

Comparison of artesunate and quinine in the treatment of severe falciparum malaria: a randomized control trial

Manish B. Nandeshwar^{1*}, Ujwala P. Gawali², Amit A. Bansode³

¹Department of Pharmacology,
Government Medical College,
Nagpur, Maharashtra, India,

²Department of Pharmacology,
Dr. V. M. Government
Medical College, Solapur,
Maharashtra, India,

³Tata Consultancy Services,
Pune, Maharashtra, India

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***Correspondence to:**

Dr. Manish B. Nandeshwar,
Email: dr.manishnandeshwar@gmail.com

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ABSTRACT

Background: Severe malaria is a medical emergency that required prompt clinical assessment and management. Very few studies underwent to evaluate the best possible treatment for severe malaria.

Methods: This is a prospective, randomized, open-labeled, study to evaluate the efficacy and safety of artesunate compared with quinine. Totally, 50 patients were included in each group. Patients above 18 years, peripheral smear positive and fulfilling the WHO criteria were included. The endpoint of the study was fever clearance time (FCT), parasite clearance time (PCT) and coma resolution time (CRT), and the adverse effect if any were compared for safety analysis.

Results: FCT and PCT were much less with artesunate (29.64 and 39.72 hrs) as compared to quinine (51.12 and 55.20 hrs). CRT was less with quinine (25.80 hrs) than artesunate (42 hrs). The incidence of adverse effects such as hypoglycemia and QT prolongation are significant with quinine compared to artesunate.

Conclusions: Artesunate is a better alternative for severe malaria with minimal side effects.

Keywords: Malaria, Artemisinin, Quinine

INTRODUCTION

Malaria is the most important parasitic disease of mankind and major life-threatening condition.¹ Severe malaria occurs when infection with *Plasmodium falciparum* parasite is complicated by severe organ failure or metabolic abnormality for example cerebral malaria, pulmonary edema, acute renal failure, severe anemia, and/or bleeding. Acidosis and hypoglycemia are the most common metabolic complications. Any of these complications can develop rapidly and progress to death within hours or days.²

Severe malaria constitutes medical emergency that requires rapid clinical assessment and management. Widespread and unscientific use of drugs leads to the development of resistance.

For most of the last 300 years, quinine has been the drug of choice and the conventional therapy for severe malaria. The primacy of quinine in the treatment of severe malaria has been challenged by the introduction of artemisinin derivative artesunate.³

Very few trials were conducted between artesunate and quinine in severe malaria. Hence, we tried to assess the efficacy and safety of artesunate and quinine in the treatment of severe malaria.

METHODS

The study was conducted in tertiary care center, between December 2011 and December 2013. Institutional Ethics

Committee approved the study design. Written and informed consent was obtained from all the patients or their immediate relatives in case of unconscious patients.

Patients admitted by the physician above 18 years of age, peripheral smear positive for *P. falciparum*, patients fulfilling the WHO criteria of severe malaria (Table 1) and the patients who gave consent for the study were included.

Children and pregnant women, hypotension on presentation (i.e. blood pressure <90/60 mmHg), hypoglycemic patients (patients blood glucose <40 mg/dl), patients with QTc interval >0.45 sec in electrocardiography (ECG) and patients who have received any antimalarial drugs in last 3 months were excluded from the study.

Considering the acceptable margin of fever clearance time (FCT) as 15 hrs between the two groups with 80% power and 95% confidence required that 96 patients to be included in the study.

Total 102 patients were enrolled in the study that fulfill the inclusion and WHO criteria for severe malaria, of which 2 patients refused to give consent for the study. Therefore, 100 patients were randomized, 50 patients were allocated to each group (Figure 1).

Efficacy assessment

Parasite clearance time (PCT) is the time interval from initiation of therapy to the first of three consecutive negative blood smear taken 6 hrs apart.

FCT is the time required from initiation of therapy to the time the patient’s axillary temperature first dropped below 99° F and remained below 99° F for 48 hrs.

Coma resolution time (CRT) which is the time required from initiation of therapy to the time the patient get fully conscious.

Patients in artesunate group were given 2.4 mg/kg body weight intravenously on the 1st day followed by 1.2 mg/kg 12 hrs later and then 1.2 mg/kg/day. When the patient was able to swallow tablets, oral artesunate 2 mg/kg over the course of 7 days was administered.

Quinine was given in a loading dose of 20 mg/kg infusion in 500 ml of 5% dextrose OR 0.9% saline over 4-6 hrs. This was followed by 2 hrs infusion of 10 mg/kg 8 hourly daily. As soon as the patient tolerate orally, oral quinine 10 mg/kg was given every 8 hourly over the course of 7 days.

All the patients were admitted in general ward except those who required intensive treatment and ventilator support were shifted to intensive care unit.

Following clinical and laboratory examination was done at the time of admission and during the treatment.

Clinical examination

The vital signs were monitored, general and systemic examination was done regularly.

Laboratory examination

Complete blood count, urine examination, and blood sugar level were done on admission and during treatment.

Hemoglobin and platelet count were also monitored

Kidney function test and liver function test was done in all patients.

Cerebrospinal fluid examination was done in patients with diagnosis of cerebral malaria to rule out the meningitis.

X-ray chest and ECG were done before and during the treatment.

The diagnosis and the efficacy assessment of the treatment were done by blood smear examination for *P. falciparum*. The

Table 1: WHO criteria for severe malaria.³

| Presence of one or more of the following clinical or laboratory features | |
|--|------------------------|
| Clinical manifestations | |
| Prostration | Impaired consciousness |
| Respiratory distress | Multiple convulsions |
| Circulatory collapse | Pulmonary edema |
| Abnormal bleeding hemoglobinuria | Jaundice |
| Laboratory test | |
| Severe anemia | Hypoglycemia |
| Acidosis | Renal impairment |
| Hyperprolactinemia | Hyperparasitemia |

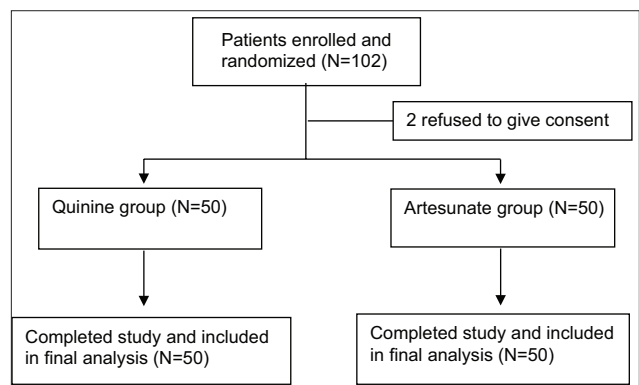


Figure 1: Patient enrolment comparing artesunate and quinine.

peripheral smear was obtained from all the patients at the time of admission, and during the treatment period 6 hourly for 1st day, 12 hourly for next day and 24 hourly thereafter for next 5 days. The number of parasites per 200 white blood cells was counted. The total leukocyte count of 8000/ μ l was assumed for the patients. The parasite index was expressed as per mm.³

The temperature of the patients was recorded at the time of admission, 6 hourly for next 24 hrs and 8 hourly thereafter.

Patients were assessed for hypoglycemia, hypotension, neurological sequelae, ECG abnormality, and other systemic side effects during the period of hospitalization for safety analysis.

Efficacy endpoint and the other parametric data were analyzed using the Student's *t*-test. Demographic data and other non-parametric variables were analyzed using Z test for the difference between population proportions. $p < 0.05$ is considered as significant to show a statistical difference between the two groups.

RESULTS

Both the groups were comparable at baseline as regards to age, clinical and laboratory characteristics as no statistically significant difference in both arms (Table 2).

Efficacy assessment of the study shows that PCT was significantly less with artesunate compared to quinine (39.72 vs. 55.20 hrs). FCT was much less with artesunate (29.64 hrs) compared to quinine (51.12 hrs) (Table 3).

The CRT between the two groups were analyzed in patients who had coma, i.e., 8 (16%) patients in artesunate group and 10 (20%) patients in quinine group. The CRT was statistically less in quinine group (25.80 hrs) compared to artesunate group (42 hrs) (Figure 2).

One patient in quinine arm and two patients in artesunate arm succumbed to illness. The mortality rate in quinine arm was 2%, and that of artesunate arm was 4% ($p=0.56$). The patient who expired in quinine arm had acute respiratory distress syndrome (ARDS) due to secondary bacterial pneumonia and in artesunate arm who succumbed to illness, one had circulatory collapse leading to cardiorespiratory arrest and other had ARDS due to non-cardiogenic pulmonary edema.

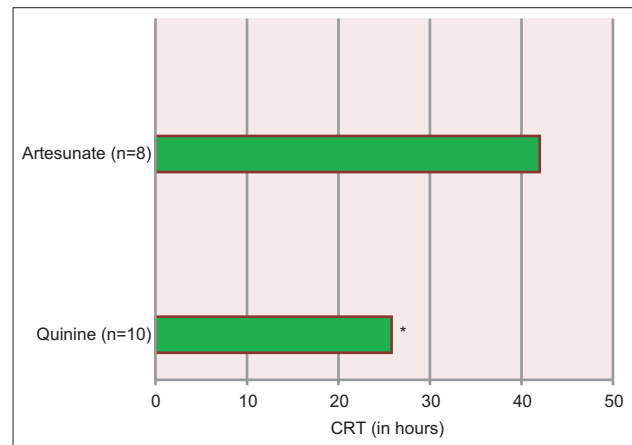


Figure 2: Coma resolution time between two groups.
*Statistically significant lower coma resolution with quinine.

Table 2: Baseline demographic, clinical and laboratory characteristics of the study groups.

| Characteristics | Quinine n=50 | Artesunate n=50 | p value |
|----------------------------|---------------|-----------------|---------|
| Age (years) | 37.30±12.64 | 39.16±13.56 | 0.48 |
| Sex distribution | | | |
| Male | 32 (64) | 34 (68) | 0.67 |
| Female | 18 (36) | 16 (32) | 0.67 |
| Clinical characteristics | | | |
| Temperature (°F) | 101.56±1.0 | 101.2±0.93 | 0.06 |
| PR (/min) | 103.4±9.0 | 101.2±8.9 | 0.22 |
| BP | | | |
| Systolic (mmHg) | 120.96±6.90 | 121.44±6.91 | 0.73 |
| Diastolic (mmHg) | 79.2±7.13 | 80.2±5.75 | 0.45 |
| GCS | 5.8±1.22 | 5.75±1.28 | 0.07 |
| Laboratory characteristics | | | |
| Hb (g/dl) | 10.42±0.75 | 10.75±1.13 | 0.09 |
| TLC (/μl) | 8269.2±1123.5 | 8394.6±1243.5 | 0.60 |
| Platelet count (/μl) | 238713±68241 | 257882±61336 | 0.14 |
| Blood sugar (mg/dl) | 110.97±12.12 | 113.35±14.22 | 0.37 |
| Parasite index (/μl) | 22720±4792 | 22095±4686 | 0.51 |

Values are expressed as mean±standard deviation or number (%), Number of patients who had coma were considered, i.e., 8 patients in artesunate group (n=8) and 10 patients in quinine group (n=10), BP: Blood pressure, TLC: Total leukocyte count, GCS: Glasgow coma scale

Table 3: Mean PCT and mean FCT (in hours) between two groups.

| Efficacy end points | n=50 | | p value |
|---------------------|-------------|------------|---------|
| | Quinine | Artesunate | |
| PCT | 55.20±14.55 | 39.72±9.98 | <0.01 |
| FCT | 51.12±15.10 | 29.64±6.90 | <0.01 |

FCT: Fever clearance time, PCT: Parasite clearance time

In quinine arm, 4 (8%) patients develop hypotension, 3 (6%) had anemia, 2 (4%) had thrombocytopenia and 10 (20%) had coma. In artesunate arm, 2 (4%) developed hypotension, 2 (4%) had anemia, 1 (2%) had thrombocytopenia. This difference was found to be statistically insignificant. Hypoglycemia in quinine arm was 6 (12%), and that of artesunate arm was 1 (2%). This difference was statistically significant. Whereas QT prolongation in quinine arm was 4 (8%) while there was no QT prolongation in patients on artesunate therapy. This difference was also statistically significant (Figure 3).

DISCUSSION

Newton et al.⁴ reported lower PCT with artesunate compared to quinine (62.5 vs. 76 hrs) but no difference as regards to FCT and CRT between two drugs.

Tran et al.⁵ reported more rapid reduction in the level of parasitemia with artemether compared to quinine (72 vs. 90 hrs) while time required for fever clearance were longer in artemether compared to quinine (127 vs. 90 hrs).

In African children of cerebral malaria, Kyu et al.⁶ reported shorter FCT and PCT with artemether compared to quinine.

Mohanty et al.⁷ found that FCT, PCT, and CRT were significantly less in artesunate group (p<0.05).

Patel et al.⁸ found that artesunate is superior in faster fever (p<0.01) and parasite clearance (p<0.001) while coma resolution is faster with quinine as compared to artesunate (p<0.001).

Our study shows early fever clearance (29.64 vs. 51.12 hrs) and parasite clearance (39.72 vs. 55.20 hrs) with artesunate compared to quinine. While coma resolution is faster with quinine compared to artesunate.

Lower FCT with artesunate might be because it prevents merogony in addition to the rapid blood schizonticidal action that also continues at a later stage of parasite development and thus prevents the occasional alarming sharp rise in parasitemia that occurs immediately following treatment. This inhibition of parasite development at an early stage prevents subsequent cytoadherence and rosetting that are important pathological mechanism in severe malaria.⁹ Further, artesunate achieves therapeutic plasma

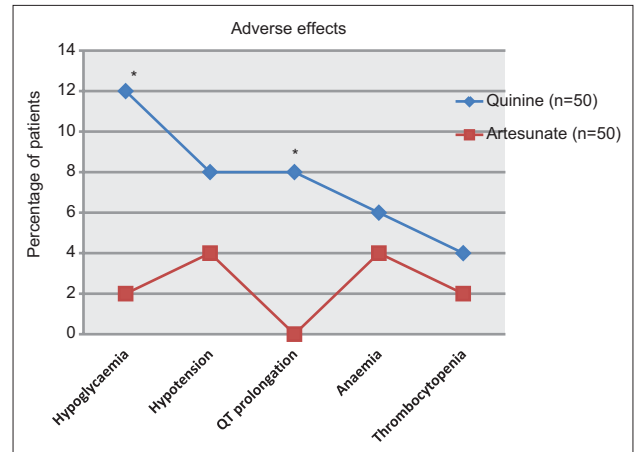


Figure 3: Incidence of adverse effects in both treatment groups. *Incidence of hypoglycemia and QT prolongation are more with quinine.

concentration rapidly.¹⁰ Artesunate is also known to cause oxidative damage to parasitized red blood cells that was not reported with quinine.¹¹

Our study showed benefits in terms of fever and parasite clearance with artesunate with minimal adverse effects. Hypoglycemic events and prolongation of QT interval are more with quinine. However, coma resolution is faster with quinine. Larger studies are required to be carried out in future to analyze the effectiveness of quinine in severe malaria.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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