Efficacy of Artesunate-Amodiaquine Combination Therapy for Uncomplicated Malaria in Patients in South-Eastern Nigeria

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KEY WORDS: Artesunate-amodiaquine, Efficacy, Parasitemia, Nigeria.

ABSTRACT

Context/Objective: Artemisinin combination therapy (ACT) is currently the recommended first line treatment for uncomplicated malaria. However, with a plethora of ACTs currently available in Nigeria, it is pertinent to establish the efficacy of these drugs in clinical settings. This study aimed at evaluating the efficacy of the artesunate-amodiaquine combination in a rural community of south-eastern Nigeria.

Method: This was a randomized prospective study, which employed the assessment of day 14 clinical and parasitemia responses. It was conducted in a hospital in Ibagwa, a rural community in the outskirts of Enugu State, Nigeria. Patients who consented to enrolment had detectable parasitemia, no history of prior antimalarial drug use and a history of fever. Each patient received appropriate doses of the artesunate-amodiaquine combination and on days 4 and 14, parasitemia levels were determined microscopically and clinical responses assessed physically.

Results: Results showed a preponderance of children (71.4%) and females (62.2%) in this study. Fever, weakness, headache and malaise were the most reported complaints on day 1. By day 14, there was complete resolution of fever, emesis, and pains in all the patients with the least effect seen on weakness, pallor and hematomegaly. Cure rate in this population on days 4 and 14 were 67% and 99% respectively. There were no significant changes in hemoglobin, electrolyte sedimentation rate and leukocyte count. Severe weakness was the only reported side effect.

Conclusion: This study showed a high efficacy of this combination in treatment of uncomplicated malaria in this population with few side effects.

INTRODUCTION

Treatment of uncomplicated malaria continues to generate a lot of concern particularly because of the consequences of its high prevalence in the tropics and sub-Saharan

Table 1: *Dosages of artesunte-amiodaquine for the patients according to ages*

Patient	1st day of treatment	2nd day of treatment	3rd day of treatment
Children under 1 year, weight less than 10 kg	½ tablet of artesunate ½ tablet of amodiaquine	½ tablet of artesunate ½ tablet of amodiaquine	½ tablet of artesunate ½ tablet of amodiaquine
Children from 1-7 years, weight 10-20 kg	1 tablet, artesunate, 1 tablet, amodiaquine	1 tablet, artesunate, 1 tablet, amodiaquine	1 tablet artesunate, 1 tablet amodiaquine
Children from 7 years to 13 years, weight 21-40 kg	2 tablets artesunate, 2 tablets amodiaquine	2 tablets artesunate, 2 tablets amodiaquine	2 tablets artesunate, 2 tablets amodiaquine
After 13 years, weight more than 40 kg	4 tablets artesunate, 4 tablets amodiaquine	4 tablets artesunate, 4 tablets amodiaquine	4 tablets artesunate, 4 tablets amodiaquine

Each tablet of artesunate contained: 50 mg artesunate
Each tablet of amodiaquine contained: 200 mg amodiaquine.

parts of Africa. Globally, an estimated 400 - 900 million acute infections occur annually with at least one death every 30 seconds[1,2]. About 85-90% of fatalities from malaria occur in sub-Saharan Africa[1]. The battle against malaria continues to face daunting challenges mounted by drug resistance to most antimalarial drugs, insecticide resistance by mosquitoes and other climatic and socio-cultural factors[3]. Drug resistant P. falciparum is a serious problem and contributes to the increasing malaria-related morbidity and mortality[4, 5]. Resistance to the classical antimalarial drugs, notably – chloroquine, sulfadoxine-pyrimethamine, mefloquine, quinine is well documented[6, 7]. Continued concerns of impending multi-drug resistance has caused a shift from monotherapy to combination therapy which includes drugs like the artemisinins currently recommended by WHO as a means of prolonging the effectiveness of first-line treatment regimens[8, 9]. In Africa, the treatment policy with regards to uncomplicated malaria advocates the first line use of artemisinin-based combination therapies (ACTs)[10]. Several of these ACTs are currently available in Nigeria of which the artesunate-amodiaquine (AA) combination is common. Although this combination has been shown to be effective and safe for use in many other African settings[11], information about its efficacy in Nigerians is very scarce and it is not known if its deployment would result in the beneficial effects associated with such ACTs. Assessment of the efficacy of AA in the treatment of malaria patients in south eastern Nigeria is significantly important given the intensity of malaria transmission in this endemic region and its consequences and the possible impact of information from such studies on disease management policy. Our main objective in this study was to evaluate the efficacy of artesunate-amodiaquine (AA) combination in a rural population in the endemic regions of south-eastern Nigeria.

MATERIALS AND METHODS

Study design

This was a randomized prospective non-comparative study conducted between June and October 2009.

Study site

The study site was a hospital (St Raphael's hospital, Ibagwa-aka) located at the heart of Igbo-eze Local Council of Enugu State, Nigeria. It is a 20-bed in-patient hospital that serves towns within the Local Government Council and neighboring communities made up of natives from the east and migrants

***Table 2**. Patient's demographic characteristics and presenting complaints before treatment*

Demographic characteristic	Frequency (n) (%)
Sex	
Male	37 (37.8)
Female	61 (62.2)
Age range, (yrs)	
2-12	70 (71.4)
13 and above	28 (28.6)
Mean ± SD	25 ± 9.2
Range	2-45
Presenting complaints	
Fever	90
Vomiting	64
Abdominal pains	40
Malaise	83
Headache	85
Weakness	96
Nausea	70
Loss of appetite	76
Spenomegaly	35
Hepatomegaly	44
Pallor	22
Chills	47

n represents number of occurrence; Fever represents temperatures 37.5^{o}C and above: SD= standard deviation.

from northern and southern parts of the country. This part of the country is predisposed to heavy malaria attacks throughout the year (hyperendemic), especially during the wet seasons when this study was conducted.

Test protocol

The Medical Board of the Hospital granted a written ethical consideration. Sample size estimation was done by taking the population proportion of clinical failures (15%), a confidence interval of 95% and a precision value of 5%. An acceptable minimum of 96 patients was obtained but 105 patients were recruited to make up for any loss during follow up. Patients were informed of the study and oral consent to participate in the study was obtained from adult patients (18 years and above) and parents of children below 18 years. Patients used in this study who fulfilled the necessary criteria, detectable parasitemia levels, temperature levels above 37.5^{0}C or a history of fever a day or two before the study, no history of prior antimalarial drug use 2 weeks prior to the study and no other diagnosable co-existing illness were included.

The enrolled patients were clerked for their age, sex, weight and presenting complaints by the attending physician. Patients' blood samples were collected and parasitemia levels evaluated by two laboratory

***Table 3**. Presenting complaints after treatment (n=98).*

Symptoms/signs	Number of patients with symptoms/signs					
	Day 0	Day 2	Day 4	Day 6	Day 10	Day 14
Fever	90	50	20	2	0	0
Vomiting	64	40	24	5	1	0
Abdominal pains	40	20	9	4	2	0
Malaise	83	80	82	80	70	55
Headache	85	70	60	30	12	2
Weakness	96	96	97	98	96	80
Nausea	70	65	67	60	40	20
Loss of appetite	76	75	70	70	30	20
Splenomegaly	35	35	33	30	30	20
Hepatomegaly	44	44	44	43	43	40
Pallor	22	22	24	26	24	20
Chills	47	25	15	0	0	0

scientists independently. Patients were then given different doses of the artesunate-amodiaquine combination drug (generics, IDI) as shown in Table 1 based on body weight measurements. The drugs were administered orally in the presence of a trained nurse and patients who vomited repeatedly were excluded from the study. Children (aged between 0-9 years) were given crushed tablets mixed with honey. Patients were encouraged to come for 2 days of treatment and again on day 4 and 14 in which their blood were collected on slides, stained and counted microscopically. Clinical response follow-up was done on alternate days and then on days 10 and 14. A fourteen day parasitemia and clinical response duration instead of the customary 28 days was done due to difficulty in establishing recrudescence or re-infection after fourteen days of treatment. Similar studies also employed this method[12, 13]. Hematological data were also assessed using hemoglobin count, erythrocyte sedimentation rate and leukocyte count. Side effects were also noted and taken as worsened or new events observed after treatment. Rescue treatments for severe malaria (quinine injection) and hyperthermia (antipyretics) were provided.

Outcome was measured by cure rate (adequate clinical and parasitological response-ACPR) which was defined as percentage of patients with absence of detectable parasites in blood smears after repeated counts on day 14 of the study. Also fever clearance time was checked and defined as time for body temperature to fall to or below 37.5oC after drug treatment. Improvements in other symptoms and hematological values were also noted. Treatment failures (early treatment failure, late clinical failure and late parasitological response) were also noted. Early treatment failure (ETF) was defined as any sign of severe malaria on any treatment day, parasitemia levels on day 2 is higher than day 0 and persistent parasitemia on day 4 with measured fever. Late clinical failure (LCF) was defined as any sign severe malaria on any day after treatment days and detectable parasitemia and fever on any day after treatment. Late parasitological failure (LPF) was defined as detectable parasitemia and fever on day 14 without any earlier treatment failure.

Data was analyzed as descriptive statistics using SPSS (version 13, Chicago IL) and presented as frequencies or percentages for clinical and hematological data.

RESULTS

One hundred and five patients were recruited for this study and two (2) were excluded due to undetectable parasitemia levels but with clinical signs and symptoms of malaria. Five other patients were also excluded due to poor follow-up resulting from missing one dose of the drug or not visiting for clinical assessment after drug administration. Demographic and initial clinical characteristics for the remaining 98 patients are shown in Table 2.

The clinical presentations during and after treatment are shown in Table 3. On day 2, fifty patients (44%) had fever clearance which was different from day 0 (92%) and a fever clearance rate of 100% on day 10. Chills completely resolved by day 6 in all the patients. Other notable changes included total remission of vomiting and abdominal pains by day 14. Changes in organs were not pronounced as symptoms such as hepatomegaly and splenomegaly reduced by 9% and 42% by the 10th day respectively.

The parasitemia levels and hematological data are displayed in Table 4. Three days after treatment (day 4), 66 (67%) patients had a complete parasite clearance while 32 patients all had parasitemia level of 1-10 cells/100 fields. Also five (5.1%) patients had detectable parasitemia and fever simultaneously (ETF is 5). After day 4, only 2 patients had fever from the earlier five patients with detectable parasitemia (LCF is 0). However, after 14 days, all but one (99%) had no detectable parasites in the blood without fever (LPF is 0). Thus ACPR was found in 93 patients (representing 95% of all patients who completed the study).

Table 4. *Hematological data before and after treatment of patients with malaria (n=98).*

Analyte	**Number of patients**		
	Day 0	**Day 4**	**Day 14**
Parasitemia, (cells/100 thick fields)			
1-10	60	22	-
11-100	38	10*(5)	1*
Hemoglobin (g/dl)			
10-11.9	12		10
12-13	19		24
13 and above	67		64
Electrolyte sedimentation rate (mm/h)			
6-8	67		64
9-12	19		24
13-15	12		10
White blood cell count (cells/µl)			
4000-5000	69		49
6000-8000	22		34
9000-11000	7		15

** represents parasitemia level at 1-10 cells/100 thick fields. Number in parenthesis represents ETF (patient with parasitemia and fever)*

None of the patients reportedly had anemia (defined as Hb <9 g/dl). Sixty seven patients (68%) had Hb counts higher than 13 g/dl. The number of patients with leukocytosis doubled from 7 to 15 after 14 days of follow up.

The only observed adverse effect was weakness which was reported by all the patients between the 4th and 6th day with only 18% resolving after 14 days. Three patients required admission and were placed on dextrose infusion. Severe headache persisted in 12 patients till the 10th day and only 2 on the 14th day after receiving analgesics.

DISCUSSION

This study evaluated the clinical efficacy of artesunate-amodiaqiune combination in uncomplicated malaria in a rural setting using fever and asexual parasite clearance. Data from the study showed that the associated symptoms resolved proportionally with time. Parasitaemia clearance and complete resolution of symptoms such as fever, chills and vomiting (frequent signs of malaria) in all the patients provided evidence for clinical efficacy of the regimen. However, hepatomegaly resolved poorly throughout the study. The poor resolution may be due to the duration of the study as it is likely that longer duration than that used (14 days) may be required for considerable recovery to occur. High incidence of spleen enlargement and hepatomegaly in this population (though largely from the children) reflects repeated infections in this group[14].

With a 14-day adequate clinical and parasitological response of 95%, the result of this study is comparable to others obtained in similar settings which showed a 94% efficacy in Gabonese children15 and some other African countries[11]. Studies on AA in other African countries using parasitemia clearance rates on day 14 as the primary endpoint showed 91% cure rate in Kenya; 93% in Senegal and 98% in Gabon[12]. With such a remarkable fever resolution and parasitemia clearance before day 4 seen in this study, one may suggest that AA is highly effective against the Plasmodium parasite in the population studied. Though not documented, the rate of possible recrudescence/relapse was low as late parasitological failure was seen only in a patient who had no detectable parasitemia on the 2nd day of rescue treatment with quinine which is acceptable.

The increase in white blood cell (WBC) counts might have resulted from bacterial infections which may coexist with malaria16. Changes in WBC counts were not reported in previous studies. In the Lambarene, Gabon study, white blood cell count (WBC) and neutrophils were measured on days 0 and 28 with an automated analyzer but no changes were found[17]. And so, the increase in WBC of treated patients in this study may not be due to the drug combination administered.

There was no record of discontinuation of medication by any patient. The combination appeared to be well tolerated by all patients except for complaints of severe weakness by most of the patients. Three patients (all children) were placed on dextrose infusion after complaints of severe weakness. The low rates of side effects may be due to a high prevalence of older children (8-13 years) and adults unlike in other studies[17-19] that employed only children and recorded high incidences of medication-induced emesis. However, artesunate and amodiaquine are generally safe when used in treatment of malaria[20-22].

This study had some limitations in that the sample population was small and may not be reflective of the entire community and the study lasted for 14 days instead of 28 days that would have enabled assessment of recrudescence which usually indicates treatment failure.

In conclusion, this study has shown the high clinical efficacy of artesunate-amodiaquine combination in the treatment of uncomplicated malaria in a rural community in south-eastern Nigeria. It also showed a low incidence of side effects that did not warrant discontinuation of treatment. Adherence to this regimen should be strictly maintained to preserve its therapeutic life.

ACKNOWLEDGEMENTS

The authors are grateful to the entire staff and patients of St Rapheal Hospital, Ibagwa-aka, Enugu State, Nigeria, for their technical assistance, participation and cooperation during the study.

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