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Artemisinin-naphthoquine versus Artemether-lumefantrine for treating uncomplicated *plasmodium falciparum* malaria in children: A randomized controlled trial of efficacy and safety

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Abstract *Introduction:* Artemether-lumefantrine (AL), the most frequently prescribed ACTs for uncomplicated *P. falciparum* malaria, requires multiple doses which may militate against adherence. It is necessary to evaluate the efficacy and safety of single dose ACT like Artemisinin-naphthoquine (ANQ) to enhance adherence.
Methods: This was an open label randomized controlled clinical trial. Eligible children were assigned to receive either a single dose of ANQ or six doses of AL following parental consent. A total of 108 children aged 5 – 14 years with uncomplicated falciparum malaria were enrolled and assigned as follows: 58 (ANQ) and 50 (AL). Participants were observed for 28 days and clinical and parasitological assessments carried out. Outcomes were assessed based on World Health Organization protocol.
Results: A total of 97 patients completed the study. Overall 28-day cure rate was 87.0% (47/54) and 81.4% (35/43) for ANQ and AL respectively. One patient (2.2%) in the AL group had Early Treatment Failure while seven (16.3%) had Late Parasitological Failure (LPF). LPF was also reported in seven (13.0%) patients in the ANQ group. There was no Late Clinical Failure. A mild self-limiting papular rash was noted in one child in ANQ group. There was no serious adverse event.
Conclusions: The therapeutic efficacies of ANQ and AL were comparable. A more robust, adequately powered, dose optimization study with PCR-confirmed parasitological outcome measures is needed.

Key words: Malaria, artemether-lumefantrine, artemisinin-naphthoquine, adherence, single and multiple dose therapy

Introduction

Malaria is still a major cause of childhood morbidity and mortality in sub-Saharan Africa with most cases being from *Plasmodium falciparum (P. falciparum)* infections[1]. The artemisinin combination therapies (ACTs) are currently first-line treatment for uncomplicated *P. falciparum* malaria with Artesunate-amodiaquine, Artemether-lumefantrine (AL), Artesunate-mefloquine,Artesunate+Sulfadoxine-Pyrimethamine and Dihydroartemisinin-piperaquine endorsed for deployment by the World Health Organization (WHO).[2]
Full course therapy with these ACTs is for three days. AL is the most prescribed ACT globally and is administered at 0, 8, 24, 36, 48 and 60 hours.[3] The relative short half-life of the Artemisinin compound and the slow onset of action of Lumefantrine makes this complex dose schedule necessary for maximal parasite killing[2]. Complex schedules of ACTs have been reported to contribute to poor treatment adherence, reduction in therapeutic efficacy and emergence of drug resistance[3,4]. Hailemariam et al[5] in Ethiopia reported 74.5% adherence to AL while Mace et al[6] reported 65% adherence to AL in Malawi with the under-fives being significantly less likely to adhere than those five years and above.

To improve treatment adherence especially in children, there is need to evaluate new ACTs that are much easier to administer. Artemisinin-naphthoquine (ANQ) is a fixed dose combination that can either be administered as a single dose therapy or in two divided doses taken within a 12 hours period for uncomplicated *P. falciparum* malaria. The drug has been reported to be efficacious and safe in adult population but studies in children

are limited.[7,8]
This study aimed to evaluate the efficacy and safety of a single dose therapy of ANQ versus the six dose, three day therapy of AL in children aged 5 – 14 years with uncomplicated *P. falciparum* malaria in Calabar, Cross River State of Nigeria.

Outcome measures

The primary outcome measures were Early Treatment Failure (ETF), Late Clinical Failure (LCF), Late Parasitological Failure (LPF) and Adequate Clinical and parasitological Response (ACPR) as defined in Table 1. This is based on WHO protocol for assessment of antimalarial therapeutic efficacy[9]. The secondary outcome measured was occurrence of adverse events.

Subjects and Methods

This was a randomized controlled clinical trial conducted between June 2006 and July 2007 in Ikot-Ansa Primary Health Centre, in Calabar Municipality of Cross River State, Nigeria. Malaria transmission in the area is intense and perennial. *Anopheles gambiense* and *Anopheles funestus* are the predominant vectors while *P. falciparum* is the predominant parasite in the study area.[10]

Sample size determination

Sample size was based on the demonstration of 20% difference in the 28 day cure rate between ANQ and AL, at 95% confidence interval, 90% study power, a one-tailed statistical analysis and 8% attrition rate.[11]From the above, a minimum of 50 participants were needed in each arm of the study.

Ethical considerations

Ethical clearance for this study was obtained from the Ethics Committee of the University of Calabar Teaching Hospital. Informed consent was obtained from the parent of each eligible child prior to inclusion in the study.

Patient assessment

Basic demographic and clinical information was obtained from children suspected to have uncomplicated malaria. This was followed by a general physical examination, anthropometric measurements and systemic examination. Thin and thick blood films for malaria parasite speciation and quantification as well as blood for Packed Cell Volume (PCV) estimation were performed using standard technique.[12]

Eligibility criteria

Children aged 5 - 14 years with history of fever in the past 24 hours or temperature $\geq 37.5^{o}$C on presentation, *P. falciparum* mono-infection, parasite density of 1,000 – 200,000/µl of blood were considered eligible for inclusion while those with history of ingestion of antimalarial two weeks prior to the study, haematocrit< 15%, features of severe acute illnesses or chronic illnesses were excluded from the study.

Randomization of participants

Patients were randomized using a block randomization technique. They were then assigned into one of two treatment arms using an unpredictable allocation sequence that was generated by balloting.The sequence was concealed in brown sequentially labeled opaque envelope until intervention was assigned.[13] Patients' enrollment and implementation of the randomization was performed by the study nurse.

Investigational products

The investigational products were Artemether-lumefantrine (AL) (Coartem®), 20mg Artemether + 120mg lumefantrine (Novartis Pharma, Switzerland) and Artemisinin-naphthoquine (ARCO®), 125mg Artemisinin + 50mg Naphthoquine (Kunming Pharmaceuticals Corp (KPC), China). The drugs were obtained from the manufacturers through one of their reputable wholesale/ retail outlets in Calabar. The batch number, manufacture and expiry dates were verified. The drugs were stored in a cabinet at room temperature of 20^{o}C – 30^{o}C.

Treatment and follow-up

The treatment was administered by the study nurse based on the body weight of the children. Those assigned to receive AL had six doses of the drug over three days while those assigned to ANQ had a single dose therapy[2,7]. The children were observed for at least 30 minutes by the study nurse after drug administration. Those that vomited within this period were retreated. Those assigned to AL whose parents could not come to the health facility for subsequent therapies were visited and treated at home by a member of the study team. Children with temperatures above 38^{o}C were lightly dressed, tepid sponged and given Paracetamol at a dose of 15 mg/kg.
The children were followed up for 28 days. Parents were asked to bring the children to the facility on days 1, 2, 3, 7, 14 and 28. The wellbeing of the children, assessment of side effects of the drugs and blood smears for malaria parasite were performed on those days while haematocrit estimation was done on days 0, 3, 14 and 28.

Statistical analysis

Data generated were recorded in the patients' case report form, validated and entered into STATA version 10 for analysis. The results were presented as text, flow chart and tables. Clinical and parasitological outcome measures were assessed based on WHO protocol (Table 1). 'Per protocol' analysis was used to assess patients with evaluable outcomes. Student's t- test was used to determine the difference in mean between two continuous

variables while chi-square (χ^2) test was used to test for association between categorical variables.

Fig 1: Flow chart of the clinical trial

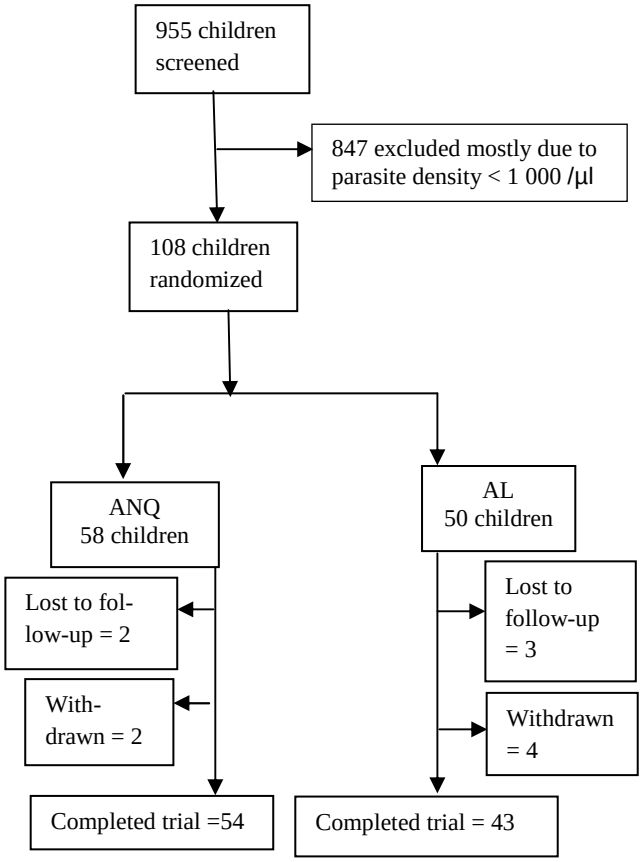

Table 1: Antimalarial therapeutic efficacy outcome measures

Terms	Definition
Early Treatment Failure (ETF)	This is the development of danger signs of severe illness 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 ≥ 37.5°C, or parasitaemia on Day 3 > 25% of Day 0 count irrespective of axillary temperature.
Late Clinical Failure (LCF)	This is defined as development of danger signs or severe malaria and /or axillary temperature ≥ 37.5°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)	This is defined as the presence of parasitaemia from Day 4 to Day 28 and axillary temperature < 37.5°C without previously meeting any of the criteria for Early Treatment Failure or Late Clinical Failure.
Adequate Clinical and Parasitological Response (ACPR)	This is defined as 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.

Results

Nine hundred and fifty five children were screened for eligibility and 847 excluded. Of the 108 children recruited, 58 were randomized to receive Artemisinin-naphthoquine (ANQ) while 50 were to receive Artemether-lumefantrine (AL). In ANQ group, 54 (93.1%) children completed the study as against 43 (86.0%) in AL group. The study profile is shown in Figure 1. The baseline characteristics of participants in both arms of the study were comparable (Table 2).

Table 2: Baseline characteristics of participants

Characteristics	ANQ mean (SE)	AL mean (SE)	p-value
Age (years)	7.48 (0.36)	7.54 (0.32)	0.9068[a]
Weight (Kg)	25.45 (1.30)	23.648 (0.366 (0.93)	0.2788[a]
Height (cm)	124.8 (2.61)	123.7 (1.75)	0.7177[a]
Packed cell volume Day 0	31.67 (0.53)	33.15 (0.54)	0.0552[a]
Axillary Temperature (°C) on Day 0	37.41 (0.16)	37.59 (0.17)	0.4431[a]
Geometric mean (95% CI) parasite density in µL (range) at enrolment	8968 [6339 - 12691]	11295 [7838 –16276]	0.4541[b]

[a]t-test for two independent groups
[b]Mann-Whitney test

Comparison of the therapeutic efficacy of ANQ and AL

Of the 54 children that completed treatment with ANQ, 47 (87.0%) had Adequate Clinical and Parasitological Response (ACPR) while 7 (13.0%) had Late Parasitological Failure (LPF). There was no report of Late Clinical Failure (LCF). In the AL group 35 (81.4%) had ACPR, 7 (16.3%) had LPF while 1 (2.2%) had Early Treatment Failure (ETF) as shown in Table 3.

Table 3: Therapeutic efficacy of ANQ and AL based on "per protocol" analysis

	ANQ (54 patients)		AL (43 patients)	
	No	%	No	%
Early Treatment Failure	0	0	1	2.2
Late Clinical Failure	0	0	0	0
Late Parasitological Failure	7	13.0	7	16.3
Adequate Clinical and Parasitological Response	47	87.0	35	81.4

Adverse events

A generalized maculopapular rash which cleared spontaneously within three days in a child treated with ANQ. This was the only clinical adverse event reported in the study.

Discussion

The study showed that the therapeutic effi.cacy of a sin-

gle dose therapy of Artemisinin-naphthoquine (ANQ) was comparable to the six-dose, three-day therapy of Artemether-lumefantrine (AL) for treatment of uncomplicated *P. falciparum* malaria in the children. Since these parasitological findings were not confirmed by polymerase chain reaction (PCR) it is possible that the 28-day "per protocol" cure rates (ACPR) of 87.0% and 81.4% recorded for ANQ and AL respectively were influenced by new infections which could not be clinically distinguished from recrudescent cases. New infections are known to occur within 28 days of treatment even with an efficacious antimalarial regimen. This is more common in areas of high malaria transmission[9]. Given that the location of the current study is characterized by high and perennial malaria transmission; it is likely that a proportion of the late parasitological failures recorded in this study were due to new infections instead of recrudescence. In a non-comparative evaluation of AL among infants and children from three African countries including Nigeria, Falade *et al*[14] reported a day 28 PCR-uncorrected cure rate of 86.5% which was adjusted to 93.9% when PCR correction for re-infection was performed.

It is noteworthy that the therapeutic efficacy of AL recorded in this study is lower than what had been earlier reported in the study area[15]. The fact that it has not been possible in this study to ascertain whether cure rates observed for either of the compounds used in the present study were due to treatment failures or new infections makes the notion on non-inferiority of these ACT regimens inconclusive. The study however adds to the body of literature on the effectiveness of single-dose ANQ and its potential role as alternative treatments in cases of treatment failures with currently recommended Artemisinin combination treatment regimens.

In the light of recent reports in decline of efficacy of Artemisinin compounds in Southeast Asia[16] it is justifiable to express the concern that the observed treatment failures in the present Nigerian study may be indicative of a decline in parasite susceptibility to Artemisinin compounds in the study area. It is worthy of note that this report of apparent decline in artemisinin efficacy is incidentally made in the same part of Nigeria where Chloroquine-resistant *P. falciparum* malaria was first documented in the country.[17]

The difference in the ACPR between ANQ and AL may likely be due to the nature of the partner drugs since both have an artemisinin compound as base. The six dose regimen of AL given over three days has been shown in clinical trials and a Cochrane systematic review to be more efficacious than the four dose regimen.[18] Based on the fact that increasing frequency of administration of the artemisinins is associated with an increase in cure rate, the six dose regimen of AL was expected to achieve a higher cure rate than the single dose of ANQ. The reverse was rather the case in this study. This seeming paradoxical result may be attributed to the pharmacokinetic and pharmacodynamic differences between Naphthoquine and Lumefantrine.

Naphthoquine (NQ) is a compound that is rapidly and completely absorbed after oral administration with a relative bioavailability of 96.4% that is independent of the nature of meal the patient takes.[8] The high bioavailability of the drug makes for a thorough killing of various schizonts of plasmodia unlike lumefantrine which requires fatty meals to enhance its digestion and absorption.[19] Since children with uncomplicated malaria are usually anorexic, there is a likelihood that poor absorption with sub-optimum plasma concentration of the drug might have contributed to the relatively low efficacy of AL.[19]

There was no record of an Early Treatment Failure (ETF) in children treated with ANQ but this event was reported in a child who received AL. The child had fever on day three and persistent parasitaemia on day 3 of the study. The ACTs are known to rapidly reduce parasite biomass and resolve clinical symptoms within 48 hours of administration[4]. ETF connotes a clinical or parasitological progression in disease severity within the first three days of initiation of the antimalarial therapy.[9]
This is the first report of an ETF with AL in the study area. The 2009 drug therapeutic efficacy trial conducted among under-fives with uncomplicated malaria in nine malaria sentinel sites in the country which compared AL with Artesunate-amodiaquine (AA) reported a PCR-uncorrected cure rate of 95.7% – 99. 5% with AA and 96.3% - 99.2% with AL. ETF was reported in one child in the survey that was treated with AA.[20] The finding of ETF with AL in this study may therefore be a warning signal concerning the possible emergence of high level of parasite resistance to the drug.

The only clinical adverse event recorded in this study was generalized papular rash which cleared spontaneously within three days in a child treated with ANQ. Nausea, vomiting and diarrhea have been reported for both drugs, cough and anaemia were reported with the use of AL[14] while dizziness and pruritus were noted with the use of ANQ.[10]

ANQ may have a programmatic advantage over AL being a single dose therapy. The ease of its administration enhances adherence to treatment and so will prevent the likely occurrence of drug resistance. Busy and less educated caregivers of sick children will find a single dose therapy of ANQ convenient. This therefore makes ANQ a potential drug for deployment as first-line therapy for uncomplicated *P. falciparum* malaria in endemic regions. The inability to perform a PCR-correction to ascertain possibility of reinfection is acknowledged as a limitation that could have an influence on the interpretation and applicability of the results of this study.

Conclusion

The efficacy of a single dose therapy of ANQ is quite comparable to the 6 dose therapy of AL in the treatment of uncomplicated falciparum malaria in Nigerian chil-

dren. An adequately powered, non-inferiority randomized head-to-head trial of the two drug regimen with PCR-correction will help clarify unresolved issues on the efficacy and public health value ANQ and other ACTs especially AL.

Authors' contributions

MM: Conception/design of study.
FO and EU: Clinical assessment of patients.
CO and OO: Performed the laboratory assessment of the patients.
AO and EU: Analyzed the data.
EU and MM: Preparation of manuscript

Conflict of Interest: None
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