

# Efficacy of Artemether – Lumenfantrine against Uncomplicated Plasmodium falciparum Malaria in Infants and Children in Uyo, Nigeria

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## Abstract

Coartem is recently approved artemisinin- based tablet that provides effective antimalarial treatment for children in many sub-saharan countries. This study evaluates the efficacy of this drug in 120 children weighing 5-25kg with uncomplicated falciparum malaria in Uyo. Six doses of coartem were given over 3 days with follow up at 7, 14 and 28 days. Treatment rapidly cleared parasitaemia and fever. The overall 28-day cure was 80.1%. Cure rate at 7 and 14 days exceeded 90%. No severe adverse side-effects, clinical failures or parasitological failures were observed among these patient. Coartem therefore appear efficacious for the treatment of uncomplicated malaria in Nigeria.

## INTRODUCTION

Malaria is one of the most serious diseases in the tropics claiming millions of lives yearly. Malaria in Africa mainly due to a blood parasite, Plasmodium falciparum. Children under the age of five years and pregnant women are the most afflicted with this debilitating disease. The problem of malaria is compounded by the declining sensitivity of P. falciparum to the array of available antimalarial drugs<sup>1</sup>. Resistance to antimalarial is responsible for an increase in morbidity and mortality in many sub-saharan countries<sup>2</sup>.

In Nigeria malaria is identified as the most prevalent type of infective and parasitic disease<sup>3</sup>. Estimates show that this parasitic disease accounts for no less than 300,000 deaths from more than 20 million clinical attacks while 10-20% of hospital admissions are due to malaria. The problem of malaria in Nigeria is complicated by the emergence of drug resistant malaria parasites. As a response to increasing levels of resistance to antimalarials drug, World Health Organisation recommends that all countries experiencing resistance to conventional monotherapies such as chloroquine, amodiaquine or sulfadoxine – Pyrimethamine (SP) should use combination therapies preferably those containing artemisinin derivatives (ACTs – artemisinin based combination therapies) for falciparum malaria<sup>4</sup>.

Artemether – Lumefantrine also known under the brand name coartem<sup>R</sup> is a new artemisinin – containing fixed combination antimalarial treatment that has proved to be well tolerated and highly effective against Plasmodium falciparum<sup>5</sup>. The goal of chemotherapy in malaria is often to effect a clinical cure or parasitological clearance or to limit the development of drug resistance<sup>6</sup>. Accurate and effective surveillance systems for monitoring antimalarial drug efficacy have been recognized as an essential basis for decisions on the use of drug. The main purpose of this study was to ascertain the therapeutic efficacy of coartem in the treatment of uncomplicated P. falciparum malaria in Uyo, South Eastern Nigeria. The data obtained from this study would provide useful information for future management of uncomplicated falciparum malaria in Nigeria.

## MATERIAL AND METHODS

### STUDY SITE

The study was carried out between July and December, 2007 in Uyo, Southern Nigeria. Uyo is located on latitude 503' North and longitude 757' East. It is the capital city of Akwa Ibom State Nigeria. Akwa Ibom State is located within the lowland coastal plain region of Nigeria between latitude 432' and 553' North and longitude 725' and 825' East. The state lies on the Eastern Niger Delta and shares the hot humid

tropical climate of the region marked by two distinct seasons – dry (November to March) and wet (April to October) seasons. As in the entire country malaria is endemic and the transmission is intense (stable) and peaks during the rainy season.

## **PATIENTS**

This study followed the World Health Organisation<sup>7</sup> recommendation, for the in-vivo investigations of antimalarial drug efficacy, in terms of treatment, follow up and data analysis. The study was conducted in children with fever weighing 5-25kg, who were attending Nedeke Paediatrics Specialist Hospital, Uyo, using the WHO 28 day in-vivo protocol, patients, were enrolled in the study, if they satisfied the following inclusion criteria, weight between 5 and 15 kg, mono-infection with *P. falciparum* parasitaemia, with parasitaemia in the range of 1000 to 100,000 asexual parasites per  $\mu$ l of blood, presence of auxiliary temperature  $\geq$  37.5C and a history of fever in the preceding 24 hr, informed consent by parents and guardians, ability to come for the stipulated follow-up visits and easy access to health facility. Key exclusion criteria were presence of general danger signs such as inability to drink or breastfeed, vomiting everything, recent history of convulsion, lethargic or unconscious state, unable to sit or stand up and use of any drug known to influence cardiac function (e.g. Halofentrine) within 4 weeks before screening. Also excluded were those showing signs and severe and complicated *falciparum* malaria namely cerebral malarial. A detailed inclusion and exclusion criteria has been given elsewhere<sup>8,9</sup>.

## **TREATMENT**

Since there was no existing medication approved for a direct comparison, an open label, non comparative trial of three day regimen of artemisinin based tablet coartem (co-artmethar) comprising artemether 120mg plus lumefantrine 20mg was used in this study. The enrolled children (5-25kg) were allocated to one of three body weight group, 5 – 10kg or 10-15kg each given six doses of one coartem tablet. 15-25kg, each given six doses of two coartem tablets. Doses were administered under doctor's supervision at 0, 8, 24, 36, 48 and 60 hours. Tablets were given with food or drink whenever possible. In children who were unable to swallow tablets, the tablets were crushed and suspended in sterile water for dosing. Treatment began on the day of enrolment (day 0). After drug administration on day 0, the patients were asked to return on days 1 and 2 to complete the drug regimen and for clinical assessment. They were also given

appointment papers for days 3, 7, 14 and 28 for clinical examination and blood smears. Patients were also asked to return to the clinic on days other than these if they developed any additional complaints or any change in their condition compared to pre-administration of the drug if a patient did not report at the hospital for the scheduled visit, every effort was made to trace them to their homes.

## **DISCONTINUATION OF TREATMENT**

Adverse events, unsatisfactory therapeutic effects, loss of patient to follow up, patients non-compliance or consent withdrawal as a result of treatment failure were criteria for discontinuation. All discontinued patients were followed up for 28 days for safety assessment where possible.

## **TREATMENT EFFICACY**

This was determined based on parasitological cure rates on days 7, 14 and 28 by the times to parasite and fever clearance and from the proportions of patients without gametocytes. Recrudescence denoted clinical recurrence of malaria after the initial clearance of parasite from the circulation. Parasite reappearance was interpreted as either true recrudescence or a new infection. In this study treatment efficacy for cure rates was described as uncorrected since DNA polymerase chain reaction (PCR) analysis was not performed.

## **SAFETY ASSESSMENT**

All adverse events were monitored and recorded on case report forms. Treatment emergent symptoms of malaria were defined as adverse events occurring anew or worsening from baseline but occurring before possible recurrence of parasitaemia.

## **SAFETY EVALUATION**

Assessment of possible treatment related adverse events during acute diseases is difficult, due to the background dominance of malaria related signs and symptoms. Malaria clinical features were therefore recorded at baseline, during treatment and during follow-up visits.

## **PARASITE COUNT**

At screening prior to enrolment thick and thin blood films were examined. A second Geimsa stained thick film was examined with a binocular microscope with an oil immersion objective lens to quantify the parasitaemia, parasitaemia was measured counting the number of asexual parasites against a number of leukocytes in the thick blood

film based on a putative count of 8000 leukocytes per microlitre of blood or an adequate mean WBC in the population under investigation. The number of asexual parasites was counted against 200 leukocytes using a hand tally counter. The parasite microlite of blood was calculated by using the formula.

**Figure 1**

$$\text{Parasite density} = \frac{\text{No of parasite x WBC count (8000)}}{\text{No. of leukocytes counted 200}}$$

Temperature = Auxiliary temperature was recorded using a digital electronic thermometer.

**ETHICAL CONSIDERATION**

This study was approved by the ethical committee of St. Luke’s General Hospital, Anua, Uyo. The Study ensured adherence to good clinical practice and conformed to TDR standard operating procedure (SOP). Informed consent for the minors were obtained from their parents and guardians.

**RESULTS**

A total of 210 subjects were screened because their parents or guardians complained of symptoms suggestive of malaria and had not taken any antimalarial medication within the previous seven days. A total of 120 patients fulfilled the criteria for enrolment but a total of 113 patients completed the study. The demographic and disposition of each patient is shown in Table 1. Five patients discontinued treatment as a result of withdrawal and protocol violation, while 2 patients, completed treatment but were lost to follow-up. The gender distribution was approximately equal for the population and for each body weight group.

**Figure 2**

Table 1: Demographic characteristics of the patients enrolled in the coartem treatment arms

	Body weight			Total
	5 – 10 kg	10 – 15 kg	15 – 25 kg	
<b>Patients n (%)</b>				
Enrolled and treated	50	40	30	120
Discontinued treatment	2	1	2	5
Discontinued during follow-up	1	1	0	2
<b>Sex n (%)</b>				
Male	26	20	18	64
Female	26	19	11	56
<b>Age (years)</b>				
Median	1.1	2.3	5.9	2.3
Range	0.4-3.5	0.9-7.0	3.2-10.2	0.4-3.5
<b>Parasite density (no./mm<sup>3</sup>)</b>				
Median	14380	18421	24,530	
Range	1065-210,000	1472-220,110	11,110 – 140,030	
<b>Body Temp.</b>				
Median	38.5	38.3	38.5	38.5
Range	37.5-40.0	37.5-39.8	37.5-41.0	37.5-41.0
<b>Body weight</b>				
Median	8.8	11.8	19.2	9.8
Range	5.0-9.9	10.0-14.9	15.0-25.0	5.0-25.0

**EFFICACY OF COARTEM**

The result showed that both 7 and 14 days uncorrected cure rate was 100%. However, 3 of the 113 patients who completed the 28 days of follow up had low grade parasite density of 110 parasite and 340 parasite /mm<sup>3</sup> blood respectively. We could not determine whether it was as a result of recrudescence or of new infection since no polymerase chain reaction technique was used (Table 2).

**Figure 3**

Table 2: Parasitological Cure rates

Cure rates	Body weight			Total
	5 - 10 kg (n = 50)	10 - 15kg (n = 40)	15 - 25kg (n = 30)	
7	50/50 (100)	40/40 (100)	30/30 (100)	
14	50/50 (100)	40/40 (100)	30/30 (100)	
28	43/50 (86.0)	34/40 (85.0)	26/30 (86.7)	

**TIMES TO PARASITE AND FEVER CLEARANCE**

Time to parasite clearance in 113 children was determined

from the spread sheet data WHO/MAL/82.988 parasitaemia cleared in 40 children within 24 hours and 73 children within 48 hours and the remaining 2 children within 72 hour.

**Figure 4**

$$\frac{(40 \times 24) + (73 \times 48) + (2 \times 72)}{113} = 40.8$$

### **ANTI-GAMETOCYTE ACTIVITY**

Only a very low proportion of patients 15/113 had gametocyte on day 0 – 3, none of the children had gametocyte after 14 days. Symptoms of malaria disappeared in almost all patients during the first 3 days of the study.

### **ADVERSE EVENTS**

The adverse events reported during the study were gastric disturbance (5 cases), excessive sleepiness (5 cases) and dizziness (one case) were all mild and self-limiting, none of the patients withdraw because of side effects.

### **DISCUSSION**

Multi-drug resistant plasmodium malaria is a major public health problem in Nigeria. The failure of chloroquine the first-line treatment and other antimalarials have rendered *P. falciparum* malaria a particularly dangerous disease in Nigeria and clearly resulted in many avoidable deaths. The result of the present and previous investigations<sup>9,10,11</sup> indicates that if fully implemented the recent change in the national policy for the treatment of malaria in children in Nigeria from CQ or SP used alone to ACT for both first and second line treatment would greatly reduced malaria attributable morbidity and mortality in the country. The 100% clinical and parasitological response observed in this investigation is in consonance with other reports<sup>9,12,13</sup>. The antigametocyte effects of the six doses regimen are compatible with decreased risk of developing drug resistance. The data suggest that coartem ultimately cleared gametocyte from peripheral blood. Similar findings have been documented elsewhere<sup>9,13</sup>. In the present study it was observed that 3 of the children had parasitaemia consisting of trophozote on the 28<sup>th</sup> day, it is not unlikely that this might be due to new infection in an area with stable malaria. Since we did not carry out PCR study we could not determine whether it was new infections or recrudescence. As a first-line treatment for malaria in Nigeria, Coartem appears to be very effective. The adverse events observed in this study have been reported by Novartis the manufacture's of coartem as possible side effects of drugs.

The effective use of coartem in Nigeria is limited by the costs of the drug. In this study the drug was provided to the patients free of charge. However, in pharmacy shops in Nigeria, the tablets for a full course of treatment currently costs about N1000 or \$10. Such prices are beyond the reach of the poor man from the rural communities who are the most afflicted with this debilitating diseases. In view of the high cost of this ACT, it is suggested that the cost of the drug to the patients be subsidized or provided free of charge, (as it is currently being done for antiretroviral drugs ) if the quest to control malaria through the use of ACT is to be achieved

We conclude from this study that our results have confirmed the efficacy of six-dose regimen of coartem in the treatment of uncomplicated malaria in children weighing 5-25 kg. Treatment result in rapid clearance of parasitemia and fever gives high cure rates. This study has supported the decision made by the Federal Ministry of health in Nigeria which recently changed it malaria treatment guidelines and adopted ACT as first line therapy for uncomplicated malaria.

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