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Effectiveness of a 6-dose regimen of Artemether-Lumefantrine for unsupervised treatment of uncomplicated childhood malaria in Calabar, Nigeria

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Abstract *Background:* The six dose regimen of Artemether-Lumefantrine (AL), has high efficacy in clinical trials and is the first-line drug for treating uncomplicated malaria in Nigeria. The complex dosage schedule could militate against its effectiveness.

Objective: To assess the effectiveness of AL prescribed under routine outpatient conditions in the treatment of uncomplicated malaria.

Methods: An open label, non-comparative trial to assess the effectiveness of AL in children 6 to 59 months with uncomplicated *P. falciparum* and parasite density between 1,000 and 250,000/μL. Enrolled children received 6-dose course of AL (20/120mg tablets). The first dose was administered in the health facility and caregivers were instructed on how to administer the remaining five doses at home.

Results: Of the 1035 screened, 215 eligible children were enrolled and 193 completed the study. Twenty-two (22) patients withdrew from the study (18 were lost to follow-up, 3 violated protocol and 1 withdrew consent). Adequate clinical and parasitological response (ACPR) was observed in 90.7%; late clinical failure in 7 (3.6%) and late parasitological failure in 11 (5.7%).

Conclusion: This study showed high efficacy of AL in treating uncomplicated *P. falciparum* malaria in under-fives in Nigeria. Adherence by caregivers to the treatment regimen was quite good and so, should continue to be used in the home setting.

Key words: Artemether-lumefantrine, effectiveness, adherence, uncomplicated malaria.

Introduction

The global burden of malaria is well described[1,2] with 90% of global episodes of clinical malaria and mortality occurring in sub-Sahara Africa. The malaria control situation became worse following the emergence of anti-malarial drug resistance and more recently by reports of resistance to artemisinin product from South East Asia. Early diagnosis and prompt treatment during malaria episodes are the key components of the global strategy for malaria control.[3]

In Nigeria, about 50% of the population suffers at least one episode of malaria every year and malaria accounts for over 45 per cent of all out-patient visits. The disease accounts for 25 % infant and 30 % childhood mortality in the country.[4] Results of randomized control trials conducted in different parts of the world including Nige-

ria,[5-8] showed that artemisinin-based combination therapy (ACT) are efficacious and safe . In line with the recommendation of world health organization (WHO), the Nigerian Federal Ministry of Health changed the malaria treatment policy in 2005,[9] to artemisinin-based combination therapy. Artemether-Lumefantrine (AL) was the first ACT approved for use as first-line in the treatment of uncomplicated falciparum malaria.

Artemeter-Lumefantrine is co-formulated hence it is less likely to be misused as monotherapy unlike the co-packaged ACTs.[8] However, its use as the drug of choice in Nigeria can be limited by partial adherence with the recommended 6 dose regimen and the interval of 8 hours between the first and the second dose, 24 hours between the first and the third dose, and 12 hourly intervals between the remaining doses. The main concern of AL use is its timed dosage multi-dose schedule, raising the

question of whether it will remain effective when used on an unsupervised basis in the community.

The effectiveness of an intervention is the ability to achieve the desired aim when used in an unsupervised setting and it depends on compliance with the recommended treatment regimen.[10] Poor adherence is likely to decrease treatment effectiveness and expose the parasite to sub-therapeutic drug levels which may favour development of resistance to the drug.[10] Most clinical trials assess the efficacy and safety of drugs under supervised settings. The cure rate of a drug reported from clinical trial may not be the same as that observed under routine out patient conditions. Since there could be differences between the efficacy of a drug during clinical trial and its effectiveness on routine use, it is important to assess the effectiveness of AL, the first line anti-malarial drug presently in use in Nigeria.

The aim of this study was to assess the effectiveness of AL under routine outpatient conditions in the treatment of uncomplicated malaria in under-five children.

Methods and Patients

Design: This was an open label non-randomized trial to determine the effectiveness of AL for treating uncomplicated *P. falciparum* malaria in children aged 6 to 59 months.

Study Population: The study was conducted over 13 month period from June 2006 to June 2007. Children with features suggestive of uncomplicated malaria, attending the outpatient clinic at a Health Centre in Ikot Ansa, Calabar Municipality, South Eastern Nigeria were screened for inclusion.

Inclusion criteria: Participants were eligible for inclusion if they were between 6 and 59 months old, had fever (axillary temperature $\geq 37.5°C$) or history of fever in the past 24 hours with *P. falciparum* asexual parasites between 1000 and 250,000/μL. In addition, participants were resident in the study area to be eligible for enrolment. Finally, a signed informed consent was mandatory for inclusion in the study.

Exclusion criteria: Participants were excluded if there was known allergy to any of the study drug components, vomiting study drug two or more consecutive times; packed cell volume <15%, other manifestation of complicated malaria and any other danger sign of childhood illness such as severe malnutrition, not able to sit, stand or drink, recent history of convulsion, lethargic or unconsciousness.

The Ethical Review Committee of the University of Calabar Teaching Hospital approved the protocol for the study. A written informed consent was obtained from each parent/legal guardian of eligible participants prior to enrolment.

The intervention: was a co-formulated preparation of Artemether (20mg) and Lumefantrine (120mg) in each tablet presented in a blister form. The dosing schedule requires intervals of 0, 8, 24, 36, 48 and 60 hours, the interval between the first two doses are crucial to the eventual outcome of treatment. The blister pack contains pictures and instructions on how the drug should be administered. The dosage is based on the child's weight. The detail of the dosage of AL is shown in Table 1.

Table 1: Dosage schedule of artemether-lumefantrine

	Number of tablets/recommended time of administration					
	Day 0		Day 1		Day 2	
Weight (kg)	0 Hours	8 Hours	24 Hours	36 Hours	48 Hours	60 Hours
5 – 15	1	1	1	1	1	1
15 – 25	2	2	2	2	2	2
25 – 35	3	3	3	3	3	3
> 35	4	4	4	4	4	4

Drug administration: Once a participant was enrolled, the first dose of AL was administered to the patient in the health facility under the supervision of the study nurse. The child was then observed for 30 minutes in the health facility. If the child vomited within this period, another dose was given and the participant observed for another 30 minutes. A child that vomited two or more times within one hour of commencement of drug administration was classified as repeated vomiting and withdrawn from the study. Such participant was referred to the next level of care for treatment with parenteral antimalarial. Those that tolerated the first dose were sent home with further instructions on how to administer the remaining doses. Emphasis was laid on the importance of giving the second dose eight hours after the first dose, then two doses per day in the morning and evening for the following two days. Parents/guardians were also informed that the drug is best given with fatty foods or shortly after breastfeeding for children that were still breastfeeding.

Clinical Assessments: Clinical assessments include history of illness, measurement of axillary temperature and weight of participants on day 0 and during follow up visits on days 7, 14 and 28. Patients were not reviewed on Days 1, 2 and 3 so as not to induce adherence to the drug. Guardians/parents were advised to bring back the participant to the health facility if the health condition deteriorated. Participants that were not brought on schedule for follow-up visits were visited at home the same day and where that was not possible within two days after the scheduled visit date. Rescue medication for this study was quinine in line with the Nigerian national malaria treatment guidelines.

Laboratory investigation: Thick and thin blood film specimens were used to screen for presence of malaria parasites. During each visit, blood smears were collected, prepared and stained in 3% Giemsa solution for 30 minutes. Smears were read to 100 fields with quanti

quantification of *P. falciparum* asexual parasites on the thick smear (per uL) and gametocytes (number per 1000 white cell count). Parasites were enumerated using thick film as described by Shute.[11] Parasite density was calculated, assuming a normal leucocyte level of 8,000/µl. The thin film was used to speciate the parasites. Packed cell volume was determined on days 0, 14 and 28 with sample collected in a heparinized capillary tube and centrifuged for 5 minutes at 10,000 G.

Withdrawals: Participants who were lost to follow up or those that withdrew consent were classified as withdrawals from the study. Also, participants who took other anti-malarial drugs during this period were withdrawn from the study. All withdrawals were followed up for safety except those that were lost to follow up.

Outcome measures: Therapeutic efficacy was assessed on follow up visits using WHO guidelines for assessing therapeutic efficacy in intense transmission areas.[12] Primary outcome measures were

- Day 28 cure rate: adequate clinical and parasitological cure rate (ACPR)
- Treatment failures which could be
    1. Early treatment failure (ETF)
    2. Late clinical failure (LCF)
    3. Late parasitological failure (LPF)
- Adherence to recommended treatment schedule.

Secondary outcome measure was safety and tolerability. Safety and tolerability was evaluated by the risk of occurrence of an adverse event (AE), classified as mild, moderate, severe or serious. A serious adverse event was defined as any AE resulting in death or in persistent or significant disability/incapacity, life-threatening, requiring hospitalization or significant medical intervention to prevent serious outcome. Presence of adverse events was assessed based on the assessment given by the mother or guardian.

Table 2: Definition of therapeutic efficacy measures

Therapeutic outcome measure	Definition of term
Adequate clinical and parasitological response (ACPR)	Absence of parasitaemia on Day 28 irrespective of axillary temperature without previously meeting any of the criteria of Early Treatment Failure, Late Clinical Failure and Late Parasitological Failure
Early treatment failure (ETF)	Development of danger signs or severe malaria on Days 1, 2 or 3 in the presence of parasitaemia, or parasitaemia on Day 2 higher than Day 0 count irrespective of axillary temperature, or parasitaemia on Day 3 with axillary temperature $\geq 37.5^\circ$C, or parasitaemia on Day 3 > 25% of Day 0 count irrespective of axillary temperature.
Late clinical failure (LCF)	Development of danger signs or severe malaria and / or axillary temperature $\geq 37.5^\circ$C on any day from Day 4 to Day 28 in the presence of parasitaemia without previously meeting any of the criteria for Early Treatment Failure
Late parasitological failure (LPF)	The presence of parasitaemia from Day 4 to Day 28 and axillary temperature $< 37.5^\circ$C without previously meeting any of the criteria for Early Treatment Failure or Late Clinical Failure

Analysis: Endpoints were assessed based on intention to treat analysis. Data generated were recorded in a log book and individual patient's case record files and later double - entered into EPI-Info version 3.5.1 software. Data was analyzed on the same software.
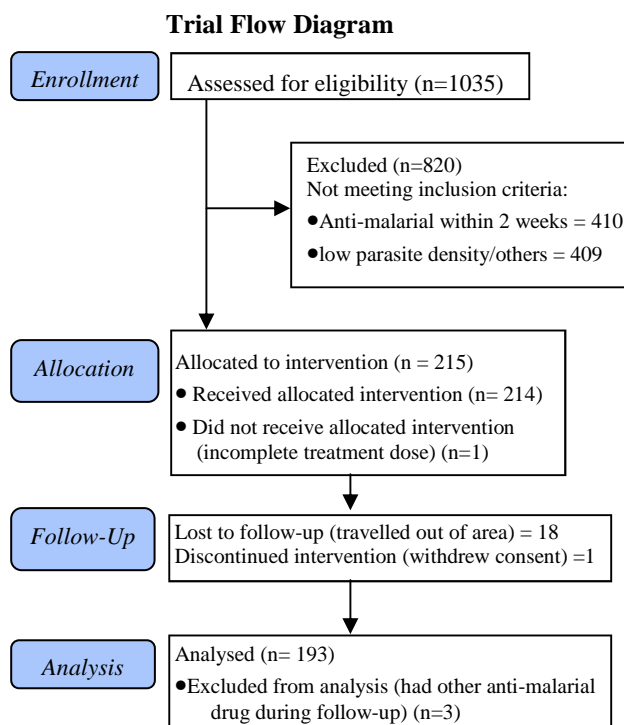
Results
General characteristics

One thousand and thirty five children were screened for eligibility, of whom 215 (20.7%) were enrolled. Baseline characteristics are shown in Table 3.

Table 3: Baseline Characteristics of patients

Characteristics	Mean (SD) N=215
Age in years(mean ± SD)	2.50±1.70
Males (%)	123 (57.2)
Females (%)	92 (42.8)
Height in cm (Mean ± SD)	91.7 (13.2)
Weight in Kg (Mean ± SD)	12.7 (3.2)
Axillary Temperature (Mean ± SD)ºC	37.6 (1.14)
Packed Cell Volume Day 0	28.0 (4.9)
Mean parasite density in µL (range)	35,312 (1,009-228,889)

Enrolment and follow-up: Figure 1 shows the patient flow from screening, treatment, follow-up to completion. Four hundred and ten (50%) of the 820 excluded patients were due to use of anti-malarial drug within two weeks of screening. There were 22 withdrawals in this study as follows; 18 were lost to follow up (traveled out of study area), 3 violated protocol (took anti-malarials outside study drug) and one withdrew consent. A total of 193 (89%) participants completed the study and had adequate data for analysis of the study outcomes.

Fig 1: Patient flow diagram for the study

Trial Flow Diagram

Treatment outcome: Table 4 shows the results of the 28-day therapeutic efficacy of AL. The number of evaluable participants with adequate clinical and parasitological response (ACPR) was 175 (90.7%). Late clinical failure (LCF) was observed in 5 participants. There were 11 late parasitological failures; 2 on Day 14, 2 on Day 25 and 7 on Day 28.

Assessment of patient adherence to treatment: Out of the 215 enrolled participants empty blisters were returned for 210 suggesting that most of the participants (97.6%) adhered to the recommended dosage schedule. Caregivers were interviewed to ascertain how and when drugs were given to child. Four caregivers reported that they had misplaced the empty blisters hence did not return them. One parent did not return the blister because the child improved so she reserved the last 2 doses (5th and 6th dose) for next episode of malaria attack.

Table 4: Effectiveness of unsupervised artemether-lumefantrine

Treatment Outcome	Number of Participants	Percent
Day-28 cure (Adequate clinical and parasitological response - ACPR)*	175	90.7%
Late clinical failure (LCF)	7	3.6%
Late parasitological failure (LPF)	11	5.7%

*PCR confirmation not used.

Adverse Events: There were 48 mild adverse events during the study; the most common were cough (7.0%) and vomiting study drug at least once (7.0%). Others were catarrh (2.3%), headache (2.3%), abdominal pain (1.3%) and rashes (1%). No serious adverse event was observed in any of the study participants.

Change in Haemoglobin: The packed cell volume increased in all participants by the end of the follow up period. The mean haematocrit value increased from 28% at baseline (Day 0) to 33% on Day 28.

Discussion

This study has shown that Artemeter-Lumefantrine is effective with a cure rate of 90.7% when administered in unsupervised setting. Reports from a multicentre study on the effectiveness of home management of malaria in which Nigeria was one of the study sites gave a PCR-corrected cure rate of 90.9%,[13] The cure rate of this study though uncorrected for reinfection is similar to the PCR –corrected cure rate of the multi-centre study. In a randomized trial of effectiveness of AL in Ghana, Kobbe et al[14] reported parasitological cure rate of 88.3% for AL, which is similar to the findings of this study. However, in a report from Uganda, higher cure rate of 98.0% was observed when AL was given in unsupervised setting.[15] It therefore appears that the drug has satisfactory efficacy even when used in an unsupervised setting.[13-15.]

In this study, 97.6% of the caregivers adhered to the dosage recommendation. Since the effectiveness of any drug combination therapy is dependent on adherence with the treatment regimen,[10] it is assumed that the efficacy reported in this study is as a result of acceptable compliance with the treatment regimen. It therefore appears that majority of caregivers in this locality adhere to the 6 doses of AL although it is difficult to say whether they observe the 8 hours interval between the first and the second doses. In the study by Ajayi et al[13], average adherence for the 3 countries that participated in the study was 94%. However, Depoortere et al[16] in southern Sudan reported that 18.3% of the participants were 'not adherent' to the dosage schedule. However, in their study emphasis was placed on giving the drug with milk or fatty foods and some of the caregivers did not administer the drug because of lack of milk or fatty food to precede the drug. In this study, emphasis was not placed on giving drug with milk or fatty food because an earlier efficacy test in the same centre did not lay emphasis on the dietary component and the cure rate obtained in this study is similar to that of the previous study.[8]

Several factors may have contributed to the high adherence observed in this study. Firstly, the fact that caregivers were required to return the empty blisters on day 7 may have played an indirect role in enhancing adherence. Secondly, the packaging of the drug might also have promoted adherence. The sealed-blister design contains visual depictions of time intervals and number of tablets to be taken by the patients.[16,17] However, the packaging is universal and available to non-study parents, hence it is considered an important aid by the manufacturers to promote adherence. Also the added verbal explanation by the team members to caregivers have been shown to improve adherence.[17]

AL was well-tolerated with no serious adverse events and only few mild adverse events in this study further confirms the safety of the combination. This has been documented by other studies.[8,18]

The limitations of this study include the non-randomized design, and the absence of a comparator. Also, the small sample size of the study makes generalization difficult. On the other hand, polymerase chain reaction was not used to differentiate actual parasitological failures (recrudescence) from new infections hence day-28 cure rate could have been higher than reported. Finally, the adherence observed in this semi-urban setting cannot be generalized to the typical rural communities.

Conclusion

Despite the complexity of the 6 dose AL regimen, the high day 28 parasitological cure in this and other studies shows that the drug is effective when used in unsupervised outpatient settings in Nigeria, even among caregivers with low level of education. It is important for

healthcare providers to give sufficient explanation on the correct method of administering drugs to caregivers. We recommend multicentre, randomized trials with larger sample sizes across the country to confirm the effectiveness of artemether-lumefantrine as this is essential to help ensure long-term treatment efficacy for the population.

Authors contributions
FO: Contributed in protocol writing, coordi nated da collection and writing of manuscript.
MM: Conceptualized and directed the study, supervised the analysis, preparation of manuscript.
CO: Data collection and wrote initial draft of manuscript
AO: Data analysis and input to manuscript writing
EU: Data collection and contributed to manuscript writing
KE: Contributed in manuscript development

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