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Original Article

ASSESSMENT OF THE THERAPEUTIC EFFICACY OF TWO ARTEMISININ-BASED COMBINATIONS IN THE TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA AMONG CHILDREN UNDER 5 YEARS IN FOUR DISTRICT HOSPITALS IN SIERRA LEONE

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Abstract

Plasmodium falciparum has developed resistance to almost every class of antimalarial compounds. As a result of this, the World Health Organization has recommended artemisinin-based combination therapy as first line treatment for *P. falciparum* malaria. There is however need for the continuous monitoring of the efficacy of these antimalarials in order to provide timely information on trends of the emergence of resistant strains. We assessed the therapeutic efficacy of oral artesunate – amodiaquine and artemether-lumefantrine combinations in the treatment of uncomplicated *P. falciparum* malaria in four District Hospitals in Sierra Leone. A total of 320 children under five years partiiccipated in the study sites (Kenema, Rokupa, Bo and Makeni). Oral Artesunate-amodiaquine combination was administered to participants in Kenema and Rokupa whilst Artemether-lumefantrine combination was administered to participants in Bo and Makeni. The new WHO Protocol for recruitment of participants in therapeutic efficacy trials in high transmission zones was adopted for the study with filter paper blood samples taken from each participant on days 0 and 28 to distinguish between treatment failure and new infection. When uncorrected for PCR analysis, 96% (95% CI: 902 – 989) and 100% (95% CI:63.1 – 100) responses were obtained in Kenema and Bo respectively with Artesunate-amodiaquine combination whilst 94.3% (CI 95 : 88.1 – 979) and 100% (95% CI: 96.5 – 100) were obtained with Artemether-lumefantrine combination in Bo and Makeni respectively. When corrected for PCR on the other hand, a 100% (95% CI) Adequate Clinical and Parasitological Response was obtained for the two drugs in all four study sites. Results from this study indicate that both Artesunate-amodiaquine and Artemether-lumefantrine combinations remain highly efficacious in Sierra Leone with presently no observed emergence of resistant strains to both drugs.

Keywords:

Artemisinin-based combination, uncomplicated falciparum malaria, children, Sierra Leone

Introduction

Malaria remains a major cause of morbidity and mortality and is estimated to cause 881,000 deaths globally per year. Sub-Saharan Africa is disproportionately affected, suffering 91% of global malaria deaths with 88% occurring in children under 5 years of age (WHO 2008).

Recent reports however indicate that in almost 40% of the world's malaria endemic countries reported cases have dropped by half over the last decade (Johnson et al 2010). *Plasmodium falciparum*, which causes the most life-threatening malaria has developed resistance to almost every class of antimalarial compound (WHO 2010), as a result of which the

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World Health Organization has recommended artemisinin-based combination therapy (ACT) as first-line treatment of *P. falciparum* malaria. ACT is the combination of artemisinin or an artemisinin derivative (artesunate, artemether, dehydraartemisinin) and a partner drug (amodiaquine, mefloquine, piperaquine, lumifantrine, sulphadoxine, pyremethamine) having a markedly longer half life in the blood stream than artemisinin.

Hence, the rationale for ACT is that the artemisinin precipitously reduces the parasiteamia, and the less potent but longer-acting partner drug kills any residual parasites over 1 – 2 weeks (Fairhurst et al 2012). Recent reports suggest an impaired parasite response to artemisinin monotherapy in the Cambodia-Thailand border region (Dondorp et al 2009; Anderson et al 2010). Here in Sierra Leone treatment failures with artemisinin monotherapy have also been reported (Sahr et al 2001).

There is no available data on the efficacy of ACTs in Sierra Leone although limited data does suggest that failed treatment to these drugs is rare (Sahr et al 2009). No nationwide survey has been attempted to monitor the efficacy of the ACTs in Sierra Leone since their introduction in 2008. The introduction of a new antimalarial drug requires continuous monitoring in order to provide timely information on the emergence of resistant strains. The objective of this study was to assess the therapeutic efficacy of oral Artesunate-amodiaquine and oral Artemether – lumifantrine combination therapies in the treatment of uncomplicated *P. falciparum* malaria and corrected for PCR analysis in children under 5 years in four (4) District hospitals in Sierra Leone.

Patients and Methods

a. Study design

This was a randomized efficacy study of oral artesunate-amodiaquine and oral artemether – lumifantrine combination therapies for the treatment of uncomplicated *P. falciparum* malaria in children under 5 years, conducted according to the principles of Good Clinical Practice. Study sites were randomly assigned to 1 of 2 study drugs: (1) Oral Artesunate – amodiaquine combination therapy or (2) Oral Artemether – lumifantrine combination therapy, administered according to the recommendation of the World Health Organization.

The study was approved by the Ethics and Research Committee of the Ministry of Health and Sanitation.

b. Data collection

Data was collected in four Government Hospitals: Kenema, Rokupa, Bo and Makeni. All four Hospitals are supervised by Medical Doctors with established Under-five Clinics and Laboratories. Only children below five years were enrolled in the study. The new WHO Protocol (WHO 2008) for recruitment of participants in therapeutic efficacy trials in high transmission zones was adopted. Filter Paper blood were taken from each participant on Days 0 and 28 for PCR analysis where indicated to distinguish between parasitological failure and new infection. Inclusion criteria used in the study were: children below 5 years, axillary temperature $\geq$ 37.5^{0}C, mono-infection with *Plasmodium falciparum,* parasitaemia $\geq$ 1000 parasites/µl of blood, and informed consent from accompanying parents or guardians.

Participants with severe or complicated malaria according to the WHO classification (WHO 1996) were excluded from the study and treated with parenteral artemisinin. The two study drugs were provided by WHO and passed the general counterfeit test of the Pharmacy Board of the Ministry of Health and Sanitation.

Both artesunate-amodiaquine and artemether – lumifantrine were administered orally under the direct supervision of a nurse. Participants were followed-up on Days 1, 2, 3, 7, 14, 21 and 28 during which their general conditions were assessed and blood smears prepared for the demonstration and quantification of *Plasmodium falciparum* parasitaemia. Axillary temperature was recorded for each participant on all follow-up days and the response to treatment recorded according to the WHO recommendation (WHO 1996): Adequate Clinical and Parasitological Response (ACPR), Early Treatment Failure (ETF) and Late Treatment Failure (LTF). Briefly, ACPR was defined as absence of parasitaemia on day 14

irrespective of axillary temperature < 37.5^{0}C and irrespective of parasitaemia without previously meeting any of the criteria of ETF. Therapeutic response was classified as ETF if the subject developed one of the following conditions during the first three days of follow-up:

a. Axillary temperature ≥ 37.5^{0}C on Day 2 with parasitaemia greater than that on Day 0.
b. Axillary temperature ≥37.5^{0}C on Day 3 in the presence of parasitaemia.
c. Parasitaemia on Day 3 ≥ 25% of count on Day 0.

Therapeutic response was classified as LTF if a participant's axillary temperature was ≥ 37.5% in the presence of parasitaemia on any day from Day 4 to Day 14 without previously meeting the criteria of ETF.

Ethical Clearance

Ethical clearance for the conduct of the study was obtained from the Ethics and Research Committee of the Ministry of Health and Sanitation.

Result

A total of 320 children below 5 years were enrolled in the study. Of these, 101 were from Kenema, 8 from Rokupa, 106 from Bo and 105 from Makeni. Artesunate-amodiaquine combined therapy was administered to participants in Kenema and Rokupa, while artemether – lumifantrine combined therapy was administered to participants in Bo and Makeni. Table I summarizes the therapeutic efficacy of the two study drugs amongst the 320 participants from the four study sites without PCR analysis of the filter paper blood to distinguish between true parasitological failure and re-infection. From Table I, 96% and 100% Adequate Clinical and Parasitological Responses were observed with Artesunate-amodiaquine combined therapy in Kenema and Rokupa respectively (95% CI). For Artemether-lumifantrine combined therapy on the other hand, 94.3% and 100% Clinical and Parasitological Responses were observed in Bo and Makeni respectively (95% CI). After PCR analysis of the filter blood samples of the participants with apparent Clinical and Parasitological failure in Kenema for artesunate-amodiaquine and Bo for artemether-lumifantrine combined therapies, a 100% Adequate Clinical and Parasitological Response was obtained for the two study drugs in the four study sites (Table II).

Table 1. Therapeutic efficacy of artesunate + amodiaquine in two sites and artemether+lumefantrine in two sites, Sierra Leone.

Treatment outcome	Artesunate + amodiaquine		Artemether + lumefantrine	
	Kenema (n = 101)	**Rokupa (n = 8)**	**Bo (n = 106)**	**Makeni (n = 105)**
% Early Treatment Failure (95% CI)	0.0 (0.0-3.6)	0.0 (0.0 – 36.9)	0.0 (0.0 – 3.4)	0.0 (0.0 – 3.5)
% Late Treatment Failure (95% CI)	1.0 (0.0 – 5.4)	0.0 (0.0 – 36.9)	0.9 (0.0 – 5.1)	0.0 (0.0 – 3.5)
% Late Parasitological Failure (95% CI)	3.0 (0.6 – 8.4)	0.0 (0.0 – 36.9)	4.7 (1.5 – 10.7)	0.0 (0.0 – 3.5)
% Adequate Clinical & Parasitological Response (95% CI)	96.0 (90.2 – 98.9)	100 (63.1 – 100)	94.4 (88.1 – 97.9)	100 (96.5 – 100)
Kaplan-Meier Cumulative Treatment Failure Rate	0.0	0.0	5.6 (2.6 – 12.1)	0.0

PCR uncorrected responses

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Table 2. Therapeutic efficacy of artesunate+amodiaquine in four sites and artemether+lumefantrine in four sites, Sierral Leone.

PCR Corrected Response

Treatment outcome	Artesunate+amodiaquine		Artemether+lumefantrine	
	Kenema (n=101)	Rokupa (n=8)	BO (n=106)	Makeni (n=105)
% Early Treatment failure (95% CI)	0.0 (0.0-3.7)	0.0 (0.0-36.9)	0.0 (0.0-3.6)	0.0 (0.0-3.5)
% Late Clinical Failure(95% CI)	0.0 (0.0-3.7)	0.0 (0.0-36.9)	0.0 (0.0-3.6)	0.0 (0.0-3.5)
LateParasitologicalFailure(95 % CI)	0.0 (0.0-3.7)	0.0 (0.0-36.9)	0.0 (0.0-3.6)	0.0 (0.0-3.5)
% Adequate Clinical & Parasitological response(95% CI)	100 (96.3-100)	100 (63.1-100)	100 (96.4-100)	100 (96.5-100)
Kaplan-MeierCumulative Treatment Failure *Rate*	0.0	0.0	0.0	0.0

Discussion

Child mortality from *P. falciparum* malaria increased significantly in the 1980s when chloroquine-resistant parasites arrived in Sub-Saharan Africa (Trape 2001; Dondrop et al 2010). As the parasite developed resistance to more antimalarial drugs, the World Health Organization recommended ACTs as first-line treatment for uncomplicated *P. falciparum* malaria. Although the most common ACTs are Artemether-mefloquine and Artemether-lumifantrine (WHO 2006), the Ministry of Health and Sanitation in Sierra Leone recommend Oral Artesunate-amodiaqine and oral artemether-lumefantrine for the treatment of uncomplicated *P. falciparum* malaria.

When the results are not corrected for with PCR analysis, a 3% and 4.7% Late Parasitological failures were observed in Kenema and Bo respectively. With PCR corrected responses on the other hand, results suggest that both oral Artesunate-amodiaquine and oral artemether-lumefantrine combination therapies are highly efficacious in the treatment of uncomplicated *P. falciparum* malaria as evidenced by the 100% ACPR in all four study sites.

Although there are no available reports on treatment failures with ACTs in Sierra Leone, a number of research groups in South –East Asia have started detecting the first signs of artemisinin resistant which may threaten to compromise the efficacy of ACTs (Fairhurst 2012). Recent clinical and molecular studies suggest the emergence of ACT-resistant *Plasmodium falciparum* in the Cambodia-Thailand border area, were the standard ACT is Artesunate-mefloquine combination therapy (Wongsrichanalia et al 2000). They suggested that the treatment failures reported might be due to mefloquine used as monotherapy in the treatment of *P. falciparum* malaria long before the introduction of ACTs.

Sahr et al (2001) reported 4 cases of apparent treatment failure with Aretsunate use as monotherapy. Using the WHO criteria for the classification of treatment outcome with antimalarial drugs, all four treatment failures were reported as ETFs. In a therapeutic efficacy study conducted in Ghana by Abuaku et al 2012 to evaluate Artemether-lumefantrine in the treatment of uncomplicated malaria in children under 5

years in three ecological zones, they reported an overall pre-corrected cure rate of 95.4% (95% CI: 90.3 – 98.0). These results are similar to our PCR uncorrected response of 96.0% (95% CI) and 94.3% (95% CI) obtained in Kenema and Bo respectively. They concluded from their study that Artemether-lumefantrine remains efficacious in Ghana for the treatment of uncomplicated malaria. Post corrected PCR cure rates in our study demonstrated a 100% ACPR (95% CI) in all four study sites on Day 28. This shows that both oral Artesunate-amodiaquine and artemether-lumefantrine are highly efficacious in the treatment of uncomplicated *P. falciparum* malaria in Sierra Leone and emergences of resistant strains of the parasite to the two drugs are yet to appear. It is therefore recommended that the Ministry of Health and Sanitation undertakes continuous monitoring of the efficacy of these drugs so that timely information on the emergency of any treatment failures could be reported.

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