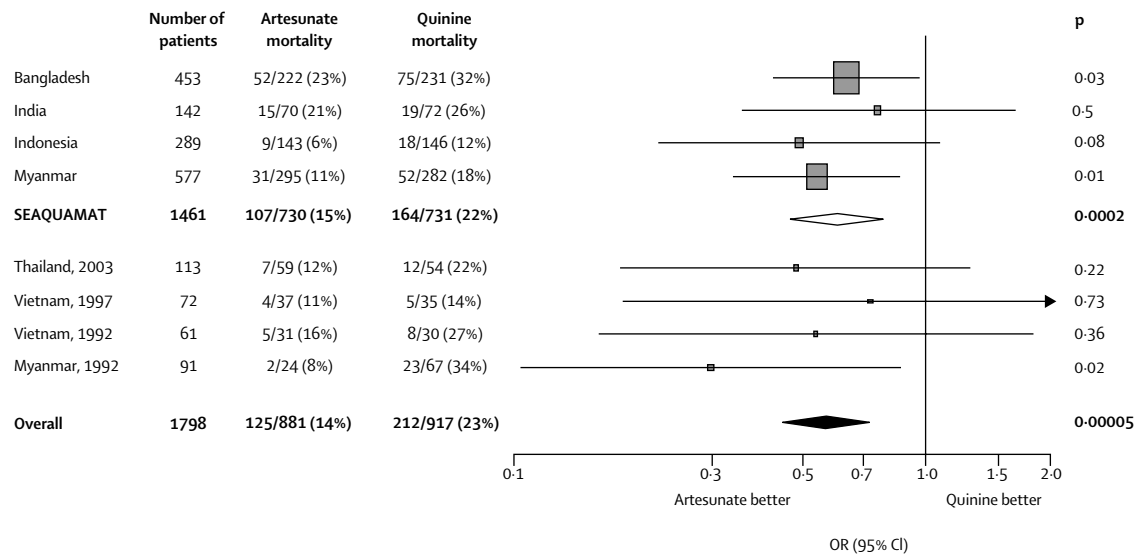

Figure 3: **Forest plot of mortalities comparing parenteral quinine and artesunate in treatment of severe malaria in SEAQUAMAT and previously published studies[23,26–28]**

Size of boxes proportional to number of events in individual trial and thus contribution to overall effect. Diamond=summary stratified OR and 95% CI.

	Number of patients	Artesunate mortality	Quinine mortality	OR (95% CI)	p	Ratio of OR (95% CI)	p for ratio of OR
Blood-smear positive	1382	105 of 689 (15%)	167 of 693 (23%)	0·62 (0·47–0·82)	0·0007	2·84 (0·36–22·2)	0·84
Blood-smear negative	79	2 of 41 (5%)	7 of 38 (18%)	0·22 (0·03–1·68)	0·11		
Adult	1259	102 of 531 (16%)	153 of 626 (24%)	0·61 (0·46–0·81)	0·0005	1·42 (0·41–4·85)	0·71
Child	202	5 of 97 (5%)	11 of 105 (11%)	0·43 (0·13–1·42)	0·15		
Male	1075	78 of 546 (14%)	123 of 529 (23%)	0·56 (0·41–0·77)	0·0003	0·81 (0·43–1·53)	0·26
Female	386	29 of 184 (16%)	41 of 202 (20%)	0·69 (0·40–1·21)	0·19		
Pregnant female	49	2 of 23 (9%)	3 of 26 (12%)	0·75 (0·09–6·41)	0·79	1·11 (0·12–10·25)	0·54
Non-pregnant female	337	27 of 161 (19%)	38 of 176 (22%)	0·68 (0·38–1·20)	0·18		
Pre-treatment	309	19 of 167 (11%)	37 of 142 (26%)	0·40 (0·21–0·75)	0·003	0·6 (0·3–1·21)	0·08
No pre-treatment	1152	88 of 563 (16%)	127 of 529 (22%)	0·66 (0·49–0·9)	0·008		
Low mortality site	783	34 of 397 (9%)	59 of 386 (15%)	0·53 (0·34–0·83)	0·005	0·83 (0·47–1·47)	0·26
High mortality site	678	73 of 333 (22%)	105 of 345 (30%)	0·64 (0·45–0·91)	0·01		
"Severe malaria"	1050	101 of 509 (20%)	152 of 541 (28%)	0·65 (0·48–0·87)	0·003	1·58 (0·56–4·58)	0·81
Not "severe malaria"	411	6 of 221 (3%)	12 of 190 (6%)	0·41 (0·15–1·11)	0·07		
Cerebral malaria*	563	82 of 272 (30%)	108 of 291 (37%)	0·71 (0·49–1·02	0·06	1·61 (0·87–2·98)	0·93
Not cerebral malaria*	820	23 of 418 (6%)	49 of 402 (12%)	0·44 (0·27–0·73)	0·001		
Renal failure*	282	51 of 136 (38%)	76 of 146 (52%)	0·51 (0·31–0·84)	0·007	0·74 (0·39–1·41)	0·18
No renal failure*	1026	47 of 525 (9%)	65 of 501 (13%)	0·69 (0·46–1·02)	0·06		
Unspecified*	74	7 of 28 (25%)	16 of 46 (35%)	0·66 (0·21–2·05)	0·47		
Jaundiced*	674	63 of 338 (19%)	85 of 336 (25%)	0·69 (0·47–1·01)	0·05	1·22 (0·7–2·15)	0·76
Not jaundiced*	708	42 of 351 (12%)	72 of 357 (20%)	0·57 (0·37–0·86)	0·007		
Severe anaemia*	318	18 of 157 (16%)	29 of 161 (18%)	0·6 (0·34–1·43)	0·32	0·96 (0·46–1·96)	0·45
No severe anaemia*	1011	81 of 508 (16%)	118 of 503 (24%)	0·63 (0·46–0·86)	0·004		
Unspecified*	53	6 of 24 (25%)	10 of 29 (35%)	0·81 (0·24–2·74)	0·73		
Acidosis*	613	77 of 294 (26%)	121 of 319 (38%)	0·58 (0·41–0·82)	0·002	0·83 (0·37–1·84)	0·32
No acidosis*	642	14 of 338 (4%)	18 of 304 (6%)	0·7 (0·34–1·43)	0·32		
Unspecified*	127	14 of 57 (25%)	18 of 70 (26%)	1·05 (0·45–2·43)	0·91		
Shock*	165	12 of 75 (16%)	27 of 90 (30%)	0·35 (0·15–0·85)	0·02	0·54 (0·21–1·37)	0·1
Not shocked*	1217	93 of 614 (15%)	130 of 603 (22%)	0·66 (0·49–0·87)	0·006		
Hyperparasitaemia*	229	28 of 121 (23%)	57 of 108 (53%)	0·26 (0·14–0·49)	0·0001	0·34 (0·17–0·69)	0·001
No hyperparasitaemia*	1153	77 of 568 (14%)	100 of 585 (17%)	0·77 (0·55–1·07)	0·11		

All analyses stratified by study site, and done by intention to treat unless otherwise indicated.[29] *Done on confirmed malaria (smear-positive) subset.

Table 4: **Results of prespecified subgroup analyses**

ventilation, vasopressor support, and dialysis). There was significant heterogeneity in the use of dialysis by study drug, which was restricted to Myanmar, and results from a small excess in dialysis at one study site in patients randomised to artesunate compared with three other study sites in the country where more quinine patients were appropriately dialysed (there are no dialysis facilities at the other three sites).

Two centres were discontinued during the trial; they recruited 155 patients of whom 13 died. Subgroup analyses were done in accordance with the prespecified analysis plan (table 4). With the exception of hyperparasitaemic patients, in every case the ORs for the treatment effect did not differ significantly between the subgroups.

There were 202 children (younger than age 15 years) in the study of whom 89 were aged younger than 6 years. The overall mortality in children was 8% (16 of 202). Although the treatment effect in favour of artesunate did not differ significantly from that in adults, by itself it was not significant in children. The treatment effect associated with artesunate was as good in patients who had received effective antimalarial treatment before admission as in those who had not (ratio of ORs 0·6, 95% CI 0·3–1·21). Pretreatment included quinine in 187 patients, an artemisinin derivative in 67, chloroquine in 64, and sulphadoxine-pyrimethamine in 19 (some patients received more than one drug). Post-hoc (not pre-specified) analyses of pretreatment drug subgroups revealed no significant patterns with respect to the treatment effect.

Patients with hyperparasitaemia (admission parasitaemia >10%) had a significantly greater treatment effect with artesunate than non-hyperparasitaemic patients (ratio of ORs 0·34, 0·17–0·69, p=0.001).

Discussion

Our findings in this large multicentre trial show that parenteral artesunate reduces mortality in patients with severe malaria by over a third compared with quinine. Although there were considerable differences in the intensive-care support available between the trial sites, this large reduction in mortality was consistent across countries and in all prospectively defined subgroups. Randomisation was adequate, and there were no significant confounding factors. The benefits of artesunate were evident mainly after the first day of treatment. This finding suggests that the lethal pathological processes in falciparum malaria that killed some of our patients shortly after admission were not preventable by improved antimalarial treatment, but after 24–48 h on treatment a clear and large advantage of artesunate emerged. This benefit presumably derives from greater parasiticidal activity. The main pharmacodynamic difference between artesunate and quinine is the much broader stage-specificity of action of the artemisinin compounds.[30] Artesunate kills circulating ring-stage parasites, which can then be removed by the spleen, whereas quinine does not.[31–33] Both artesunate and quinine are active against the more pathological cytoadhering stages that sequester in the venules and capillaries of vital organs. Thus, artesunate prevents maturation of the younger parasite stages and thereby prevents sequestration,[34] which reduces consequent microcirculatory obstruction.[26] This method of action is consistent with the finding that the difference in mortality between the two groups was greatest in those patients with high parasitaemias—ie, those for whom prevention of sequestration would be expected to provide the greatest benefit. The large reduction in mortality associated with artesunate treatment emphasises the central quantitative role of parasitised erythrocyte sequestration in the pathology of malaria, and it argues against a major role for hypothetical immuno-pathological processes that are quantitatively unlinked to the sequestered parasite biomass.

In the 1980s and early 1990s artemotil (arteether), and later artemether, were strongly supported over artesunate by WHO-TDR. This preference was declared before evidence of clinical benefit or data on human pharmacokinetics became available. In a meta-analysis of randomised trials,[15] which enrolled 1919 patients with severe malaria, artemether did not reduce mortality significantly when compared with quinine. In the prospectively defined subgroup of adults in southeast Asia there was a significantly lower mortality in the artemether recipients, which was not seen in African children. This finding was not sufficient to change treatment policies. In our trial, done mainly in adults, artesunate reduced the mortality of severe malaria by over a third compared with quinine. The size and direction of the treatment effect is similar to that seen in the much smaller previously published trials that compared artesunate and quinine, and a combined meta-analysis of these and the current trial gave an overall mortality OR in favour of artesunate of 0·57 (0·45–0·73), p=0·00005 (figure 3).[24,27,28,35] The most likely explanation for the much larger reduction in mortality with artesunate than with artemether is the pronounced difference in the pharmacokinetic properties of the two artemisinin compounds. Artemether is an oil-based formulation that is absorbed slowly and erratically after intramuscular injection, whereas both artesunate and quinine are water soluble and are absorbed rapidly and reliably after intramuscular injection,[16–22,36] and both can be given intravenously. Thus the pharmacodynamic advantage of artemether over quinine might have been offset by its poor absorption kinetics after intramuscular injection.

In our study, quinine was associated with hypoglycaemia. The incidence of reported hypoglycaemia after

starting treatment was relatively low by comparison with other series where blood glucose has been actively monitored,[11,25] and is probably an underestimate since clinical signs of hypoglycaemia are often absent in severe malaria. No other severe adverse effects could be attributed to either drug.

This trial was done mainly in adults in areas of low and unstable transmission. The results cannot be extrapolated directly to the treatment of severe malaria in children in areas of higher transmission. The clinical evolution of severe malaria is more rapid, and the range of vital organ dysfunction is different in children than in adults.[37] Furthermore, a greater proportion of the total mortality occurs within the first day after the start of treatment in children than in adults, providing less opportunity for a better antimalarial to save lives. In the artemether versus quinine trials,[15] no benefit of artemether was evident in African children. This finding suggests that the superiority of artesunate over quinine in severe malaria might be less obvious in African children. A trial with similar design to ours has just begun in Africa, the aim of which is to provide a definitive answer to this question.

For adults with severe malaria, artesunate should be the treatment of choice. The drug is more effective than quinine, is simple to administer, and is safe. The only serious adverse effect that has been clearly linked with artesunate is a rare type-1 hypersensitivity reaction, which arises in about one in 3000 treated patients.[38] By contrast, quinine is locally toxic (particularly as the acidic dihydrochloride salt) after intramuscular injection (often causing sciatic nerve damage), cannot be given by bolus intravenous injection, requires three-times daily administration, is associated with potentially serious hypoglycaemia, and is less effective than artesunate. Unfortunately, despite 20 years of use in east Asia, there is still no generally available formulation of parenteral artesunate made to Good Manufacturing Practices standards. Quality assured, affordable parenteral artesunate should be made widely available in malaria endemic areas as a matter of urgency.

Contributors

The coordinating committee designed the study; all investigators in Bangladesh, Myanmar, India, and Indonesia did the trial with support from the teams in Thailand; all investigators and the coordinating committee reviewed and discussed the results; the writing committee did the data analyses and prepared the report, which was then reviewed by all investigators.

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Conflict of interest statement

N J White is chairman, and M A Faiz and E Tijtra are members of the WHO antimalarial treatment guidelines committee. None of the other triallists or members of the writing committee has any conflict of interest.

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