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COMPARISON OF INTRAMUSCULAR ARTEMETHER AND INTRAVENOUS QUININE IN THE TREATMENT OF SUDANESE CHILDREN WITH SEVERE FALCIPARUM MALARIA

I. ADAM, H.M. IDRIS, A.A. MOHAMED-ALI, I.A. A/ELBASIT and M.I. ELBASHIR

ABSTRACT

Objectives: **To compare the efficacy of intramuscular artemether and intravenous quinine in the treatment of severe *falciparum* malaria.**
Design: **An open randomized controlled clinical trial.**
Setting: **New Halfa Teaching Hospital, Eastern Sudan, in the period November 2001-January 2002.**
Subjects: **Forty one male and female children; 21 on artemether and 20 on quinine.**
Main outcome measures: **Fever clearance time, parasite clearance time, coma resolution time and side effects of the two drugs.**
Results: **The two groups (artemether and quinine) were well matched in the admission variable. The mean ± (SD) fever clearance time was 30.5 ± (20.9) hours in the artemether group, while it was 18.0± (8.1) hours in the quinine group; the difference was highly significant (P=0.02). The mean parasite clearance time was shorter in the artemether group than in the quinine group, but it was not statistically significant, (16.0 vs. 22.4 hours; p>0.05). In comatose patients (three in the artemether group, three in the quinine group) the time of recovery from coma was significantly shorter in artemether group than in quinine group (12.5 vs. 20.16 hours; P<0.05). Recrudescence of *P. falciparum* (confirmed by polymerase chain reaction) occurred in one out of fifteen patients (6.6%) in the quinine group seen on day 28, which was successfully treated by sulphadoxine-pyrimethamine. In the quinine group, one patient died and one patient developed hypoglycaemia.**
Conclusion: **Artemether caused faster parasite clearance than quinine, but quinine lowered the temperature in shorter time than artemether. The results obtained show that artemether can be used as safe and effective alternative drug for the treatment of severe *falciparum* malaria in the wake of the growing resistance to quinine in Sudan.**

INTRODUCTION

Malaria is a major health problem in tropical countries especially sub-Saharan Africa, where about 90% of clinical cases occur. There are nearly 500 million clinical cases of malaria worldwide each year and 1.1 to 2.7 millions die annually, the majority of whom are children under five years in Africa(1). Children have also been shown to be at higher risk for developing drug resistant falciparum malaria than older individuals(2).

In parts of tropical Africa where *P. falciparum* is holoendemic, infants tend to get cerebral malaria but the main clinical manifestation of malaria is severe anaemia in children after the age of two years(3). In other parts of Africa, where the transmission is less intense, the predominant severe disease syndrome is cerebral malaria(4).

The management of severe falciparum malaria represents major challenge for clinicians, and it carries high mortality even with the currently recommended regimen of intravenous quinine(5,6). Unfortunately, falciparum malaria is becoming increasingly resistant, in most of the endemic areas worldwide, to most available drugs including chloroquine and quinine(7,8). However, quinine is still the recommended drug of choice for the treatment of severe falciparum malaria in many areas in spite of the growing resistance, side effects and narrow therapeutic ratio.

In New Halfa, Eastern Sudan, where this study was done, malaria is mesoendemic and more than 90% of the infection is due to *P. falciparum*(9). In a recent study done in this area we have shown that 76% and 9.6% of the treated falciparum malaria patients were chloroquine and quinine resistant, respectively(10). Artemesinin derivatives, relatively new drugs with different mode of action, have been shown to clear malaria parasite significantly more rapid than quinine(11). Artemether is the only registered drug of artemesinin derivatives in Sudan. It has been found to

be superior to quinine in the treatment of simple uncomplicated falciparum malaria(12).

With the emergence of resistance to quinine in Sudan there is urgent need to look for alternative drugs for the treatment of severe malaria. This study was carried to evaluate the efficacy and safety of artemether in comparison to quinine in the treatment of severe *P. falciparum* malaria.

MATERIALS AND METHODS

Study area: The study was carried out in New Halfa, an agricultural area in Eastern Sudan, 500 km from Khartoum. It is 450 m above sea level, located between 15-19 Latitude, North and 35-36 Longitude, East. It is characterised by average annual rainfall of 238 mm and average annual relative humidity of 35. There is a permanent irrigation system. The area itself is made up of iso-villages constituting a population of 400,000. The area is medically served by one teaching hospital, one single doctor hospital and five dispensaries. It is mesoendemic for malaria with the peak of transmission during the period between September-January following the rainy season. The predominant malaria parasite species is *P. falciparum* with *P. vivax* and *P. malariae* occasionally seen.

Subjects: The subjects included in the study were children with severe falciparum malaria recruited from malaria patients attending the sugar cane industry hospital out-patient clinic in New Halfa during the period between November 2001 and January 2002 (Table 1). Informed consent was obtained from the parents of each child before being included in the study. Detailed record was made for each patient including personal data, medical history, physical examination, last malaria attack, and use of anti-malaria's. Data were recorded in special case report form.

Criteria for inclusion as severe malaria were; cerebral malaria, repeated convulsions, severe anaemia with haemoglobin less than 5 gm/dl, hyperpyrexia (temperature of 40°C or more, hyperparasitaemia (parasite count more than 100,000 rings/µl or combinations of these criteria. Coma was assessed by Blantyre coma scale. A physician was available all the time for monitoring physical signs (assessing the degree of coma, temperature, pulse, blood pressure and respiratory rate) every eight hours until discharge after seven days or more.

Each child was randomized in one of the two groups; quinine or artemether group (envelopes containing the assigned treatment were opened sequentially at the time when each patient was recruited to the study). They were kept in hospital for at least seven days and then followed up weekly as out-patient for a minimum of 28 days.

Investigations: Using finger prick blood, thick and thin blood smears were prepared from each patient, stained with Giemsa (pH 7.0, diluted in PBS) and counted against 200 white blood cells (WBCs) assuming that the number of WBCs is 6000/min^3 of blood. Trophozoites and gametocytes of *Plasmodium falciparum* were recorded separately with their densities. The blood films were prepared and examined by highly expert technician and cross-checked by another technician blinded about the results and verified by the supervisor if there was any controversy. Thin blood films, fixed in methanol and Giemsa stained were done when the parasite species was doubtful. The blood films were repeated every eight hours till two consecutive films were negative, then daily till day seven and then on days 14, 21 and 28. Haemoglobin and capillary blood glucose were done on presentation. Capillary blood glucose was estimated two hours following the drug administration. Chest X-Ray was done if indicated.

All patients were staying in the same area during the follow up period. Therefore, the possibility of re-infection or recrudescence could not be ruled out. Three spots of blood were taken on filter paper initially and later if parasites re-appeared microscopically during the follow-up period. Primers from 3 polymorphic *P. falciparum* antigens; merozoite surface protein-1 and 2 (MSP-1 and MSP-2) and glutamate-rich protein (GLURP) were used in PCR to differentiate between true recrudescence and re-infection basically as described recently(14).

Evaluation criteria: The efficacy and safety of artemether and quinine were assessed according to parasite clearance

Table 1

Different admission variables in the artemether and the quinine groups, as mean ± (SD) or percentage of total number as appropriate

Variable	Artemether group (n=20)	Quinine group (n=21)	P-Value
Age(years)	4.1(2.5)	3.59(3.2)	0.42
Duration of illness(days)	3.5(3.2)	3.1(2.3)	0.23
Respiratory rate/min	32.6(5.7)	31.2(6.7)	0.52
Weight(kg)	12.15(5.4)	11.8(3.8)	0.32
Temperature(°C)	38.5(0.76)	38.6(0.87)	0.42
Haemoglobin (g/dl)	6.5(21.8)	6.8(1.6)	0.7
Parasite count/mm^3	3.443.43(45462)	33215.95(57161.24)	0.48
Female	9(45)	11(52.4)	0.74
Male	11(55)	10(47.6)	0.85
Palpable spleen	6(30)	8(38)	0.33
Fever	20(100)	21(100)	0.36
Cough	10(50)	11(52.4)	0.64
Diarrhoea	5(25)	7(33.3)	0.27

time, fever clearance time and coma resolution time. Parasite clearance time was defined as the time passed from admission and start of treatment until we get two consecutive negative blood smears. Coma clearance was attained if a Blantyre coma score of 5 was recorded for at least 24 hours. Fever clearance was defined as the time after which the temperature remains normal (axillary temperature below 37.5°C). All these variables were calculated from the time of a admission.

Treatment: The patients were treated by one of the two regimens, either intramuscular artemether (Kunming Pharmaceutical Factory, Kunming, People's Republic of China) loading dose of 3.2mg/kg, followed by 1.6 mg/kg daily for the following four days. On the other hand a loading dose of 20mg/mg of quinine dihydrochloride (Renudin, France) dissolved in 10 ml/kg 5% dextrose solution given by intravenous infusion over four hours. This was followed eight hours later by 10 mg/kg quinine dihydrochloride dissolved in 10 ml/kg of 5% dextrose solution over four hours, and then this was repeated every eight hours, for at least 72 hours, then if the patient could tolerate, oral quinine to be continued for a total of seven days

Other medications included paracetamol as necessary to lower the temperature, intravenous fluids to restore the hydration, in case of severe anaemia packed red blood cell under cover of frusemide 1mg/kg intravenously and diazepam to control the convulsions. All the drugs were given under strict supervision of the team.

Statistical analysis: Data obtained was entered into a computer database. SPSS (Statistical Package for Social science) software was used for statistical analysis. Simple frequency distributions cross tabulation, descriptive statistics, mean, test and chi-square tests; Fisher's exact tests were used when applicable. P-value< 0.05 was considered significant for testing the hypotheses.

Ethics clearance was obtained from the Federal Ministry of Health and Medical Research Board at the Faculty of Medicine, University of Khartoum.

RESULTS

Forty one patients were recruited to the study, 20 patients in the artemether group and 21 in the quinine group. Table 1 shows the admission variables in the two groups, they were well matched and no statistical differences between the variables seen.

The admission criteria were shown in Table 2, the most common criteria were repeated convulsions; cerebral malaria was the presenting manifestation in seven patients (17.07%) whereas jaundice and renal failure were not seen in any case.

The differences between the variables in the two groups were shown in Table 3. In comatose patients, the coma resolution time was significantly short in the artemether group than in the quinine group (mean, 12.5 vs. 20.16 hours; P<0.05).

The parasite clearance time was shorter in artemether group than in quinine group, but it did not reach statistical significance, (16.0 vs. 22.4 hours; p>0.05). However, the time to clear the fever was statistically short in the quinine group than in the artemether group (P=0.02). One comatose patient in the quinine group died 12 hours after the admission (his data was not included in the analysis of coma resolution time, fever clearance time and parasite clearance time), he didn't show any improvement and his blood film was positive shortly before his death.

Table 2

Type of severe P. falciparum malaria manifestation as percentage of the total number in each group

Inclusion criterion	Artemether group (n=20)	Quinine group (n=21)	P-value
Cerebral malaria	15	19	0.85
Convulsions (at least two in 24 hours)	65	52.4	0.85
Epistaxis	5	9.5	0.9
Hyperpyrexia	15	19	0.43
Severe anaemia	15	14.3	0.49
Hyperparasitemia	20	14.3	0.85
Two manifestations or more	45	42.8	0.97

Table 3

The outcomes measured in the two groups, quinine group as mean ± (SD) in hours.

Outcome	Artemether	Quinine	P-value
Coma resolution time	12.5(5.2)	20.0(16.9)	0.001
Fever clearance time	30.5(20.9)	18.0(8.15)	0.02
Parasite clearance time	16.0(9.2)	22.4(11.49)	0.36

One of fifteen patients (6.6%) in the quinine group seen on day 28, presented with symptoms suggestive of malaria *P. falciparum* was detected microscopically and a true recrudescence was confirmed by genotyping of the parasite by PCR. This patient was successfully treated by sulphadoxine-pyrimethamine.

Gametocytes were observed in 4/20 (20%) patients in the quinine groups during the follow-up period (day 4-7), but they were not seen in any of artemether group and were not detected in any of the studied patients on the presentation (P=0.05).

One patient (5%) in the quinine group developed hypoglycaemia, following quinine infusion. Neurological deficits were not observed in any patient during the follow-up period.

DISCUSSION

The cinchona alkaloids have been in use to treat agues and fevers for many years. Quinine was the treatment of choice for severe malaria until 1940, when the synthetic aminoquinoline anti-malarials were introduced. Chloroquine replaced quinine until the development of chloroquine resistance in *P. falciparum* in the 1960s. Unfortunately, the propensity of *P. falciparum* to develop resistance to anti-malarial drugs has continued and quinine efficacy has declined and resistant strains have been confirmed in different parts of malaria endemic areas including the African continent(14,15). There is great need to find effective alternative drug for the treatment of severe malaria in the light of the growing quinine resistance. Artemisinin derivatives were relatively new, and their chemical structure distinguishes them from other currently available anti-malarial drugs and renders them less liable to cross resistance(16).

Among the patients involved in this study, 17.07% presented with cerebral malaria. Only one of these patients, in the quinine group died 12 hours after admission. In the rest of cerebral malaria patients the coma resolution time was significantly shorter in the artemether group than in those of the quinine group. Although the number of patients involved in this study was not large enough to derive solid conclusions, it agrees with previous studies which had shown that the duration of coma was significantly short, and the mortality was lower with artemether than with quinine(17). However, in another study it has been shown that the coma resolution time was not different in children given artemether and those given quinine(18).

Although the parasite clearance time was shorter in the artemether group, it didn't reach statistical significance. In spite of this, quinine lowered temperature significantly more quickly than artemether. Such finding might be explained by the antipyretic action of quinine (artemether lacks this property). However, no statistically significant difference between these variables was found when artemether and quinine were compared in a recent study done on Nigerian children(19).

While four patients in the quinine group showed gametocytes in the blood between days 4-7, no gametocytes were seen in any of the patients treated with artemether, (P=0.05). This finding is of high significance since it shows the role of artemether in reduction of gametocytes carriage and thus transmission potential especially in mesoendemic areas like our situation(21).

Recrudescence of *P. falciparum* occurred in one out of fifteen (6.6%) patients in the quinine group seen on day 28. It has been shown previously, in a neighbouring area, that no recrudescence in patients treated with artemether, while in three out of 18 patients treated with quinine there was re-infections or true recrudescence on days 14, 21 and 28(12). Quinine resistance has been recently demonstrated in the area of the study by *in-vivo* test(10).

In conclusion, artemether could be a useful alternative in the face of the growing problem of resistance of *P. falciparum* to quinine in the treatment of severe falciparum malaria in Sudan, particularly it is more easily administered, and without hypoglycaemic effect.

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