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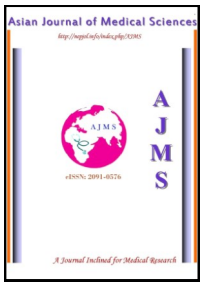

Temperature changes in the course of treatment of severe malaria patients with artemether and quinine

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Abstract

Objective: Severe malaria is a medical emergency with devastating multi-systemic effects, if not promptly treated with sensitive and safe drugs, death is imminent. Quinine and artemether are antimalarial drugs that are used in treating severe malaria. Efforts in this study were directed at comparing temperature changes in the cause of treatment of severe malaria patients with artemether and quinine in Ikenne local Government area of Ogun State, Southwest Nigeria.

Material & Methods: 32 patients in the study were randomly assigned to receive either artemether or quinine under medical supervision. 16 patients were allocated into two treatment groups. Patients in the quinine treatment were given 10mg/kg body weight quinine into 5% dextrose/saline intravenously 8hourly whilst artemether group were given 1.6mg/kg body weight intramuscularly for 5days. The patients temperature were then followed up for 14days.

Results: A total of 28 out of 32 patients enrolled into the study had temperature ≥ 37.5 ^{o}C at day 0. The mean fever clearance time for quinine treatment group was 46.50± 20.49 hours while that of artemether group was 72.0 ± 27.7 hours (p=0.006). Fever was completely resolved in both treatment group at day 14.

Conclusion: Results from this study indicated that quinine relative to artemether has a faster and sustained recovery from increased in temperature.

Key Words: Severe malaria; artemether; quinine; temperature

1. Introduction

Malaria causes more than one million deaths worldwide each year, and over 90% of them occur in Africa. *Plasmodium falciparum* causes the most serious form of the disease.[1,2] It is a major health problem in Africa, Asia, Central America, Oceania and South America and 40% of the world's population is exposed to it. Malaria may mimic any febrile illness where it is responsible for 30-50% of fever cases and should be suspected in any febrile child. [3,4]

Malaria, being responsible for 15-20% of hospital admission can indeed be life threatening and requiring intensive care. Appropriate drugs (with possible anti pyretic property) that are sensitive to malaria parasitemia and pyrogens must be used and encouraged. Malaria attack sometimes result in psychosis, stunted growth, malnutrition, chronic anemia.[5,6] The disease if not treated promptly could result in severe malaria which include cerebral malaria.[7] As a result of high morbidity and mortality associated with severe malaria, there is need for experienced and committed medical personnel, supportive care monitors and facilities.[8,9] In Nigeria, Malaria is deadly with an all - year transmission and peak rate in wet season.[8,10]

Severe Malaria is approximately 2% of clinical attacks of malaria in African children. About 1-2million deaths occur, most of them in young children (under 5 years) with a child dying every 30 seconds.[3,11] Severe malaria is defined by the presence of one or more pernicious signs and symptoms including cerebral malaria (even with correct treatment, the lethality rate among children

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with cerebral malaria approaches 20%), fever of about 38°C and above (this may be irregular or continuous), irritability, prostration, jaundice, convulsion, hypoglycemia (blood glucose <40mg/dL), anemia (Hemoglobin <5g/dL) and at times unconsciousness. There may be renal failure, hemolysis, hepato- splenomegaly, respiratory distress, circulatory collapse and bleeding diathesis.[12,13]

The presentation is usually intense in severe cases, among children under 5 years, non immunes and pregnant women,[8] as it may require hospitalization with intensive care facilities. Hyperpyrexia is defined as body temperature >37.5°C. Temperature is a recognized diagnostic tool used by clinicians, healthcare givers, parents and older children as it is suspect presence of clinical malaria.[14] Fever is also commonly used to assess severity, while reduced fever indicates clinical improvement and recovery from malaria attack. Normal stable temperature is equally an index of request for discharge of patients from hospital admission.

In the course of malaria treatment, analgesics are often prescribed. The rationale is two folds - treating malaria induced fever and Myalgia, therefore the need to evaluate possible antipyretic property among anti-malaria medications in current use for severe malaria. These include Quinine (a much older drug) and Artemether (active metabolite of artemisinin) which is relatively new drug.

The overall objective of this study is to:

1. Evaluate pattern of temperature changes (among severe malaria patients) in the course of treatment of severe malaria pediatrics patients with Quinine and Artemeter.

2. Compare fever clearance time in severe malaria patients during treatment with Quinine and Artemether.

2. Material and Methods

2.1. Drugs

1. Artemether 80mg/ml (Rhone-Poulence, Rorer France)

2. Quinine 600mg/ml (Evans Pharmaceuticals)

3. 5% dextrose saline

2.2. Patients and Methods

Patients were recruited in Ikenne local Government area of Ogun State at Overcomers Specialist hospital, Ilishan and General hospital Ikenne. The hospitals have facilities for resuscitating and handling emergency. Ethical and parental approval for the study was obtained from Olabisi Onabanjo University OOUTH joint ethical review committee and informed consent from the parents or guardians. A four hourly temperature check (axillary and rectal) was carried out on all patients included in this study by a registered nurse.The clinical examination and parents/patients observation were recorded daily for 8 days [0-7] and on day 14.

Inclusion Criteria[14]

1. Children from either sex with age ranging from 1 year to 12years.

2. Fever with temperature greater than 37.5 °C within the last 24 hours.

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.

7. Absent history of administration of antipyrexia

Exclusion Criteria[14]

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

I. 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 treatments 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. The clinical examination and observation made were recorded daily for 8days (0-7) and on day 14. At each visit, patient (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) 10mg/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 10mg/kg dose and then repeated 8hourly. The quinine infusion was later changed to oral medication when patient's clinical condition allowed for this. An oral dose of 10mg/kg was given 8hourly (osonuga et al, 2006). The duration of treatment was 7days. The patients were monitored for toxic reactions i.e. hemolysis, convulsions, restlessness, disturbed vision.

The patients in the artemether group received 1.6mg/kg artemether twice on day 0 and then 1.6 mg/kg daily for the next four days through deep intramuscular route[8]. 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

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.

Statistical Analysis

Data was analyzed using Epi-info version 6 (11), proportions were compared by calculating chi-square with Yates's correction. Normally distributed data for example, weight and temperature were compared by student's t-test. Mean value was given in the text (and tables). Standard deviation and p-value less than 0.05 were taken as statistically significant.

3. 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 $\pm$ 3.63 and weight ranged from 7kg to 35kg, mean 19.83 $\pm$ 8.22.

Commonest Clinical Features at Presentation

The commonest clinical features at presentation in the two groups are shown in Table 1. 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 similar in the two groups.

Table1: Commonest Clinical Presentations at Recruitment

Clinical presentation	Quinine	Artemether	p-value	Total
Age (Years)	8.24 $\pm$ 3.44	6.00 $\pm$ 3.71		7.00 $\pm$ 3.65
Weight (kg)	20.78 $\pm$ 7.80	18.88 $\pm$ 8.72		19.83 $\pm$ 8.22
Fever	13(48%)	14(52%)		27(96%)
Vomiting	14(43.8%)	10(31.2%)	0.10	24(75%)
Poor appetite	15(46.9%)	16(50%)	0.31	31(96.9%)
Nausea	2(6.3%)	3(9.4%)	0.63	5(15.7%)
Body aches	8(25.0%)	5(15.6%)	0.28	13(40.6%)
Yellow eyes	5(15.6%)	3(9.4%)	0.41	8(25.0%)
Grunting	5(15.6%)	5(15.6%)	1.00	10(31.2%)
Diarrhea	2(6.3%)	1(3.1%)	0.54	3(9.4%)
Cough	8(25.0%)	10(31.3%)	0.48	18(56.3%)
Jaundice	8(25.0%)	8(25%)	1.00	16(50%)
Pallor	15(46.9%)	16(50%)	0.31	31(96.9%)
Respiratory distress	9(28.1%)	11(34.4%)	0.47	20(62.5%)
Convulsion	10(31.3%)	13(40.6%)	0.24	23(71.9%)
Coma	2(6.3%)	3(9.4%)	0.63	5(15.7%)
Dehydration	16(50.0%)	16(50.0%)		32(100%)
Temp. (^{o}C)	14(50%)	14(50%)		28(100%)
Drowsing	10(31.3%)	12(37.5%)	0.45	22(68.8%)

*Values are significantly lower at $p < 0.05$

Therapeutic Responses to Treatment

Temperature (^{o}C) changes as observed in table-2. A total of 28 out of 32 patients that enrolled into the study had

temperature higher or equivalent to 37.5 °C at day 0. Fourteen out of 16 (87.5%) in quinine group and 14 out 16 (87.5%) in artemether group had fever on day 0.

Table 2: Changes in temperature (°C) in the course of treatment

Variables	Quinine	Artemether	p-value	Total
Day 0	38.64 ± 0.92	38.4 ± 1.09	0.51	38.52 ± 1.01
Day 3	37.16 ± 0.36	37.42 ± 0.32	0.037	37.29 ± 0.36
Day 7	36.95 ± 0.15	37.06 ± 0.34	0.26	37.00 ± 0.26
Day 14	37.00 ± 0.29	37.01 ± 0.31	0.68	37.00 ± 0.29

*Values are significantly lower at $p < 0.05$

At day 3, 50% of the patients' artemether groups were still running fever, while only 6.3% of the patients in quinine group still had fever. The fever clearance time for quinine was 46.5 ± 20.49 hours while that of artemether was 72 ± 27.71 hours.

Table 3: Fever clearance time (Hours)

Drugs	Clearance Time (Hours)
Quinine	46.50 ± 20.49
Artemether	72.00 ± 27.71
P value	0.006

*Values are significantly lower at $p < 0.05$

4. Discussion

A comparative study on temperature changes and fever clearance time in course of treating 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 (Table 1).

The commonest presenting symptoms were poor appetite, fever, vomiting, and pallor and are in agreement with the findings of Sowunmi et al[15], Shazia M et al[13]. 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 suggested that it may be due to preferential sequestration of parasites in gastric vascular beds[15]. The common finding on examination was a body temperature of 37.5 °C and above which occurred in 87.5% of the patients. This is similar with findings of previous research [16,17]

Hyperpyrexia as a common finding among severe malaria patients, may also be included as a malariometric index as sowunmi et al suggested for Hepatomegaly and Splenomegaly.[17] Temperature at enrolment in the study was 36.5% to 40.5 °C with mean of 38.5 °C for and 38.4 °C for quinine and artemether groups respectively.

Day zero (0) indicated that quinine treatment group had more pyrexic patients than artemether treatment group (38.64 ±0.92°C and 38.4±1.09°C respectively). By day 3, both groups demonstrated normal body temperature pattern according to the definition of pyrexia[14]. However, patients in quinine group with 37.16±0.36°C are a better temperature group than artemether (37.42±0.32°C).

Temperature of Quinine group at day 7 (36.95°C + 0.15) is much better than artemether group (37.06°C + 0.34) while at day 14, both drugs recorded similar temperature pattern (see table 2). Fever clearance time of quinine group was 46.5 ± 20.5 hours. This is quicker than that of artemether group which was 72 ± 27.7 hours. This is consistent with other workers' findings. Salako et al.[17-20] The current study has demonstrated that quinine has a shorter fever clearance time than artemether and this rapid fever clearance may be attributed to possible antipyretic properties. Some other studies indicated that Artemether has lower fever clearance time [21,22] . However most authors agree that the statistical disparity is not much[10,12,13, 23, 24] (as observed in table 2). Our study showed that quinine relative to artemether has demonstrated faster fever clearance time and hence still has role in treating severe malaria induced hyperpyrexia.

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