

Comparative study of efficacy of artesunate plus cotrimoxazole and artesunate plus chloroquine in the treatment of malaria in Nigerian children: a preliminary report

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Abstract

Background & objectives: The study was undertaken to evaluate the efficacy of cotrimoxazole plus artesunate and to compare the efficacy of this combination with that of artesunate plus chloroquine in the treatment of acute uncomplicated falciparum malaria in children.

Methods: Children aged between 0.5 and 12 yr with clinical and parasitological evidence of *Plasmodium falciparum* malaria were randomized to receive either artesunate plus cotrimoxazole or artesunate plus chloroquine. They were followed-up with clinical and parasitological assessment for a period of 14 days.

Results: In all, 57 out of 81 (31 in the artesunate plus cotrimoxazole group and 26 in artesunate plus chloroquine group) completed the study as per protocol and were evaluated. Pre-treatment clinical and parasitological parameters were similar in the two treatment groups. The time to clear fever and other symptoms were similar in the two groups 1.0 ± 0 vs 1.14 ± 0.38 ($p > 0.05$). Parasite clearance times were also similar; 1.65 ± 0.49 days vs 1.58 ± 0.67 days respectively for artesunate plus cotrimoxazole and artesunate plus chloroquine ($p > 0.05$). The cure rates on Day 14 were 100% for both artesunate plus cotrimoxazole and artesunate plus chloroquine groups. Both drug combinations were well-tolerated in the small population of children.

Conclusion: These results indicate that artesunate plus cotrimoxazole has similar efficacy to artesunate plus chloroquine in the treatment of acute uncomplicated *P. falciparum* malaria in children resident in an endemic area of south-west Nigeria.

Key words Artesunate; chemotherapy; chloroquine; cotrimoxazole; malaria; Nigeria

Introduction

Consequent upon widespread resistance to chloroquine and most other antimalarial drugs, combination chemotherapy has become standard of treatment of acute uncomplicated symptomatic falciparum malaria^{1,2}. Combination therapy provides adequate case treatment and delay the development of resistance^{3,4}. Artemisinin based combination chemotherapy is preferred as a result of the rapidity of action but non-artemisinin based chemotherapy may be

considered as alternative regimen⁴. In Nigeria, the National Malaria Control Programme recommends artemether-lumefantrine or artesunate-amodiaquine for the treatment of acute symptomatic malaria at all levels of health care including home management¹. Artesunate have sometimes been combined with chloroquine or sulphadoxine-pyrimethamine⁵.

Cotrimoxazole, a combination of sulphamethoxazole and trimethoprim is a broad spectrum antibacterial agent with proven efficacy in the treatment of *Plas-*

modium falciparum malaria^{6–8}. The mechanism of action of cotrimoxazole and, perhaps resistance of *P. falciparum* to the drug is similar to that of sulphadoxine-pyrimethamine⁹. Malaria and bacterial respiratory tract infection do coexist in children and in such instances cotrimoxazole has sometimes been prescribed with chloroquine or other common anti-malarial drugs¹⁰. The cost, ease of procurement and administration make cotrimoxazole an attractive antimicrobial agent. In the present study, the efficacy of artesunate plus cotrimoxazole was compared with that of artesunate plus chloroquine and we concluded that both regimens have comparable efficacy.

Material & Methods

Patients: A total of 81 children aged 0.5 to 12 yr presenting at the outpatient department of Aremo Maternity, Ibadan, Nigeria were randomized to receive either artesunate plus cotrimoxazole or artesunate plus chloroquine between April 2008 and March 2009. The criteria for inclusion were fever or history of fever during 24–48 h preceding presentation, pure *P. falciparum* parasitaemia of at least 2000 asexual forms per microlitre of blood, no antimalarial drug administration in the two weeks preceding presentation, absence of concomitant illness, and consent of parents or guardians. Children with history suggestive of sickle-cell anaemia, haematocrit of <20% and those with history of intolerance to any of the study drugs were excluded from the study. Withdrawal criteria included: development of concomitant illness, withdrawal of consent or violation of study protocol as approved by the Ethics Committee of Oyo State, Ministry of Health, Secretariat, Ibadan, Nigeria.

Prior to enrolment, a careful history was obtained from the accompanying parent or guardian and physical examination including body weight and axillary temperature were performed after which thin and thick blood films were prepared for parasite identification and quantification. Samples were also collected into capillary tubes for determination of haematocrit and two drops of blood were spotted on filter paper for molecular characterization at a later date.

Drug treatment and follow-up: The children were randomly allocated to receive artesunate at a dose of 4 mg/kg bw in two divided doses daily for three days plus either cotrimoxazole at an equivalent dose of 20 mg/kg bw of sulphamethoxazole component twice daily for three days or chloroquine at standard dose, 10 mg/kg bw as single daily doses on Days 0 and 1, and 5 mg/kg bw on Day 2. All drugs were administered orally and in tablet form. All doses of chloroquine and morning doses of cotrimoxazole and artesunate were administered by a physician (FA) at the clinic and each child was observed for at least two hours in order to ensure that the drug was not vomited. Each parent or guardian gave an account of drug (evening dose) administration at home, each time the child was seen for follow-up to ensure that the drug had been properly administered. Follow-up schedule was only till Day 14 because it was considered adequate in areas of intense transmission¹¹.

Evaluation of response: Clinical observations were recorded daily for five days (Days 0–4), on Days 7 and 14. Thick and thin blood films for parasite quantification were prepared at the same time as clinical observations. A repeat sample was taken for assessment of haematocrit on Days 7 and 14. At each visit, the guardians or parents and, when possible the children were interviewed and examined for evidence of adverse reactions to the drugs. Children with temperature $\geq 39^{\circ}\text{C}$ were exposed to fan in addition to receiving paracetamol given to all febrile cases.

Giemsa stained blood films were examined by light microscopy under an oil immersion objective $\times 100$. Asexual parasitaemia in thick films was estimated by counting asexual forms relative to leucocytes, 500 asexual forms of *P. falciparum*, or the number of such parasites corresponding to at least 200 leucocytes, were counted, whichever occurred first. The parasite density was subsequently calculated by assuming a leukocyte count of 8000/ μl of blood (Number of parasites/Number of leukocytes $\times 8000$)¹². The parasite clearance time (PCT) was defined as the time from drug administration until there was no patent asexual parasitaemia. The fever clear-

ance time (FCT) was defined as the time from drug administration until the axillary temperature fell to 37.4°C or below and remained so far at least 72 h. This definition was necessary because of the routine use of paracetamol during the first two days of treatment.

Classification of response to drug treatment was according to criteria of World Health Organization¹¹. Early treatment failure (ETF) was defined as development of danger signs on Days 1–3; Day 2 parasitaemia higher than Day 0 or parasite count on Day 3 was >25% of the Day 0. Late clinical failure (LCF) was defined as development of danger signs after Day 3 in the presence of parasitaemia and axillary temperature >37.4°C between Day 4 and Day 14. Adequate clinical and parasitological response (ACPR) was defined as absence of malaria associated symptoms and malaria parasite on Day 14.

Statistical analysis: Data were analyzed using *Epi-Info* version 6¹³. Proportions were compared by calculating χ^2 with Yates’s correction. Normally distributed continuous data were compared by Student’s *t*-test. Data not conforming to normal distribution,

for example, parasite density, were log transformed or compared by the Mann-Whitney U-test or the Kruskal-Wallis test. Values are given in the text and Tables as means \pm standard deviation (SD); values of $p < 0.05$ were taken as statistically significant.

Results

Clinical features at presentation: In all, 81 children were enrolled for the study but only 57 (70.4%) completed the scheduled follow-up and were evaluated. Of the 24 children who could not be evaluated, four patients inadvertently received concomitant medication (amodiaquine and pyrimethamine-sulphadoxine in one and three cases, respectively), the remaining 20 children did not attend follow-up clinics on Day 4 (5) and Day 7 and subsequent visits (15 patients). However, they all cleared parasitaemia and symptoms before last visit to the clinic. The 57 (22 females and 35 males) who completed the study received artesunate plus cotrimoxazole (31) and artesunate plus chloroquine (26). The presenting symptoms were similar in the two groups. Fever or history of fever was documented in all and vomiting was the second commonest symptom found in 27

Table 1. Anthropometric and parasitological data at enrolment of children presenting with falciparum malaria and treatment outcome on Day 14

Characteristics	Artesunate plus cotrimoxazole (n = 31)	Artesunate plus chloroquine (n = 26)	<i>p</i> -value
Female : Male	12 : 19	11 : 15	
Mean age in years (Range)	6.10 \pm 3.56 (0.5–12)	6.29 \pm 4.56 (0.67–12)	<i>p</i> : 0.27
Mean weight in kg (Range)	19 \pm 7.3 (7–32)	19 \pm 10.85 (6–40)	<i>p</i> : 0.31
Geometric mean parasite density/ μ l (Range)	16596 (2287–72492)	13996 (3300–73580)	
Mean FCT in days	1 \pm 0	1.14 \pm 0.38	<i>p</i> > 0.05
Mean PCT in days (Range)	1.65 \pm 0.49 (1–2)	1.58 \pm 0.67 (1–3)	<i>p</i> : 0.65
Day 14 treatment outcome (%)			
ETF	0	0	
LCF	0	0	
ACPR	100	100	

ETF—Early treatment failure; LCF—Late clinical failure; ACPR—Adequate clinical and parasitological response.

(47.4%) of the children. Anorexia was documented in 21 (36.8%) of the children, thus, relatively more commonly found symptom than headache (29.8%) in this small population of children treated for malaria.

Clinical and parasitological responses: The mean FCT was similar in the two groups: 1 ± 0 vs 1.14 ± 0.38 days, ($p > 0.05$) respectively for artesunate plus cotrimoxazole and artesunate plus chloroquine. ACPR was observed in all of the enrolled patients in both treatment groups by Day 14. Anthropometric and parasitological characteristics of the children are shown in Table 1. The enrolment geometric mean parasite density for artesunate plus cotrimoxazole and artesunate plus chloroquine was similar 16,596 and 13,996 per μl of blood, respectively. Table 1 also shows the rates of parasite clearance and cure rate for the children. In all, 20 (64.5%) and 13 (50%) patients who received artesunate plus cotrimoxazole and artesunate plus chloroquine, respectively have cleared (asexual) parasitaemia by Day 1. By Day 2, all the children who received artesunate plus cotrimoxazole and 24 of 26 (92.3%) who were treated with artesunate plus chloroquine had cleared their parasitaemia. The remaining two children in the artesunate plus chloroquine group had cleared parasitaemia by Day 3. The PCT was similar in the two treatment groups, 1.65 ± 0.49 and 1.58 ± 0.67 for artesunate plus cotrimoxazole and artesunate plus chloroquine, respectively ($p > 0.05$).

Untoward drug effects: In all, three patients had documented unwanted effects of the drugs and all had received artesunate plus chloroquine and complained of pruritus. The pruritus was mild and lasted for three days in children and requiring only reassurance.

Discussion

In Nigeria, both chloroquine and cotrimoxazole enjoy wide usage amongst the clientele of public health facilities^{10,14,15}. Cotrimoxazole is effective in the treatment of microbial diseases notably bacterial and protozoan infections including *Pneumocystis carinii*

and *P. falciparum* whereas chloroquine was the first-line antimalarial drug used as monotherapy until recently^{6,7}. Cotrimoxazole has sometimes been prescribed with commonly used antimalarial drugs once there is suspicion of co-existing bacterial infection¹⁰. The present study attempted to evaluate the efficacy of cotrimoxazole and chloroquine as a partner drug in artemisinin based combination therapy for acute uncomplicated falciparum malaria. The follow-up schedule used in the study is considered adequate for the preliminary *in vivo* evaluation of efficacy of antimalarial in areas of intense transmission, particularly PCR correction will be required to differentiate recrudescence from reinfection, a likely occurrence after two weeks of treatment¹¹.

The socio-biological characteristics of the children in the two treatment groups were similar and responses to treatment were also comparable. The two regimens had similar fever clearance time which was also comparable to previous studies involving the use of combination therapy¹⁶⁻¹⁹. Parasite clearance time in the artesunate plus cotrimoxazole and artesunate plus chloroquine groups were similar and comparable to previous studies in the same area. The cure rate on Day 14 was also similar in the two groups and compares with similar studies in this area¹⁶⁻¹⁹.

Artesunate is common to the two regimens and has been recommended for use in combination with amodiaquine in the National Malaria Programme in Nigeria¹¹. Artesunate has also been previously evaluated in combination with sulphadoxine-pyrimethamine, however, only few studies on the efficacy of artesunate in combination with cotrimoxazole or chloroquine exist^{17,18,20}. Combination of two failing drugs such as chloroquine and sulphadoxine-pyrimethamine cannot be recommended for obvious reasons. The use of a failing drug as partner to artemisinins should also be approached with extreme caution considering that artemisinins may be left unprotected, thus, >80% efficacy would be expected from partner drugs²¹. However, criteria for selection of combinations of antimalarial drugs had earlier been noted to include: therapeutic efficacy of the

combination irrespective of the efficacy of the individual components, safety of the drugs especially amongst high risk groups, potential for consumer compliance, potential for widespread use, potential to delay or prevent development of resistance, cost-effectiveness as well as product availability and production capacity¹¹. Both chloroquine and cotrimoxazole, considering experience and outcome of this small study, might have satisfied these criteria but larger community-based study with a period of follow-up of 28 days or longer should be undertaken prior to promoting the use of combinations other than have been previously recommended²¹. Further, this study might have over-estimated the efficacy of the regimens used since a significant proportion of recrudescence may not appear until after Day 14.

In view of the substantial childhood morbidity and mortality attributable to malaria and respiratory tract infections in sub-Saharan Africa, combination containing cotrimoxazole may offer some advantage. Such combinations may also be useful in resource poor areas where facilities for diagnosis may be inadequate. Previous studies in the same area had suggested that cotrimoxazole and cotrimoxazole containing combinations may have relatively reduced propensity to support gametocyte generation, at least when compared with sulphadoxine-pyrimethamine^{18,19,22}. The long experience with the use of chloroquine in all populations including pregnant women and those with genetic abnormality involving erythrocyte may support the use of the drug as a partner to artemisinin derivatives. It may yet be too early to advise any change in the antimalarial drug policy given the narrow scope of the present study. Adverse reactions encountered in the study were in general mild and did not necessitate discontinuation of drug treatment in the few children who all had pruritus.

Conclusion

Cotrimoxazole or chloroquine in combination with artesunate is efficacious in the treatment of acute symptomatic malaria in a small group of Nigerian children. Both drug regimens were well tolerated also.

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