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*Original Research Article*

# Artemether-Lumefantrine Combination for Non-Comorbid Falciparum Malaria: A Clinico-Parasitological Efficacy Study

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ABSTRACT

With the emergence of chloroquine resistance, Artemisinin Combination Therapy use was advocated for by the WHO and this has been fully adopted by Nigeria for treating malaria due to *P. falciparum* infection. The present study focused on assessing the clinico-parasitological efficacy of Artemether-Lumefantrine, following the need to monitor the efficacy of ACTs as a tool for early detection of resistance. The WHO 2009 protocols for studying the efficacy of antimalarial agents were adopted. The study enrolled 75 adult patients living within Anambra state, diagnosed with falciparum malaria and met the inclusion criteria of the study. Patients were administered 6 doses of Artemether-Lumefantrine and monitored for 28days for any therapy failure or adverse events. Early treatment failure of 15.95% was recorded. Although ACPR, cure rate and parasite clearance were above 70% (76.8%, 97.10% and 80.4% respectively). The study also showed clearance of asexual stage (gametocytes) by day 3 of treatment. There was a satisfactory efficacy and safety of AL thus supporting the continued use of AL as the drug of choice for non-complicated malaria in the studied population.

***Keywords***: *P. falciparum*, Artemisinin-Based-Combination therapy, Malaria, Artemether-lumefantrine, Antimalarial Drug, Resistant Plasmodium Falciparum Malaria.

## Introduction

Malaria presents a continued threat to community health, with high morbidity and case fatality rate.[1] World Health Organization (WHO), yearly malaria report, shows that a larger proportion of malaria burden for the period under consideration is in Sub-Saharan. [2] Despite remarkable progress recorded in malaria control, the surge in artemisinin resistance in countries like Asia continues to pose a potential threat to use of ACTs. The WHO in 2005 recommended the use of ACTs for malaria treatment following increased report of the ineffectiveness of chloroquine and other non-artemisinin antimalarial.[3] In Nigerian population, artesunate-amodiaquine and artemether-lumefantrine are considered as first line agents, the latter being the most commonly used throughout the country. Although ACTs has been proven to be potent with rapid onset of action, its widespread use in the management of falciparum malaria increases the chances of drug resistance with a consequent effect on malaria control.[4] Studies have shown continued decline in the effectiveness of ACTs in Southeast Asia,[5,6] and most recently, clinical artemisinin resistance reported in Uganda.[7] Reports of partial artemisinin resistance defined as a delay in malaria parasite levels decline (parasitaemia decline) in up to 10%, or more, of study subjects on day 3 of drug administration) has also been documented in parts of Africa.[7-9] In response to these resistant and suspected resistant reports, the World Health Organization has recommended regular monitoring of ACTs to assess their efficacy and provide evidence-based data that are useful for national programs.[3]

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This study is thus aimed at assessing both the clinical and the parasitological effectiveness of artemether-lumefantrine, being the ACT of choice in Nigeria. This is based on the need to constantly monitor antimalarial drug efficacy and resistance as it would provide timely treatment scheme to lessen the resistance threat.

## Materials and Methods

*The site and design of the study*

The study was undertaken in Amansea town in Anambra State of South-east Nigeria; a town where there is observed very high risk of malaria infection coupled with poor knowledge, attitude and practice of people living in the community towards malaria prevention, treatment and control. It is part of a bigger, open-prospective efficacy study of artemisinin-combination-therapies for the management of non-complicated falciparum malaria.

*Study population and sample size*

Convenient probability sampling was adopted for the selection of participants presenting at the study site. With a 4% treatment failure rate of ACT in Nigeria[10]; a confidence level of 95%; a precision around the estimate of 5% and a 20% loss-to-follow-up, the sample size (N) for the study was estimated using the formula: $N= (Z\alpha^2PQ)/d^2$, where,
Zα: 95% confidence interval, P: prevalence of population resistant to ACTs, Q: 1-P, and d: margin of error of confidence interval

A minimum of 70 participants were enrolled in the study. This is in line with WHO recommended sample size of at least 50 for drug efficacy study. The safety of Artemether-Lumefantrine was evaluated by noting all untoward events using the case follow up questionnaire.[11]

*Inclusion / exclusion criteria:* The study recruited men and non-pregnant women above 18 years of age and who presented with fever or a history of it, had non-comorbid falciparum infection, malaria parasite count of 50-5000/200 white blood cells or a parasite density range of 2 x $10^3$ - 2 x $10^5$ parasites in one microliter of blood, available for the follow-up period, with oral and/or written informed consent. Patients who are afebrile but met the parasite load conditions were also enrolled

for the study. Exclusion criteria for the study includes, patients with symptoms of co-morbid malaria, mixed or mono-non-falciparum infection, intolerance to artemether/lumefantrine, severe malnutrition or other underlying chronic diseases. Also, patients presently on medications that can affect the pharmacokinetics of the study drug were also excluded.

*Patient management and follow-up*
Patients, who were eligible and so recruited for the study, were treated with 160mg/960mg of artemether/lumefantrine daily in two-divided doses for 3 days. The first three doses were administered at 0, 8 and 16 hours and followed by every 12 hours for the remaining dose. Morning dose were administered under strict observation by the care giver, while evening doses were taken at home by the participants. To ensure compliance and appropriate administration of the evening dose, each participant was called via a mobile phone to ascertain if, they had taken the evening dose as well to find out if they had vomited or reacted to the drug after administration. Patients who vomited within an hour of medication administration were given a repeat dose of the medication.
Participants were monitored for 28 days to evaluate the clinical and parasitological efficacy of the test drug. Study patients were scheduled for follow-up 0n days 1, 2, 3, 7, 14, 21, and 28. For every visit, including the day of enrollment, clinico-parasitological evaluations were done. Parasitological examinations involved the preparation of thick blood films which were examined by a specialized microscopist. The parasite density was determined by counting the number of asexual parasites seen per 200 leukocytes (or per 500, leukocytes if the asexual parasites were < 100 parasites/200 white blood cells). A sample was recorded negative if after observing in high-power fields, no asexual parasite was seen.

*Classification of response*
Treatment outcomes[11] were designated as;

a. *Early Treatment Failure (ETF)* if there are danger signs or complicated malaria on days 1, 2 or 3 or day 2 parasite density being more than day 0 or on day 3,
b. *Late Clinical Failure (LCF)* if there is parasitaemia any day as from days 4 to 28 and if any of the criteria for ETF were not fulfilled
c. *Late Parasitological Failure (LPF)* if there is fever on any day after day 3 and if any of the criteria for ETF or LCF were not met
d. *Adequate Clinical and Parasitological Response (ACPR)* if there are no parasitaemia on day 28 and if any of the criteria for ETF, LCF or LPF were not fulfilled.

The study also categorized treatment response on the basis of the time for parasite clearance as

a. *Sensitive* (clearance of asexual parasite by day 7 without failure after day 7);
b. *Mild resistance* (positive parasitaemia between day 7 and 28 days of treatment completion following early disappearance of symptoms and parasites
c. *Moderate resistance* (decrease in parasitaemia by >75%at 48 hours but failure to clear parasites within 7 days; and
d. *Severe resistance* (parasite in the peripheral blood does not decline by >75% within 48 hours of therapy initiation).

Cure rate refers to the proportion of participants that have the blood circulating throughout their body cleared of asexual malaria parasites post-treatment and proportion whose circulating blood were cleared of malaria parasites, in their asexual phase, on days 14, 21 and 28 of follow-up.

*Ethical consideration*
All study participant gave an oral or written informed consent, indicating interest to participate in the study. The Ethics Committee of Nnamdi Azikiwe University Teaching Hospital reviewed and approved the study protocol and assigned it the Reference number: NAUTH/CS/66/VOL.15/VER.3/034/2022/023.

## Results and Discussion

Management of uncomplicated *P. falciparum* in Nigeria in the past years with the six dose AL regimen had been effective. However, with the recent reports of diminishing parasite clearance in Southeast Asia,[5,6] and most recently Uganda in East Africa,[7] there is need for regular assessment of the efficacy of artemisinin-based treatments as recommended by WHO. This will help to curb the emergence of resistance. In line with the WHO recommendation, this present study being a part of a larger study aimed at monitoring ACT efficacy is targeted at determining the effectiveness of Artemether-Lumefantrine, the drug of first-choice, in Nigeria, for the management of non-comorbid *falciparum* malaria. A total of 210 participants febrile and afebrile upon examination but suspected for malaria were screened for the study. Seventy-eight participants met the inclusion criteria without fulfilling any of the exclusion criteria and thus were enrolled for the study. Study drug was adequately tolerated by patients. About two third of the screened participants were excluded from the study because of lack of parasitaemia or the parasite density below that stipulated in the inclusion criteria (65.9%) and refusal to consent to or may not be available for the 28 days of follow-up (34.1%). The combined exclusion and loss-to-follow-up rate of about 12% was recorded for patients enrolled in the study. One patient violated the study guidelines and was, therefore, withdrawn while the remaining eight participants were loss to follow-up.

*Participants' baseline characteristics*
Characteristics of study participants at enrollment are presented in Table 1. The average age of the study participants was 44.75 years while age range was 18 - 85 years. The parasite density at enrollment ranged between 1664.00 and 15124.38 parasite per microliter of blood with parasitaemia between 50-380 parasites. On enrollment, 16 (23.19%) had gametocyte upon examination of their blood films.

*Clinical efficacy and Parasitological outcome*
According to WHO, for an antimalarial drug to be selected it must have a parasitological and clinical cure rates of ≥ 90%.[10] The study follow-up rate was high with 88.46% (69 of 78) of participants completing the 28 days. The data in Table 2 puts the efficacy (defined ad day 3 and 7 parasite clearance) of artemether-Lumefantrine at 80%, with cure rate of 95.7%, defined as proportion of participants who had no asexual parasitaemia days 14, 21 and 28. Treatment outcome was also determined via parasitological classification (Table 3) as described in the methods section above. Treatment failure rate defined as presence of parasitaemia and clinical signs after treatment and true resistance to AL, generally was low, 23.19% with ETF accounting for 15.95%, LCF 7.25% and 0% for LPF. Of the 11 patients who had ETF, 7 had parasitaemia on day 3; 2 with day 2 parasitaemia > that of day 0 while the remaining 2 participants had parasitaemia on days 3 and day 2 > day 0. Several factors such as concentration of test drug, pharmacodynamics or partner drugs, and host immunity can have an effect on parasite clearance.[16] None of the participants showed signs of severe malaria and Gender had no effect on efficacy and ETF.

**Table 1:** Baseline characteristics of participants at enrollment

| Variable | N | Minimum | Maximum | Mean |
|---|---|---|---|---|
| Age (years) | 69 | 18.00 | 85.00 | 44.75 |
| Parasitaemia | 69 | 50.00 | 380.00 | 123.87 |
| Parasite density (/μL of blood) | 69 | 1664.00 | 15124.38 | 4703.91 |

Male to female ratio on enrollment was 26/49, with male accounting for 28.99% and 71.01% for females, while 24 of the patients were febrile at enrollment.

**Table 2:** Efficacy and cure rate of AL

| | | Frequency | Percent | Cumulative % |
|---|---|---|---|---|
| Efficacy | NO | 13.00 | 18.84 | 18.84 |
| | YES | 56.00 | 81.16 | 100.00 |
| | TOTAL | 69.00 | 100.00 | |
| Cure rate | NO | 2.00 | 2.90 | 2.90 |
| | YES | 6.70 | 97.10 | 100.00 |
| | TOTAL | 69.00 | 100.00 | |

**Table 3:** Parasitological outcome-treatment classification

| Classification | | Frequency | % | Cumulative % |
|---|---|---|---|---|
| ETF | NO | 58.00 | 87.05 | 87.05 |
| | YES | 11.00 | 15.95 | 100.00 |
| | TOTAL | 69.00 | 100.00 | |
| LCF | NO | 64.00 | 92.75 | 92.80 |
| | YES | 5.00 | 7.25 | 100.00 |
| | TOTAL | 69.00 | 100.00 | |
| ACPR | NO | 16.00 | 23.19 | 23.19 |
| | YES | 53.00 | 76.81 | 100.00 |
| | TOTAL | 69.00 | 100.00 | |

No participant's treatment outcome was classified as LPF

**Table 4:** Parasite clearance time outcome-treatment Classification

| Classification | Frequency | % | Cumulative frequency |
|---|---|---|---|
| Sensitive | 63.00 | 91.30 | 91.30 |
| Mild resistance | 1.00 | 1.45 | 92.75 |
| Moderate resistance | 4.00 | 5.80 | 98.55 |
| Severe resistance | 1.00 | 1.45 | 100.00 |
| Total | 69.00 | 100.00 | |

Although the PCR corrected analysis is yet to be carried out, the PCR uncorrected ACPR and cure rate is 76.8% and 97.10% respectively, this shows that AL so far is still effective against *falciparum* malaria. PCR uncorrected ACPR shows a slight decrease in AL efficacy when compared to other studies,[12-15] although having a high cure rate.

*Treatment response based on parasite clearance time*

Treatment failure rate (defined as presence of parasitaemia and clinical signs after treatment) and true resistance to AL generally was low, 23.19% with ETF accounting for 15.95%, LCF 7.25% and 0% for LPF. Table 4 shows parasite clearance time of the study drug classified as sensitive or resistance (mild, moderate and severe). Logistic regression using the sensitive / resistant outcome variable did not show that any independent variable was predictive of it.

*Gametocytemia and safety*

Artemisinin antimalarial drugs have gametocidal effect. and this was evident in the ability of the study drug (AL) to clear gametocytes in 87.5% of participants that had gametocytes in their blood smear within 48 hours of treatment. From the study, 16 (23.19%) participants had gametocytemia on the day of enrollment. In addition, 2 participants who at enrollment were gametocyte negative, had gametocytes in their blood smears by days 1 and 2 although these were cleared by day 3 of follow-up thus confirming that AL reduces malaria transmission by eliminating gametocytes form the bloodstream.[12] Although the drug was well tolerated, few events such as abdominal discomfort, headache, generalized body weakness and cough were recorded (Table 5). This is not far from complaints in many other studies [22,23,24]. It is important to note that all reported untoward events were cleared by day 14 and 28 of follow-up.

**Table 5:** Adverse events recorded and frequency

| Adverse Event | Number (Total N = 69) | Frequency (%) |
|---|---|---|
| Abdominal discomfort | 5 | 7.25 |
| General body weakness | 15 | 21.74 |
| Cough | 3 | 4.35 |
| Headache | 10 | 14.49 |

## Conclusion

AL, the first-line antimalarial agent and the most commonly used ACT in Nigeria, judging with PCR uncorrected parasitological outcome remains effective against uncomplicated falciparum malaria. Although the result of the study is satisfactory there is need for constant review of the efficacy of ACTs to avoid future occurrence of resistance.

*Limitations to the study*

Several limitations may have affected the result of the study. With AL being a twice daily dosed medication, only the morning dose was administered to the patient as a directly observed therapy. Thus, there is a possibility that doses taken at home participants were wrongly taken, despite laid down efforts to curtail the occurrence of error(s) in medication administration. This can thus give a false parasite clearance result. In addition, calculation of parasite clearance rate as a continuous variable was not done in the study as blood smears were collected once a day from each participant.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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