ORIGINAL ARTICLE

Comparative Efficacy of Quinine and Artesunate in the Treatment of Severe Malaria:A Randomized Controlled Trial

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Abstract

There is a paucity of head to head studies of quinine and artesunate in Indian patients. A consensus on the best treatment for severe malaria is lacking. To compare the efficacy of quinine and artesunate in severe falciparum malaria. This is a prospective randomized controlled, opened-labeled trial, conducted in a tertiary care center in western India. Thiry-five patients above the age of 18 years, with asexual forms of plasmodium falciparum in the peripheral smear and satisfying the WHO criteria for severe malaria, formed the study population. On randomization 18 received quinine and 17 artesunate. The end points of the study were parasite clearance time (PCT), fever clearance time (FCT), coma resolution time (CRT), adverse effects of the drugs and death. The FCT (p 0.023) and PCT (p=0.04) were lower with artesunate. The CRT was lower with quinine (p 0.03). One patient in each arm succumbed to the illness (p 0.96). There was no side effect warranting a crossover to the other arm. Thus, quinine is as good as artesunate in the treatment of severe falciparum malaria.

Key Words

Falciparum, Artemesnin, Complicated malaria

Introduction

Malaria is the most important parasitic disease of mankind and pertains to be a major life-threatening condition. The ideal choice of drugs in the treatment of severe malaria is still being debated. As the controversy remains unsettled, there is an unscientific and relentless use of new generation medications in severe malaria. This has implications in emerging resistance patterns (1).

The paucity of direct head to head trials of artesunate and quinine in severe malaria was noted in a medline search. The side effects, if any, of these drugs during therapy of severe malaria are not widely reported from India. Hence, we tried to assess the efficacy and possible adverse effects of the quinine and artesunate for treatment of severe falciparum malaria in a randomized controlled, open labeled trial in our population.

Material and Methods

The study was conducted in a tertiary care centre in western India, between July 2000 and August 2002. Patients qualified for the study if they were above 18 years of age, had asexual forms of Plasmodium falciparum in the peripheral smear, gave consent for the study and satisfied the WHO criteria for severe malaria (2). Patients with contraindications to any of the drugs were excluded from the study (Table 1). The study population was randomized to receive either quinine or artesunate. The end points (Table 2) were parasite clearance time (PCT), fever clearance time (FCT), coma resolution time (CRT) and mortality. The adverse effects of the two drugs were also studied.All patients invariably received atleast 24 hours of intravenous therapy and a complete 7 day course of therapy. Oral therapy was substituted as soon as the patients could tolerate them. In case of R II or R III resistance to the drug, a provision for cross over to the other arm was present. The detection of R I resistance was beyond the purview of this study.

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Table 1. Exclusion Criteria*

Pregnancy
Hypotension on presentation (< 90/60 mm Hg)
ECG with QTc interval of > 0.45 secs
Glucose 6 phosphate dehydrogenase (G6PD) deficiency
Multi-species infestation
Patients who have received any antimalarial prior to admission for the present illness

*patients should not be having any one of these.

Table 2. End points of the study

Parasite Clearance Time (PCT/PCT^{100}) Time (in hours) from the initiation of therapy to the first negative blood sample.
Parasite Clearance Time^{50} (PCT^{50}) Time (in hours) from the initiation of therapy to 50% reduction in parasitemia.
Parasite Clearance Time^{75} (PCT^{75}) Time (in hours) from the initiation of therapy to 75% reduction in parasitemia.
Fever Clearance Time (FCT) Time (in hours) from the initiation of therapy to the time the patient's temperature falls permanently below 99°C.
Coma Resolution Time (CRT) Time (in hours) from the initiation of therapy to the time the patient is fully conscious with a GCS of 15.
Probable Adverse Reaction An adverse reaction which follows a reasonable temporal sequence from the administration of the medicine; that follows a known or expected response to the drug; and that could not be reasonably explained by the known characteristics of the disease.

Patients in the quinine arm were given a loading dose of 20 mg/kg of quinine salt over 6 hours followed by 6 hour infusions of 10 mg/kg every 8 hourly, the maximum dose being 1800 mg in the first 24 hours. In patients who remained in the severe form of the disease for more than 48 hours, the dose was reduced to 50%. No dose adjustment was made during the first 48 hours of therapy even with acute renal failure (ARF) or liver failure. Artesunate was given in the standard dose of 2.4 mg/kg iv on the first day followed by 1.2 mg/kg iv or 2 mg/kg orally on the next 6 days.

All patients were admitted in the general ward except those with features of acute respiratory distress syndrome (ARDS) who were shifted to the intensive care unit for ventilator support. All patients were kept in the hospital for at least 7 days. Supportive care was given to all patients, as advocated by WHO (3). A thorough clinical and laboratory work up of the patients was done on admission and regularly there after. The vital signs were recorded 4 hourly. The systemic and fundus examinations were done daily. The central nervous system examination was repeated at the time of regaining consciousness.

A complete blood count, ESR, urine examination, prothrombin time and X-ray chest was obtained on admission. Serial electrocardiography (ECG) and blood sugar estimations were done before, during and after the loading dose of the antimalarial drug and repeated daily. The hemoglobin, packed cell volume, platelet count, blood urea, serum creatinine and liver function tests were also monitored daily. Cerebrospinal fluid analysis was done in all patients with the diagnosis of cerebral malaria to rule out meningitis. A contrast enhanced CT scan was done in all patients with delayed response to antimalarial or with seizures and signs of raised intracranial tension. Serum lactate, fibrinogen and drug level assays were not done.The mainstay of diagnosis and assessment of the treatment response was serial blood smear examination for Plasmodium falciparum asexual forms. A finger prick blood sample was used to make thick and thin smears of all patients at the time of admission, 8 hourly for the first two days and 12 hourly there after for the next five days. A trained observer examined all blood smears. Parasitemia quantification was done from the thick smear. The number of parasites per 200 white blood cells was counted. A total leukocyte count of 8000/ ìL was assumed for the patients and the parasite count was multiplied by a factor of 40 to yield the parasite load per microlitre. All patients were screened for hypoglycemia (<40 mg/dl), hypotension (<90/60 mm Hg), neurological effects, ECG abnormalities and other systemic side effects.

Parametric data was compared using the student's t test. Non-parametric variables were analyzed using the Pearson's chi-square test. The confidence interval taken was 95%. All statistical work was done using the 'SPSS 11.0 for windows' software. A written consent was obtained from the patients or their immediate relatives (in case of unconscious patients). The ethics committee of our institute approved the study design.

Results

Out of 126 patients of severe malaria admitted under our care, only 102 patients had asexual forms of P falciparum in their peripheral smears. Following a diligent scrutiny of the inclusion and exclusion criteria, 41 patients qualified for the study. Six patients declined consent for

the trial. Thirty-five patients were randomized to the two arms. The patients in both arms were similar prior to therapy (Table 3). In the quinine arm eleven (61%) patients had coma, seven (38.9%) had ARF, six (33.3%) had thrombocytopenia, one (5%) had severe anemia and 2 (11.1%) had ARDS. In the artesunate arm eleven (64.7%) had coma, nine (52.9%) had ARF, five (29.4%) had thrombocytopenia, one (5.9%) had severe anemia and two (11.8%) had ARDS. Thirty-three patients completed the study while 2 succumbed to the illness, one each in the two arms. Two patients in each of the arms developed ARDS. No evidence of R II or R III resistance was seen in both groups. There were no side effects warranting a crossover.

On analysis of end points (Table 4) FCT was significantly lower with artesunate (32 Vs 58 hrs). The median PCT was similar in both arms but the mean FCT with artesunate (41.64 hrs) was significantly lower than with quinine (55.11 hrs, Fig.1). There was a rapid fall in parasite level in the artesunate arm at the initiation of therapy, the magnitude of which reduced on continued treatment. The population parasite clearance curve (Fig.2) depicts this. The PCT^{75} too showed earlier clearance with artesunate, but this was not statistically significant. The CRT however was significantly lower with quinine (12 hrs) compared to artesunate (32 hrs). This is represented using exponential trend lines in (Fig. 3).

Table 3. Clinical and laboratory characteristics of study groups before treatment

Factor	Quinine Arm Median (IQR)	Artesunate Arm Median (IQR)	'p' Value
Age (yrs)	31 (24.25-50)	32 (18-47.5)	0.48
Female (%)	16.67	11.77	0.67
Temperature (?F)	101 (101-102)	101 (100.5-102)	0.73
Pulse Rate (/mt)	109 (106-113)	110 (104-120)	0.75
Systolic BP (mm Hg)	120 (110-130)	110 (110-130)	0.29
Glasgow Coma Scale	5 (4 -13)	5 (4-15)	0.77
Hemoglobin (g/dl)	10.5 (8.4-11.25)	9.8 (8.7-11.2)	0.81
Total Count (/µL)	8500 (7,450-9,150)	9000 (5,250-11,500)	0.92
Platelet Count (/µL)	127,500 (75,750-190,250)	130,000 (90,000-200,000)	0.80
PT (secs)	14.75 (13.88-16.75)	15.00 (13.75-15.00)	0.77
Blood Sugar (mg/dl)	111.50 (80-140)	101 (82.5-133)	0.89
S. Creatinine (mg/dl)	1.4 (1.03-3.25)	1.8 (0.9-3.4)	0.77
ALT (U/L)	65 (38.75-125)	60 (37-105)	0.78
QTc (secs)	0.385 (0.37-0.40)	0.39 (0.38-0.40)	0.79
Parasite Burden (/µL)	37,500 (25,000-52,500)	35,000 (22,500-60,000)	0.94

Table 4. Analysis of end points

End Point	Quinine Arm	Artesunate Arm	'P' value
FCT (hrs) Median (IQR)	58 (38-72)	32 (16-40)	0.023
PCT (hrs) Median (IQR) PCT^{50} PCT^{75} PCT^{100}	24 (14-24) 40 (16-48) 48 (40-72)	8 (8-16) 32 (18-40) 48 (24-48)	 0.01 0.42 0.04
CRT (hrs) Median (IQR)	12 (8-24)	32 (8-64)	0.04
QTc prolongation (%) Median (IQR)	7.89 (5-9.84)	5.26 (2.53-7.79)	0.18
Mortality (%)	5.55	5.882	0.96

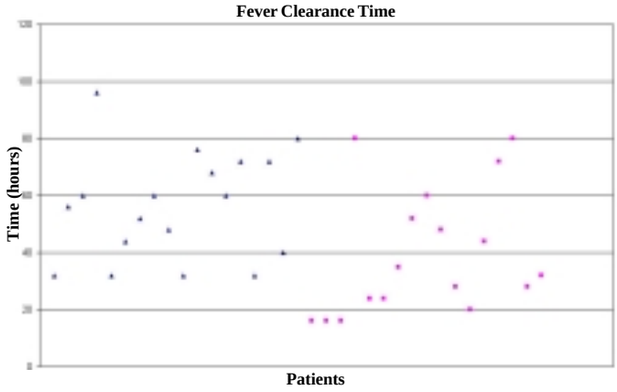

Fig. 1. Scatter diagram depicting lower fever clearance time in patients on artesunate compared to quinine. (•) Quinine arm; (-) Artesunate arm

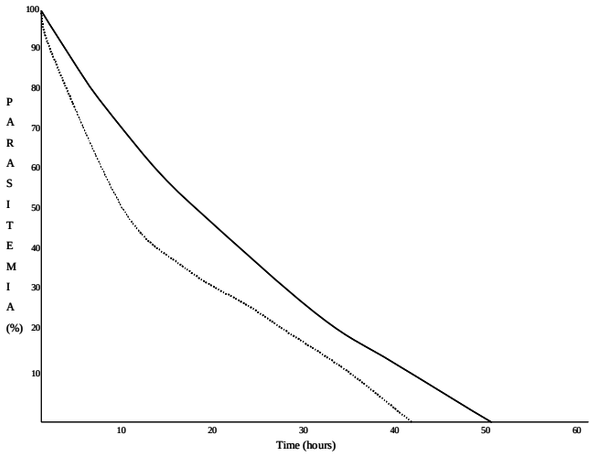

Fig. 2. Population parasite clearance curve showing significantly earlier clearance with artesunate. The area between the curves is maximum in the initial part of therapy and reduces later on depicting efficacy of artesunate early in treatment. (_____) Quinine arm; (……..) Artesunate arm.

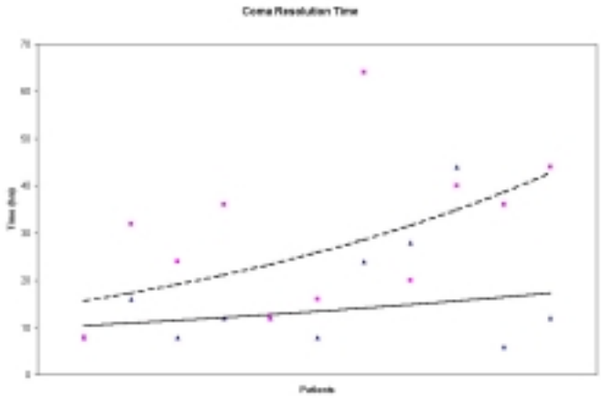

Fig. 3. Scatter diagram for coma resolution time (CRT). The exponential trend lines clearly show a lower CRT with quinine. (?) Quinine arm; (¦) Artesunate arm; (_____) Quinine arm; (……) Artesunate arm.

One patient each, in the two arms, expired during the study. The mortality rate in the quinine arm was 5.55% and that in the artesunate arm was 5.882% (p=0.96). The patient who expired in the quinine arm had ARDS, while the patient who succumbed in the artesunate arm had ARF and coma. Coma resolution was attained in the second patient before his death but ARF persisted. No adverse effects warranting discontinuation of the antimalarial was seen during the study in both arms. The median QTc prolongation in the quinine arm was 7.89 % while that in the artesunate arm was 5.26 %. This was not statistically significant. No patient developed arrhythmia.

Discussion

Fever and parasitemia cleared earlier with artesunate while coma resolution was faster with quinine. Looaresuwan *et al*. reported a faster FCT with artesunate alone than its combination with mefloquine in uncomplicated falciparum malaria (4). A Myanmar study showed a faster FCT and PCT with artesunate and mefloquine combination than with quinine and tetracycline (5). However Hien *et al*. reported a significantly lower median FCT (90hrs) and CRT (48hrs) with quinine compared to artemether (127 hrs and 66hrs) in Vietnamese adults (6). He also reported a significantly lower PCT with artemether (72 vs 90hrs). Hensbroek *et al*. showed no significant difference in FCT but a lower PCT (p=0.003) with artemether compared to quinine, in Gambian children with cerebral malaria (7). The CRT was significantly faster with quinine in this study (p=0.04).

The lower FCT with artesunate may be the result of a faster parasite clearance. This in turn may be the result of a more efficient absorption or due to its ability to prevent ongoing merogony by the later stages of the parasite (8). Artesunate is also known to cause oxidative membrane damage of the parasitized RBCs. These features have not been reported with quinine. The faster CRT seen with quinine inspite of delayed parasite and fever clearance is intriguing. The neurotoxicity of artemesnin compounds might have delayed the coma resolution (7,9). The anti-TNF alpha action of chloroquine has already been established (10). We postulate a similar anti-cytokine effect for quinine giving it the advantage in cerebral malaria. No episode of hypoglycemia, hypotension or arrhythmia was seen in any of the patients. There was no evidence of neurotoxicity with artesunate.

Conclusion

Our study showed no mortality advantage for artesunate over quinine. A larger study is required to analyze this aspect further. The quinine effect in cerebral malaria, should be analyzed in future studies. The adverse effects of neither drug were severe enough to warrant a change in the regimen. The widespread and reflex use of artemesnin compounds as first line therapy, citing adverse effects and resistance to quinine is untenable.

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