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CLINICAL ARTICLE

A randomized trial of artesunate-amodiaquine versus artemether-lumefantrine for the treatment of acute uncomplicated malaria in pregnancy

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ABSTRACT

Objective: To compare the artesunate-amodiaquine and artemether-lumefantrine combinations in the treatment of acute uncomplicated falciparum malaria during pregnancy. *Methods:* Between January and July, 2013, a double-blind randomized trial was undertaken of symptomatic pregnant women (second/third trimester) with malaria parasitemia who attended a center in Ile-Ife, Nigeria. Participants were assigned to receive artesunate-amodiaquine or artemether-lumefantrine (twice daily on days 1–3) according to a computer-generated randomization sequence. Participants and investigators were masked to group allocation. Clinical evaluations and malaria parasite counts were performed at baseline and on days 2, 3, 7, and 28. Mean interval to symptomatic relief, day-3 parasite clearance, day-28 cure rate, and adverse effects were assessed. *Results:* Of 75 women assigned to each group, 65 in the artesunate-amodiaquine group and 71 in the artemether-lumefantrine group completed the study. No significant differences between the artesunate-amodiaquine and artemether-lumefantrine groups were recorded for mean interval to symptomatic relief (2.2 ± 1.0 days vs 2.0 ± 0.8 days; $P = 0.090$), day-3 parasite clearance (58/65 [89.2%] vs 66/71 [93.0%]; $P = 0.444$), and day-28 cure rate (64/65 [98.5%] vs 67/71 [94.4%]; $P = 0.138$). Adverse effects (body weakness and pruritus) were more common among women assigned to artesunate-amodiaquine (30/75 [40.0%]) than among those assigned to artemether-lumefantrine (2/75 [2.7%]; $P < 0.001$). *Conclusion:* Efficacies of the regimens are similar among pregnant women. However, adverse effects are more common with artesunate-amodiaquine.
Pan-African Clinical Trial Registry: PACTR201310000484185.

1. Introduction

In 2013, there were approximately 198 million cases of malaria, resulting in more than 584 000 deaths [1]. About 90% of these deaths occurred in Africa, mostly in young children and pregnant women [1]. Pregnant women represent the largest subset of vulnerable adults; malaria and pregnancy aggravate each other, with the altered physiology of pregnancy and the pathologic impact of malaria creating a synergy of adversity [2]. Therefore, malaria in pregnancy is an important public health challenge that imposes substantial morbidity and mortality globally, particularly in Sub-Saharan Africa.

Artemisinin-based combination therapy (ACT) is the current gold standard for treatment of uncomplicated falciparum malaria. However, its effectiveness varies substantially by geography, meaning that countries need to closely monitor the efficacy of the ACTs in use to ensure that the most appropriate treatment option is being deployed [3]. Such monitoring is now even more important in view of recent reports of artemisinin resistance emerging on the Thai–Cambodian border in Southeast Asia [3,4].

Artemether-lumefantrine and artesunate-amodiaquine are the WHO-recommended ACT combinations for treatment of malaria in pregnancy in Sub-Saharan Africa [3]. In 2009, the Nigerian Government introduced a program of free treatment for malaria in children and pregnant women in public hospitals, and artemether-lumefantrine was the ACT adopted [3]. This intervention resulted in substantial pressure on the artemether-lumefantrine combination, and before long, unpublished concerns began to arise over cases of suspected treatment failure with

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artemether-lumefantrine that were subsequently managed successfully using artesunate-amodiaquine.

Additionally, in a resource-constrained setting such as Nigeria, affordability is an important consideration, especially when individuals have to make unsubsidized out-of-pocket payments for treatment, as is often the case. The artesunate-amodiaquine combination is substantially less expensive than is artemether-lumefantrine (₦50–₦200 [US$0.30–$1.30] vs ₦400–₦900 [US$2.51–$5.70]) for a complete course [5].

Therefore, the aim of the present study was to compare the artesunate-amodiaquine and artemether-lumefantrine combinations in the treatment of acute uncomplicated falciparum malaria among pregnant Nigerian women, with regard to parasite clearance, interval to symptomatic relief, and adverse effects.

2. Methods

A double-blind randomized study was conducted in the Obstetric Units of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria, between January 2 and July 26, 2013. The hospital is located in the tropical rainforest region of southwestern Nigeria where malaria is holoendemic [6]. It records an average of 3500 prenatal bookings and 2500 deliveries annually.

Consecutive prenatal-clinic attendees in the second or third trimester of pregnancy were eligible for inclusion when they had symptoms of malaria (e.g. fever [≥37.5 °C], headaches, and body pains), microscopically confirmed *Plasmodium falciparum* parasitemia, and no evidence of urinary tract infection on the basis of nitrite testing using urinalysis reagent strips (ACON Laboratories, San Diego, CA, USA). Women were excluded if they had complicated malaria, were in the first trimester of pregnancy, had taken antimalarials other than sulfadoxine-pyrimethamine in the previous week, reported vomiting, or had a known history of reaction to any of the study drugs.

Eligible participants were informed about the benefits and risks of participation in the present study, as well as their right to withdraw for whatever reasons without penalty. Each willing participant signed a consent form and was recruited into the study. Ethical approval had been obtained from the hospital's research and ethics committee before the study began. The study design conformed with the WHO guidelines for antimalarial efficacy trials [7] and the conduct was in accordance with the Declaration of Helsinki [8].

After enrollment, biodata, symptoms, and vital signs were recorded for each participant in an individual form. Thick and thin blood films were then prepared from a finger-prick specimen, and some blood was taken with a capillary tube for assessment of hematocrit. The thin film was fixed using methanol and both films were subsequently stained using freshly prepared 3% Giemsa solution. To determine the malaria parasite density (parasites per μL of blood) at thick film microscopy (100×), the number of asexual forms was counted relative to 200 white blood cells. The count obtained was then multiplied by 8000 (the average number of leukocytes per μL) and divided by 200 (the number of leukocytes counted) [9]. The thin film was examined for speciation [9].

Participants were then allocated to receive artesunate-amodiaquine or artemether-lumefantrine according to a computer-generated randomization sequence prepared by a statistician, which was made available only to the pharmacy which was responsible for repackaging and dispensing the study medications. Both the investigators and the participants were masked to group allocation.

Participants took one tablet of artesunate-amodiaquine (Winthrop; 100 mg artesunate/270 mg amodiaquine; Maphar, Casablanca, Morocco) or artemether-lumefantrine (Gloatem Forte; 80 mg artemether/480 mg lumefantrine; Global Healthcare Limited, Lagos, Nigeria) twice daily for 3 days, starting on day 1 and finishing on day 3. Both groups received an equal number of tablets, which were of similar size and shape.

The participants returned to the study center for routine follow-up on days 2, 3, 7, and 28. They were also given an emergency number to call if they needed urgent attention between scheduled visits. Telephone reminders and occasional home visits were used as required to minimize loss to follow-up. At each follow-up visit, the participants' symptoms since the previous visit were assessed. Physical examinations and parasite counts were repeated and appropriately documented. The hematocrit assessment was also repeated on day 28. Finally, pregnancy outcome was obtained by telephone after the expected date of delivery.

Using the WHO system, study outcome was classified as early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF), and adequate clinical and parasitological response (ACPR). ETF was defined as the occurrence of danger signs or severe malaria with presence of parasitemia in the first 3 days after initiation of treatment, day-2 parasitemia higher than day-0 levels irrespective of the axillary temperature, day-3 parasite count up to 25% of the day-0 count, or day-3 axillary temperature of ≥37.5 °C with presence of parasitemia. When parasitemia was present but the criteria for ETF were not met, the development of danger signs or severe malaria after day 3, or an axillary temperature of 37.5 °C or more between day 4 and day 28 was classified as LCF. When parasitemia was present between days 7 and 28, the axillary temperature was less than 37.5 °C, and the criteria of ETF or LCF had not been previously met, a diagnosis of LPF was made. Lastly, ACPR was defined as absence of parasitemia on day 28 irrespective of axillary temperature in cases for which the criteria for diagnosis of ETF, LCF, or LPF had not been met [7]. Treatment failure was treated with oral quinine (600 mg three times a day for 7 days) [7]. All the study investigations and medications were provided at no cost to the participants.

The required sample size for the present study was calculated using the formula for comparison of two proportions [10]. On the basis of previous studies that reported day-28 cure rates of 92.2% and 98% for artesunate-amodiaquine and artemether-lumefantrine, respectively, along with a precision of 30% at 95% confidence interval and addition of 20% for attrition [1], the required sample size was 75 participants for each group.

Data were collated and analyzed with SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). Outcome analysis was performed on both intention-to-treat (ITT) and per-protocol bases. The Kaplan-Meier method was employed for ITT analysis. Proportions were compared using the χ^2 test, and means were compared using the Student *t* test. $P < 0.05$ was accepted as statistically significant.

3. Results

Among 248 pregnant women with malaria symptoms who were screened for eligibility, 150 eligible women were enrolled (Fig. 1). Overall, 65 women in the artesunate-amodiaquine group and 71 in the artemether-lumefantrine group completed the study.

The pattern of presenting complaints was similar in both groups (Table 1). Headache, fever, and body pain were the most common symptoms at presentation. There were no significant differences between groups in terms of age, parity, estimated length of pregnancy, hemoglobin type, HIV status, use of intermittent preventive therapy in pregnancy, parasite density, or baseline hematocrit (Table 2).

There were no statistically significant differences between the two groups in any of the outcomes except adverse effects, which were significantly more common in the artesunate-amodiaquine group than in the artemether-lumefantrine group ($P < 0.001$) (Table 3).

The Kaplan-Meier analysis of the ITT population further revealed a median time to ACPR of 28 days in both groups, with censoring of 11 patients in the artesunate-amodiaquine group and eight in the artemether-lumefantrine group. The median times did not differ significantly (log-rank, Breslow, and Tarone-Ware tests; $P = 0.095$ for all).

Two participants (one in each group) were diagnosed with LCF. They both had fever on day 5, and malaria parasites were still present in their blood films. Additionally, three patients in the artemether-lumefantrine group had asymptomatic parasitemia on day 28 (uncorrected LPF).

Parasite clearance by day 3 was noted for most participants in both groups (Table 3). Among the 12 patients with parasitemia on day 3, all