

Research Article

A Comparative Study of Quinine and Artemether in the Treatment of Severe Malaria in Nigerian Children

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Abstract

Purpose: Nigeria has adopted quinine as the drug of first choice in the treatment of severe malaria and artemether as an alternative therapy. The purpose of this study was to ascertain whether artemether is a comparable alternative to quinine in the management of severe malaria in Nigerian children.

Methods: We conducted a randomized prospective study comparing quinine and artemether therapies in 90 Nigerian children with severe malaria.

Results: Mortality was lower in quinine group (13.0 %) than artemether (15.9 %), Odds Ratio (OR) = 0.446 (95 % Confidence Interval (CI), 0.124 to 1.603, $p = 0.249$). The parasitaemia clearance on day 3 by quinine and artemether was 96.8 and 99.0 % ($p = 0.422$), respectively, while on day 14 it was 100 % for both medicines. Fever clearance by quinine and artemether was 87.7 and 90 % ($p = 0.753$), respectively, on day 3 but it increased to 100 and 96.42 % ($p = 0.072$), respectively, on day 14. For the quinine group, 71.74 % of the patients spent less than one week in the hospital versus 61.76 % for the artemether group ($p = 0.829$, OR = 0.883, 95 %CI = 0.284 to 2.742).

Conclusion: Artemether is a comparable alternative to quinine in the treatment of severe paediatric malaria.

Key words: Artemether; Nigerian children; Paediatric; Quinine; Severe malaria.

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INTRODUCTION

Each year, worldwide, there are about 300 - 500 million clinical cases of malaria and an estimated 1.1 - 2.7 million deaths as result of severe malaria [1]. Over 90 % of deaths occur in children below 5 years of age, mainly from cerebral malaria in children 2 - 5 years and anaemia in children 0.5 – 2 years [2]. Neurological sequelae persisting for more than 6 months occur in more than 2 % of the survivors, and they include ataxia, hemiplegia, speech disorders, behavioural disorders, epilepsy and blindness. Severe malaria with anaemia has case fatality rate higher than 13 % [3].

Of increasing concern is the declining efficacy of quinine in parts of southeast Asia [4], a trend that could prove disastrous if it spreads to Africa, where most deaths from malaria occur. Thus, there is an urgent need to identify new forms of therapy for severe malaria that are economical and practical alternatives to quinine and, ideally, improve the clinical outcome of severe malaria. Among potential alternatives to quinine, the artemisinin (qinghaosu) derivatives have attracted special interest because of the rapidity with which they reduce *Plasmodium falciparum* parasitaemia [5]. Nigeria has adopted parenteral quinine as the drug of first choice in the treatment of severe malaria and artemether as an alternative therapy [6]. Thus, in this study, we have compared the effectiveness of quinine and artemether in some Nigerian children.

METHODS

Study setting

This study was conducted in Federal Medical Centre, Birnin Kudu, Jigawa State of Nigeria. This is a heavily malaria-infested area, as a result of its ever growing population and the presence of many ponds, pools and rivers which serve as sources of water for domestic and agricultural purposes. Malaria is

characterised by a stable, perennial, transmission in all parts of the state. The transmission of malaria is higher in the wet (rainy) season than in the dry season in the state, with a peak at the former from May to late September. The centre was chosen because it is the only tertiary health facility, the highest referral centre and also has better medical services and documentation than any other health facility in the state.

Research design

The children who met the inclusion criteria were enrolled in the study and randomly assigned to receive either quinine or artemether therapy. Patients were assigned to receive quinine if the last digit of their hospital identification number was odd and to receive artemether if the last digit of their hospital identification number was even or zero. This study was conducted from July 6 to October 24, 2007. This period was chosen because malaria transmission and hospital admission are usually high due to heavy rainfall during this period.

Children between 6 months and 12 years of age presenting with fever ($> 37.5^{\circ}\text{C}$) and *P. falciparum* infection cases, with one or more general danger signs of severe or complicated malaria were included in the study based on the following definition of severe malaria [7]:

In a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of their symptoms, the presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria:

Clinical manifestation: Prostration, impaired consciousness, respiratory distress (acidotic breathing), multiple convulsions, circulatory collapse, pulmonary oedema (radiological),

abnormal bleeding, jaundice and Haemoglobinuria.

Laboratory test: Severe anaemia, hypoglycaemia, acidosis, renal impairment, hyperlactataemia and hyperparasitaemia.

Excluded were patients with serious concomitant illness, e.g., sick cell anaemia, HIV, tuberculosis and other chronic diseases; patients without any manifestations of severe malaria; and patients with severe malnutrition and known hypersensitivity to one of the study drugs. In addition, children below 6 months and those above 12 years were not included.

Structured data collection form was used for collection of demographic characteristics, clinical and treatment variables. Laboratory report form was used for recording laboratory findings. The forms were filled by the appropriate personnel serving in the hospital. Forty-six children (28 females and 18 males) were included in the quinine treatment group and they received quinine 20 mg salt/kg body weight (bw) on admission (i.v. infusion or divided i.m. injection, as a loading dose), then 10 mg/kg bw every 8 h; the infusion rate did not exceed 5 mg salt/kg bw per hour. Forty-four children (24 females and 20 males) were included in the artemether group and they received artemether 3.2 mg/kg bw i.m. given on admission, as a loading dose and then 1.6 mg/kg bw per day for 2 days. Quinimax[®] injection manufactured by Sanofi and Paluther[®] injection manufactured by May and Baker were used in this study. A quantitative parasite count of asexual forms was performed (using the parasite/white blood cell count) at day 0, day 3 and day 14. The parasite clearance was taken as adequate clinical and parasitological response (ACPR) at days 3 and 14.

Their body temperatures were taken two times daily during the admission. Fever clearance was taken as body temperature ≤ 37.5 °C after treatment had commenced. Pediatric Coma Scale (PCS) developed by

Simpson and Reilly [8,9] was used to assess the consciousness of the patients at days 0, 1, 2 and 3. Normal aggregate score adjusted for age according to Simpson and Reilly was: 0 - 6 months: 9; > 6 - 12 months: 11; > 1 - 2 years: 12; > 2 - 5 years: 13; > 5 years: 14. Any patient who had aggregate score below his specified normal age adjusted score was taken to be comatose. Mortality was estimated by the number of patients that died in the hospital. Hospital bed-days were calculated by the actual number of days each patient spent in the hospital. The patients were admitted and treated within the study period.

Data analysis

Data analysis was performed using SPSS for Windows 13.0 (SPSS Inc., Chicago, IL). We used χ^2 tests to compare categorical data (Fisher exact for groups smaller than $n = 5$). Continuous data were tested for normality (test for skewness, Shapiro – Wilkxon test for normality). Normally distributed data were analysed with independent samples T-tests, and non-normally distributed data with Mann-Whitney U test. A two-tailed significance level of 0.05 was used. Multivariate regression analysis was performed to determine whether baseline characteristics were associated with the outcome of treatment. Age, weight, sex, severity, number of co-morbidities, initial parasite count, and initial temperature were entered into the model as linear variable or classified categories. Intention-to-treat analysis was applied.

Ethical consideration

Necessary clearance was obtained from the University of Nigeria Teaching Hospital ethical committee and written consent was also obtained from the children's care takers. Moreover, confidentiality was maintained during data collection and processing, and the procedures did not endanger or have adverse effects on the patients.

RESULTS

A total of 90 children were included in the study, 46 were treated with quinine while 44 were treated with artemether. Two patients absconded in each group, representing 4.35 and 4.55 % for quinine and artemether, respectively. Six of 46 children treated with quinine died in the hospital (13.04 %), compared with 7 of 44 patients treated with artemether (15.90 %). Thirty-one of 38 children discharged in the quinine group

came back for follow-up (81.58 %) on day 14, compared with 30 of 35 children discharged in the artemether group (85.70 %). Multivariate regression analysis showed that none of the baseline characteristics influenced the outcomes significantly; independent of these, the treatment group was the primary determinant of the study outcomes (Table 1). The clinical features on admission were similar in the two groups (Table 2).

Table 1: The results of multivariate regression analysis

Dependent variables	Predictors *								
	Constant	Age	Weight	Sex	Severity	Co-morbidity	Body Temp day 0 (°C)	Para day 0	CNS day 0
Unstandardized coefficients (B)									
^a Body temp day 3 (°C)	7.45	-0.68	0.41	-3.44	0.29	0.32	-0.97	2.96	-3.844
^b Body temp day 14 (°C)	10.36	1.80	1.57	0.08	-1.73	0.43	-3.85	2.31	0.35
^c Haemoglobin day 14 (g/dl)	8.87	2.05	-0.25	1.53	-3.49	0.29	0.19	-0.06	-2.96
^d Parasite density day3	11.27	-0.71	-0.995	1.68	2.51	-2.98	0.94	0.37	-0.81
^e Parasite density day14	4.54	2.30	-1.16	0.50	-0.52	-3.62	0.95	0.46	1.158
^f Hospital bed-days	7.45	-3.47	0.56	2.34	0.14	-0.43	3.76	-0.67	0.164
^g Consciousness status day 3	5.92	-0.16	0.17	-0.77	-3.22	0.45	-0.88	2.80	-1.736

^a R = 0.23, R² = 0.053 Adjusted R² = 0.051

^b R = 0.42, R² = 0.18 Adjusted R² = 0.18

^c R = 0.38 R² = 0.14 Adjusted R² = 0.14

^d R = 0.46 R² = 0.21 Adjusted R² = 0.22

^e R = 0.51 R² = 0.26 Adjusted R² = 0.26

^f R = 0.31 R² = 0.096 Adjusted R² = 0.097

^g R = 0.45 R² = 0.20 Adjusted R² = 0.20

* P-value > 0.05

Body Temperature on day 0 (Body Temp day 0), Parasitaemia Density on day 0 (Para day 0), Consciousness status on day 0 (CNS day 0)

Table 2: Base-line demographic and clinical characteristics of the patients

Characteristic	Quinine N=46	Artemether N=44
*Age (years)	3.2±1.7	3.8±1.3
† Sex, F/M (%F)	28/18(60.9)	24/20(54.54)
*Mean weight (kg)	14.74±8.42	12.48±5.9
† Co-morbidities (%)		
Gastroenteritis	17(36.96)	20(45.46)
Acute upper respiratory tract Infections	12(26.01)	8(23.53)
Acute lower respiratory tract Infections	2(4.35)	4(9.09)
None	15(32.61)	12(35.29)
† Comatose patients (%)	10(21.74)	7(15.90)
† Severe anaemia (haemoglobin <5g/dL (%))	13(28.26)	10(29.41)
* Body temperature (°C)	38.27±0.51	38.36±0.42
‡ Geometric mean of parasitaemia (per µL of blood) (range)	21,573.19(1,200- 210,000)	27,268.43(1,200- 200800)

† Frequency of patients (percentage); *Mean (±SD) ‡ Geometric mean (range)

Six of 46 children treated with quinine died in the hospital (13.04 %), compared with 7 of 44 patients treated with artemether (15.90 %); RR= 0.446 (95 %CI, 0.124 to 1.603, p = 0.249). Most of the deaths occurred within the first 3 days of admission in both treatment groups; 61.54, 76.92 and 84.62 % of these deaths occurred by days 1, 2 and 3, respectively. Mortality was calculated based on the patients that died in the hospital.

Parasitaemia clearance of quinine on day 3 was (96.8 %), compared with 99.0 % clearance by artemether ($p = 0.422$) by Mann-Whitney test); however, parasitaemia clearance (ACPR) was (100 %) in both drug groups on day 14. The fever clearance of children treated with quinine and artemether were 87.7 and 90.0 % ($p = 0.753$) , respectively at day 3, and 100 and 96.42 % ($p = 0.072$) in quinine and artemether, respectively, at day 14.

Although quinine showed greater effect on coma recovery on day 3, there was no significant difference when the treatment groups were compared ($p = 0.763$) (Table 3). The probability of recovering from coma in

the artemether and quinine groups, respectively, was 0.43 and 0.50 within day 1; 0.71 and 0.80 within day 2, and 0.86 and 0.90 within day 3. The proportion of patients that spent less than one week in the hospital in quinine and artemether treatment groups were 71.74 and 61.76 %, respectively (RR = 0.883, 95 %CI, 0.284 to 2.742, $p = 0.829$).

DISCUSSION

Quinine showed higher mortality prevention than artemether; the point estimate was consistent with quinine being associated with a massive 55% reduction in mortality risk *vis a vis* artemether. It had been widely anticipated that a more rapid reduction of parasitaemia would bring about a corresponding reduction in mortality. The odds ratios had wide confidence limits and one cannot exclude the possibility that artemether would reduce mortality if its use were widespread. Several smaller trials in southeast Asia suggested that treatment with artemisinin derivatives might reduce mortality by 50 % [5]. Our finding suggests that the speed of parasite clearance may be a relatively unimportant determinant of survival.

Table 3: Results of outcome parameters

Outcome parameters	Artemether	Quinine	P- value	95% Confidence Interval	RR
¥Mortality	20.59	13.04		0.124 to 1.603	0.446
¥Coma Recovery	15.90	21.74		0.065 to 9.015	0.763
ð Parasitaemia clearance on day 3	(259±81)99	(320±89)96.8	0.422		
ð Parasitaemia clearance on day 14	(122±23)100	(163±32)100	0.672		
¶Fever clearance on day 3 (temperature ≤ 37.5 °C)	(37.0±0.4)90	(37.2±0.5)88	0.753		
¶Fever clearance on day 14 (temperature ≤ 37.5 °C)	36.9(±0.5)96.4	37.3(±0.3)100	0.072		
¶Hospital bed-days (≤7 days)	(7.1±1.6)62	(7.03±1.76)71		0.284 to 2.742	0.883

¶ (Mean±SE) percentage; ¥ Percentage of patients; ð (Geometrical mean±SE) percentage

In this case, part of the explanation may be that artemether preferentially accelerates the clearance of younger parasites, which are those seen in the circulation, over more mature parasites, which are located deep in the vasculature and mediate organ damage [10].

The study revealed a shorter coma recovery time in the quinine group. There has been concern that artemether may be neurotoxic at high doses. This has been observed in studies in animals, but it is yet to be demonstrated in human beings [11]. The tendency toward a longer time to recovery from coma in the artemether group could possibly be due to such an effect.

This study showed that parasitaemia clearance on day 3 was higher in artemether group than in the quinine group. Although ACPR was 100 % at day 14 in both groups, none of them completely eliminate the parasites. This study supports findings that both artemether and quinine lack the ability to prevent malaria re-infection [12,13].

Fever clearance was higher in the artemether group than in the quinine group on day 3 and day 14 but the difference was not significant.

This effect may be attributed to the relatively higher parasitaemia clearance exhibited by artemether as well as increasingly quinine resistance. The proportion of patients that spent less than one week in the hospital were higher in the quinine group than in the artemether group but the difference was not statistically significant. The greater parasitaemia clearance found in artemether did not reflect in the number of days spent in the hospital.

The World Health Organization currently recommends that artemisinin derivatives alone should not be used as first-line treatment in Africa, in order to delay the development of resistance to this valuable class of antimalarial compounds [14].

Limitations of the study

The following limitations were inherent in the study and the results were interpreted in this light. Fourteen days were not enough for a study of this kind because the true failure rates may have been higher. It has been estimated that 28-day assessments underestimate the true failure by about 20 % for drugs with intermediate elimination half-life, such as lumefantrine and sulfadoxine-

pyremethamine (3 – 6 days half-life), and as much as 40 % for drugs with a longer elimination half-life, such as desethylamodiaquine [15,16]. The sample size was small. Loss to follow-up was 18.4 and 14.3% in quinine and artemether respectively but losses were equally distributed between the two treatments. Some baseline characteristics were based on care takers' report, which might not be true.

CONCLUSION

This study has shown that quinine and artemether are comparable alternatives. Although quinine prevented mortality to a greater extent than artemether, other non-fatal measures of disease activity showed some similarity between the treatments. Using artemether as an alternative to quinine does not only provide alternative chemotherapy against severe malaria but should also help to preserve the other against ever-emerging antimalarial drug resistance by reducing exposure of either drug to parasites.

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