*Original Article*

# Comparison of artesunate and quinine in the treatment of severe *Plasmodium falciparum* malaria at Kassala hospital, Sudan

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## Abstract

Introduction: There is a need to investigate the treatment (artesunate and quinine) of severe malaria, as this will influence the outcome of morbidity and the mortality of the disease.

Methodology: An open randomized trial conducted at Kassala, Sudan. Patients with severe *P. falciparum* malaria were randomly assigned to either intravenous artesunate at 2.4 mg/kg at 0, 12, and 24 hours, then daily, or intravenous quinine at a 20 mg/kg loading dose, then 10 mg/kg three times a day. Fever and parasite clearance and coma resolution time were compared between the two groups .

Results: The two groups (47 in each group) were well matched in the clinical and biochemical characteristics. Hypotension, convulsions, severe anemia, hypoglycemia, cerebral malaria, and jaundice were the predominant manifestations of severe malaria. The mean (SD) of the fever clearance (10.8 [5.5] *vs*. 14.0 [8.1] hours, $p = 0.028$) and the parasite clearance time (16.5 [6.4] *vs*. 21.7 [11.3] hours, $p = 0.007$) were significantly shorter in the artesunate-treated patients. In comatose patients, there was no difference between the two groups in coma resolution time. Following quinine infusion, ten patients developed tinnitus ($p < 0.001$), and four had hypoglycemia ($p = 0.033$). Tinnitus and hypoglycemia were not detected in the artesunate group. One patient in the artesunate group died.

Conclusions: Artesunate is more effective than quinine, in term of parasite and fever clearance time, in the treatment of *P. falciparum* malaria in eastern Sudan. The study found no difference between artesunate and quinine in coma resolution time.

**Key words:** quinine; artesunate; *Plasmodium falciparum*; Sudan

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## Introduction

Severe malaria is one of the medical emergencies in endemic countries where, if it is not treated, results in 100% mortality. However, the mortality is reduced to one-fifth of cases if prompt, effective anti-malarial treatment and supportive care are administered [1]. Therefore, an effective treatment with an appropriate drug is one of the main components of the World Health Organization's strategy to reduce malaria-related mortality [2]. Until recently, intravenous quinine (a cinchona alkaloid), which has potentially serious adverse effects, was the treatment of choice for severe malaria. Thereafter, artesunate was observed to be superior to quinine in the treatment of severe *Plasmodium falciparum* malaria [3-5]. Thus, intravenous artesunate has been recommended by the WHO as the first-line therapy for treatment of severe malaria [1].

Malaria is an important health problem in Sudan, where there have been an estimated nine million disease episodes and 44,000 deaths related to the disease [6]. Due to the spread of multidrug–resistant *P. falciparum*, Sudan and the majority of African countries adopted artemisinin-based combination therapies (ACTs), with artesunate + sulfadoxine–pyrimethamine (AS+SP) and artemether-lumefantrine (AL) becoming the recommended first- and second-line treatments for uncomplicated *P. falciparum* malaria, respectively [7,8]. Yet, quinine remains the main treatment for severe malaria, and intravenous artesunate is not included in Sudan's malaria treatment protocol and it is not registered in Sudan. Few published data exist on intravenous artesunate in the treatment of severe malaria in Sudan [9]. Such a study will generate data that is of paramount importance for both health planners and caregivers. Thus, the aim of the current study was to compare the efficacy of

intravenous artesunate with that of quinine in the treatment of severe *P. falciparum* malaria in eastern Sudan to add to the research on the treatment of severe malaria in Sudan [9,10].

## Methodology

*Patients*

An open randomized clinical trial was carried out at Kassala and Kuwaiti pediatric hospitals in eastern Sudan between October and December 2012 to compare artesunate and quinine for treatment of severe *P. falciparum* malaria. These two hospitals are tertiary hospitals that provide services for all patients referred from heath centers and rural hospitals. The area is characterized by unstable malaria transmission [11]. The detail of the method and clinical part of the study was published recently [12]. In summary, after patients or guardians (in cases of comatose patients and children) signed an informed consent form, clinical data (temperature, weight, and fever history) were collected using questionnaires. Those patients with one or more of the manifestations of severe *P. falciparum* malaria according to the World Health Organization (WHO) criteria – cerebral malaria, convulsion, hypotension (systolic blood pressure < 70 mmHg with cold extremities), severe anemia (haemoglobin < 7 gm/dL), jaundice, hypoglycemia and hyperparasitemia (parasite count > 100,000 asexual stage parasitemia/μL) – were enrolled [13].

Thick and thin blood films were prepared and stained with 10% Giemsa, and the parasite counts were obtained by counting the number of asexual parasites per 200 leukocytes, assuming a leukocyte count of 8,000 leukocytes/μL (for thick films) or per 1,000 red blood cells (for thin films); blood films were considered negative if no parasites were detected in 100 oil immersion fields of a thick blood film. At presentation, 5 mL of venous blood samples were taken for complete blood count using an automated cell counter (Humacount 30 TS, Wiesbaden, Germany). Serum levels of bilirubin and creatinine were measured with a semi-automated serum chemistry analyzer (Humalyzer3500, Wiesbaden, Germany).

*Treatment*

Participants were randomly allocated using computer-generated numbers in sealed envelopes to either the intravenous artesunate or quinine groups. Intravenous artesunate (from a 60 mg vial) (Guilin Pharmaceutical Co. Ltd, Guilin, Guangxi, China) was dissolved in 1 mL of 5% sodium bicarbonate to form sodium artesunate, which was diluted in 5 ml of 5% dextrose; 2.4 mg/kg body weight was given at 0, 12, and 24 hours daily until the patient able to take artesunate orally, at which point AS+SP was given and treatment was continued for 5 days. Intravenous quinine was given as an infusion loading dose of 20 mg/kg over 4 hours, then 10 mg/kg body weight was infused over 4 hours every 8 hours until the patient able to take quinine orally, at which point the full dose was completed using oral quinine at 10 mg/kg three time a day. Severe and serious complications such as severe anemia, hypoglycemia (40 m/dL), and repeated convulsion were corrected immediately as per the WHO guidelines [1], using blood transfusions that were screened for HIV and hepatitis infections. Hypoglycemia was treated by 10% dextrose and convulsion by intravenous diazepam.

*Follow-up*

Vital signs and coma scale were measured every 15 minutes for the first hour, then every 2 hours until hour 24, and thereafter every 6 hours until parasite clearance. Blood films were investigated and repeated every 4 hours. Parasite clearance time (PCT) was defined as the interval between the start of treatment and the time of the first of two sequential negative thick films. Fever clearance times (FCT) were measured from the start of antimalarial treatment to the time at which the axillary temperature first dropped below 37.5°C and remained below 37.5°C for 24 hours. Coma recovery time (for patients with a Glasgow coma score < 11 [out of 15] on admission) was measured from the start of antimalarial treatment to the time at which the score reached 15. Blood glucose levels were measured every 6 hours. Baseline investigations were performed for every patient on admission and repeated when clinically indicated. They included hemoglobin, serum urea and creatinine, serum bilirubin, and white blood cell levels.

Patients were monitored for the expected side effects such as nausea, vomiting, abdominal pain, itching, and dizziness; these were attributed to the drug if they were not present before the drug was administered.

*Ethics*

Ethical clearance for the study was obtained from the Health Research Committee at the Ministry of Health Kassala, Sudan.

*Statistical analysis*

Data were entered using SPSS software version 16.0 and double-checked before analyses. Continuous and categorical data were compared by Student's *t*-test and $\chi^2$ test, respectively. $P < 0.05$ was considered significant.

## Results

Ninety-eight patients presented with severe *P. falciparum,* out of which 94 fulfilled the inclusion criteria and were enrolled in the study (47 in each arm). There was no significant difference in the basic characteristics of the two groups (Table 1). The mean (SD) age was not significantly different between the two groups in the study. The number of males (n = 30; 63.8% *vs.* n = 24; 51.1%, p = 0.297) and number of children (< 18 years of age) were similar in the two groups of the study (n = 21; 44.75% *vs.* n = 20; 42.6%, p = 1.000) in the in the artesunate and quinine groups, respectively. Likewise, the number of children under five years of age was not significantly different between the artesunate and quinine groups (n = 10; 21.3% *vs.* n = 12; 25.5%, p = 0.808). Hypotension, convulsions, severe anemia, hypoglycemia, cerebral malaria, and jaundice were the predominant manifestations of severe malaria in this study (Table 2). Three and four of the patients in the artesunate and quinine groups, respectively (p = 1.000), had gametocytes on presentation. The mean (SD) of fever clearance time (10.8 [5.5] hours *vs.* 14.0 [8.1] hours, p = 0.028) and parasite clearance time (16.5 [6.4] hours *vs.* 21.7 [11.3] hours, p = 0.007) were significantly shorter in the artesunate group than in the quinine group. Proportions of patient with parasitemia in the first 24 hours are shown in Table 3. In comatose patients, (three and five patients in artesunate and quinine groups, respectively), coma resolution time was not different in the two groups (9.6 [2.1] hours *vs.* 8 [0] hours, p = 0.267). Following quinine infusion, 10 patients developed tinnitus (p < 0.001). Significantly fewer patients in the artesunate group developed nausea and abdominal pain, (3/25 [12.0%] *vs.* 9/20 [45.0%], p = 0.012). While four patients developed hypoglycemia after quinine treatment, none of them had hypoglycemia following artesunate treatment (p = 0.033). One patient (a 20-year-old male) in the artesunate group died due to repeated convulsions.

**Table 1.** Socio-demographic and biochemical characteristics of the two groups (artesunate and quinine) of patients of severe *Plasmodium falciparum* malaria on admission to Kassala Hospital, Sudan

| Variables | Artesunate group n = 47 | Quinine group n = 47 | P |
|---|---|---|---|
| Age, years | 23.5 (20.2) | 21.5 (17.6) | 0.605 |
| Weight, kg | 47.6 (30.0) | 45.1 (25.7) | 0.663 |
| Duration of illness, days | 4.0 (2.5) | 3.8 (2.0) | 0.756 |
| Temperature, °C | 38.4 (0.8) | 38.6 (0.8) | 0.375 |
| Hemoglobin, g/dL | 10.0 (2.9) | 9.1 (2.5) | 0.106 |
| White blood cells, µ/dL | 5,731.5 (2,344) | 5,601.3 (2,389) | 0.791 |
| Parasitemia, geometric mean parasite/µL | 240.7 | 258.7 | 0.7 |
| Blood glucose, mg/dL | 101.2 (34.3) | 106.3 | 0.158 |
| Creatinine, mg/dL | 0.8 (0.2) | 0.8 (0.5) | 0.360 |
| Bilirubin, mg/dL | 1.1 (0.8) | 1.0 (0.7) | 0.599 |

**Table 2.** Manifestations of severe *Plasmodium falciparum* malaria on admission to Kassala Hospital, Sudan

| Variables | Artesunate group n = 47 | Quinine group n = 47 | P |
|---|---|---|---|
| Hypotension | 24 (51.1) | 29 (61.7) | 0.203 |
| Repeated convulsions | 20 (42.5) | 13 (27.6) | 0.130 |
| Severe anemia | 6 (12.8) | 7 (15.0) | 0.500 |
| Hypoglycemia | 4 (8.5) | 7 (15.0) | 0.156 |
| Cerebral malaria | 3 (6.4) | 5 (10.6) | 0.714 |
| Jaundice | 3 (6.4) | 3 (6.4) | 0.661 |
| Bleeding | 1 (2.1) | 2 (4.3) | 0.500 |
| Hyperparasitemia | 2 (4.3) | 1 (2.1) | 0.500 |
| More than one manifestation | 11 (23.4) | 14 (29.8) | 0.321 |

**Table 3.** Comparing the proportion of the patients with parasitemia between the artesunate and quinine groups

| Variables | Artesunate group n = 47 | Quinine group n = 47 | P |
|---|---|---|---|
| Four hours | 34 (72.3) | 41 (87.2) | 0.072 |
| Eight hours | 29 (61.7) | 34 (72.3) | 0.364 |
| Twelve hours | 26 (55.3) | 27 (57.5) | 0.832 |
| Sixteen hours | 13 (27.7) | 19 (40.4) | 0.191 |
| Twenty hours | 5 (10.6) | 13 (27.6) | 0.035 |
| Twenty-four hours | 1 (2.1) | 2 (4.2) | 0.666 |

## Discussion

The main finding of the current study was that intravenous artesunate had a significantly shorter fever (10.8 [5.5] hours *vs.* 14.0 [8.1] hours) and parasite (16.5 [6.4] hours *vs.* 21.7 [11.3] hours) clearance time. Previously, the fever and parasite clearance time was not found to be different between artesunate and quinine in the treatment of severe *P. falciparum* malaria in children in central Sudan [9]. Perhaps that study failed to show a difference in the fever and parasite clearance time because it was a small-scale study involving only children, while in the current study, both children and adults were enrolled. Likewise, it has been observed previously that fever clearance time and parasite clearance time (16.0 and 22.4 hours, respectively) were shorter when intramuscular artemether was compared with quinine in the treatment of Sudanese children with severe *P. falciparum* malaria in eastern Sudan [10]. The mean parasite clearance time shown in this study was relatively shorter than the results (68 hours) obtained from other studies in Southeast Asia [14] and a parasite clearance time of 29.5 hours that was reported among non-immunized European travelers [15]. Interestingly, while Praygod *et al*., in their review of twelve trials (1,524 patients), found no significant difference in parasite clearance time or fever clearance time between one parenteral artemisinin derivative (artemether, β-arteether/artemotil, or artesunate) and quinine [16]; however, Sinalr *et al.* observed the superiority of parenteral artesunate over quinine for the treatment of severe malaria in both adults and children and in different regions of the world in their recent review. It is worth mentioning that in the two largest trials ever conducted concerning the treatment of severe malaria in both adults and children (over 3,000 patients), treatment with intravenous artesunate was found to be superior to quinine [4,5].

As in previous studies, the current study found no serious drug-related side effects, but found self-limited episodes of abdominal pain and nausea among the artesunate group [4,5,9]. However, hypoglycemia was observed more frequently among patients receiving quinine. This is in agreement with an earlier report in another setting in Sudan [9]. Post-treatment hypoglycemia is a recognized effect of quinine-induced insulin secretion [17]. Furthermore, quinine must be administered by rate-controlled infusion, which might further limit its use [13]. In spite of these limitations, quinine is still the treatment of choice for severe malaria in Sudan, where artesunate is not available or registered.

There was one death in artesunate group; however, this trial was not designed to investigate the mortality reduction of artesunate. The current study aimed to show that artesunate is as effective as or more so than quinine. Previous larger studies documented that artesunate is superior to quinine in mortality reduction [4,5].

## Conclusion

The current study showed that artesunate was as effective as quinine in terms of parasite and fever clearance time, and had fewer incidences of adverse effects in the treatment of *P. falciparum* malaria in eastern Sudan. No differences between artesunate and quinine in the time to resolve comas were found.

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