

Parasitaemia Changes in the Course of Treatment of Severe Malaria Patients with Artemether and Quinine (A Preliminary Study)

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Abstract

Key words:

Malaria; artemether; quinine; parasitaemia.

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Background. Severe malaria is a medical emergency with devastating multisystemic effect, if not promptly treated with sensitive and safe drugs, death is imminent. Quinine and artemether are antimalaria drugs that are used in severe malaria.

Aim. Efforts in this study were directed at comparing parasitaemia changes in the cause of treatment of severe malaria patients with artemether and quinine in Ikenne local Government area of Ogun State, Southwest Nigeria.

Materials and Methods. Thirty two patients in the study were randomly assigned to receive either artemether or quinine under medical supervision. 32 patients were allocated into two groups. Patients in the quinine group were given 10 mg/kg body weight quinine in 5% dextrose-saline infusion intravenously 8 hour intervals but changed to oral quinine (10 mg/kg body weight, 8 hr intervals) for 7 days. The patients in artemether group received 1.6 mg/kg body weight twice at day 0 and then 1.6 mg/kg bwt daily intramuscularly for the next four days. The patients were then followed up for 14 days.

Results. The parasitological density in the study group ranged from 71,500/ μ l to 140,024/ μ l with a mean of $95,122.63 \pm SD 16,044.7$. The quinine group had a range of 71,500 to 108,400/ μ l with a mean of $89,425/\mu\text{l} \pm SD 12,481.53$. The artemether group had a range of 72,500 to 140,024/ μ l and a mean of $100,820/\mu\text{l} \pm SD 17,520$. There was statistical significance between the two groups ($p < 0.05$). Parasite cleared in all patients by day 3 in quinine and artemether except in one patient in artemether group in whom parasitaemia cleared by day 7.

Conclusion. Results from this study indicated that artemether relative to quinine initiated a faster and sustained recovery from high parasitaemia level in the patients' blood.

Introduction

Malaria is the world most important protozoan disease of which at least 300 million people are infected worldwide yearly and there are between 1.0 to 1.5 million deaths per year (1). According to World Health Organization estimates, it is a major cause of morbidity and mortality in West Africa (2). Ninety percent of malaria related deaths occur in Sub-Saharan Africa (Nigeria inclusive) (3-6).

In particular, young children, pregnant women (worse in those in their first pregnancy) and non-immune individuals visiting the malarious area are the group of people at greatest risk of severe or fatal illness (4, 7). In Nigeria, *P. falciparum* is responsible for 85-90% of all infection (8). The disease if not treated promptly could result in severe malaria which includes cerebral malaria and severe anemia (9). Cerebral malaria has a mortality rate of up to 25% even with the best of treatment. Malaria attack sometimes results in

psychosis, chronic anemia, malnutrition and stunted growth (10, 11). There is an all year transmission of malaria in Nigeria with a peak rate in west season (12).

Social economic influence of malaria is closely related to poverty, but also a cause of poverty and a major hindrance of economic development (13). Malaria is one of the most common infectious diseases of public health importance. In Nigeria, 30% of pediatric deaths and 20% of maternal mortality are caused by malaria (14). People get malaria by being bitten by an infective female *Anopheles mosquito*. The disease is caused by protozoan parasites of the genus plasmodium. Only four types of the plasmodium parasites can infect humans, they are: *Plasmodium falciparum*, *P. ovale*, *P. vivax* and *P. malariae*.

Malaria being responsible for 10-15% of hospital admission can be life threatening and intensive care may be required. Appropriate drugs that are sensitive to malaria parasitemia (following clinical suspicion and laboratory confirmation) must therefore be used. Experienced medical personnel and supportive care facilities must be available to reduce already known morbidity and mortality (15).

The rapidity by which malaria still devastates children in Africa call for urgent review of malaria therapy and management. This task though enormous (in cost, personnel and facilities), if visionarily pursued will revolutionize our chronic malaria burden. It is on this basis that use of artemether to a large extent and quinines (being an older drug) need to be compared. With the increased use of these antimalarias there is need to evaluate parasitaemia clearance rates of most of these drugs hence this research was designed to investigate the rate of malaria parasites clearance of quinine relative to artemether.

Materials and Methods

Materials

Drugs: Artemether 80 mg/ml (Rhone-Poulence, Rorer France); Quinine 600 mg/ml (Evans Pharmaceuticals); 5% dextrose saline.

Non-Drug Materials: Sterile syringes (1-5 ml); Scalp vein needle (21 g and 23 g); Cotton wool, methylated spirit, Giemsa stain; 20 g intravenous canula; Fluid giving set; Clinical thermometer.

Equipment: Chamber counter; Microscope.

Patients and Methods

Patients were recruited in Ikenne local Government area of Ogun State at Overcomers Specialist Hospital, Ilishan and General Hospital Ikenne.

The hospital has equipments for resuscitating and handling emergency. Ethical and parental approval for the study was obtained from Olabisi Onabanjo University OOUTH joint ethical review committee and from the parents or guardians.

Inclusion Criteria:

1. Children from either sex with age ranging from 1 year to 12 years.
2. Fever with temperature greater than 37.5 °C.
3. Presence of convulsion, vomiting, hypoglycemia, anemia and headache.
4. Informed consent obtained from the parents and guardians.
5. Assurance that patients will be resident within catchments of study for follow-up.
6. Absence of concomitant illness such as bronchopneumonia, typhoid, meningitis, urinary tract infection.

Exclusion Criteria:

1. History of blood transfusion in the last two months.
2. Presence of concomitant illness.
3. History of previous allergy to quinine and artemether.
4. Lack of informed consent.

Withdrawal Criteria:

1. If any concomitant illness developed during the study.
2. If informed consent is withdrawn by parents or guardian.
3. If patient (or parents/guardian) is unwilling to continue in the study.
4. Failure to comply with protocol.

Study Design

Patients who satisfied the above criteria were admitted for treatment in the ward. The children were randomly allocated into 2 treatment groups; treatment Q and A for quinine and artemether respectively. On enrolment, a brief history was obtained from

accompanying adult (which may be the parent or guardian) and a clinical examination was performed. Body weight, oral and rectal temperature were recorded. The following were also documented — presence or absence of pallor, jaundice, respiratory distress, drowsiness for each patient. Before administration of any drug, laboratory tests were done. Blood sample was collected through finger prick to determine level of blood parasites and this is done by the following method:

Thick and thin blood film for parasite identification and quantification. The thick and thin films (fixed with methanol) were stained with Giemsa stain for 15 minutes. The slides were examined for malaria parasites microscopically at x 100 magnification.

Thin and thick blood films for parasitaemia assessment were in addition to day 0 repeated on days 3, 7, and 14.

The clinical examination and observation made were recorded daily for 8 days (0-7) and on day 14. At each visit, patients (in case of older children) or parents/guardian were questioned, examined and documented for the presence of any adverse reactions to the administered drugs.

Treatment Regimen

The patients in the quinine group received quinine (Evans) 10 mg/kg in 5% dextrose/saline infusion, which was administered to the patients through intravenous canula for 4 hours. This served as the loading dose. Maintenance dose was given as 10 mg/kg dose and then repeated 8 hourly. The quinine infusion was later changed to oral medication when patient's clinical condition allowed for this. An oral dose of 10 mg/kg was given 8 hourly. The duration of treatment was 7 days. The patients were monitored for toxic reactions i.e. hemolysis, convulsions, restlessness, disturbed vision.

The patients in the artemether group received 1.6 mg/kg artemether twice on day 0 and then 1.6 mg/kg daily for the next four days through deep intramuscular route. The patients were only discharged after their clinical conditions became stable and good response to treatment attained. This happened usually after the third day.

Treatment outcome and statistical analysis evaluation of safety parameters

Any adverse effect in the course of treatment

were documented and compared in the two groups. The intensity of adverse experience was classified as:

MILD: - an adverse experience that can be tolerated by the patient, causing minimal discomfort without interfering with everyday activities.

MODERATE: - an adverse experience that is sufficiently discomforting to interfere with normal everyday activities.

SEVERE: - an adverse experience which prevents normal everyday activities.

Therapy was considered safe when adverse effect were mild and moderate.

Treatment Success

Patient was considered treatment success if parasite count on day 3 was < 25% of pre – treatment count, and there was no parasitaemia on day 7 and day 14.

Statistical Analysis

Normally distributed data of body weight was compared by student's t-test. Data not conforming to normal distribution like parasite density was compared by the Kraskal –Wallis test. Mean value was given in the text and tables as means standard deviation and p-value less 0.05 were taken as statistically.

Results

Thirty-four patients who met the inclusion criteria were enrolled into the study. Two patients were withdrawn as a result of default in follow-up within 7 days. The 32 patients studied were randomly allocated to quinine or artemether study group. They were made up of 22 (68.7%) male and 12 (31.3 %) female. Their age ranged from 1 to 12 years, mean was 7 ± 3.63 and weight ranged from 7 kg to 35 kg, mean 19.83 ± 8.22 .

Clinical Features at Presentation

The clinical features at presentation in the two groups were similar (16). These features were similar in the two groups as the p-values were not statistically significant. The commonest presenting features were fever (84%), poor appetite (96.9%), pallor (96.9%), and jaundice (50.0%). The physical findings were equally similar in the two groups.

The parasitological density in the study group ranged from 71,500/ μ l to 140,024/ μ l, with a mean of $95,122.63 \pm$ SD 16044.7. The quinine group had a range of 71500 to 108400/ μ l with a mean of $89425/\mu$ l \pm

SD 12481.53. The artemether group had a range of 72500 to 140,024/ μ l and a mean of 100820/ μ l \pm 17520. There was statistical significance between the two groups P values of 0.042. Parasitaemia reduced progressively overtime in the course of treatment. Parasite cleared in patients by day 3 in quinine and artemether except in one patient in artemether group in whom parasitaemia cleared by day 7 (Table 1).

Table 1: Changes in parasitaemia (μ l) in the course of treatment.

Variables	Quinine	Artemether	p-value	Total
Day 0	89425 \pm 12481.53	100820.3 \pm 17520	0.042	95122 \pm 16044.7
Day 3	7049.06 \pm 17600.2	83.44 \pm 233.07	0.124	3566.25 \pm 12744.99
Day 7	0.00 \pm 0.00	179.69 \pm 718.75	0.325	89.84 \pm 508.23
Day 14	000	000	000	000

Therapeutic Responses To Treatment

Table 2 is a summary of the responses of parasitaemia to treatment in the study. The mean parasite clearance time was calculated for quinine to be 46.5 \pm 6.0 hours, and for artemether was 31.5 \pm 14.45 hours.

Table 2: Fever clearance time (hours).

Drugs	Clearance Time (hours)	p-value
Quinine (hours)	46.50 \pm 6.0	0.001
Artemether (hours)	31.50 \pm 14.45	

Discussion

A comparative study on varying levels of malaria parasites in course of treatment of severe malaria patients with artemether and quinine was evaluated in 32 patients who were allocated into two treatment groups. Presenting features such as clinical severity were similar in both groups and were not statistically significant.

The commonest presenting symptoms were poor appetite, fever, vomiting, and pallor and are in agreement with the findings of Ademowo (9). Vomiting was the commonest gastrointestinal manifestation of severe malaria in children and the reasons why this is so are not clearly understood but Sowunmi et al (17) suggested that it may be due to preferential

sequestration of parasites in gastric vascular beds.

Changes in malaria parasitaemia at different days in the course of treatment are shown in Table 1. The mean malaria parasite density of artemether group was higher than its quinine counterpart. The malaria parasite density clearance of 31.50 hours for artemether was lower than 46.50 hours for quinine. This is comparable with reported observation in Gambia (18). There was no reappearance of malaria parasite among the patients in both groups except one during the course of treatment and this occurred on day 7 in artemether group. This finding is in consonance with the report of Hosein, 1995 (19) where he reported occurrence of recrudescence when artemether is given in short monotherapy. The only patient with recrudescence of malaria parasites had artemether treatment extended by additional five days leading to full clearance.

The current study has demonstrated that artemether relative to quinine has more rapid malaria parasite clearance time.

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