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Comparative Trial of Artesunate and Halofantrine in the Treatment of uncomplicated Malaria in Children at a General Hospital in Enugu

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Summary

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Objective: To compare the efficacy of oral artesunate with that of halofantrine in the treatment of uncomplicated malaria in children.

Design: A randomized comparative clinical trial whereby children who met the inclusion criteria were recruited and randomized for treatment with the trial drugs.

Subjects and Method: Patients aged two years to 11 years who lived within Enugu metropolis and had fever of $\geq$37.5°C associated with *Plasmodium falciparum* parasitaemia, and without any other severe illness, were recruited. They were randomized to receive either oral artesunate or oral halofantrine at standard doses. They were then followed up for 14 days, during which period, the effects of the drugs were evaluated.

Results: Fifty-six children were enrolled, but 40 completed the study. Cure rate by day 7 was 71.4 percent for children on artesunate and 47.4 percent in the halofantrine group. Recrudescence rates in the artesunate groups were 0 percent and 4.8 percent respectively. Fever clearance time was two days for both halofantrine and artesunate. Haematocrit gains by day 7 were 3.64 percent and 3.67 percent in the halofantrine and artesunate groups, respectively. No serious adverse effects were recorded in both groups.

Conclusions: There was a high rate of treatment failure with both oral artesunate and halofantrine, although artesunate showed an apparently better efficacy. Both drugs were well tolerated and safe.

Keywords: Malaria, Artesunate, Halofantrine, Efficacy, Children.

Introduction

CHEMOTHERAPY remains the mainstay of malaria control measures in Nigeria.[1] Accordingly, the National Malaria Control Programme recommends the use of a three tier antimalarial regimen in the treatment of acute uncomplicated malaria. Chloroquine is the recommended first line drug, and other drugs such as sulphadoxine/pyrimethamine as the next choice in cases of treatment failure.[2] Increasingly, drug resistance is being encountered with these antimalarial drugs. In the south-eastern part of the country, a high level of chloroquine resistance has been reported[3] up to 25% since 1990, and recently there have been reports of resistance to the alternate antimalarial drugs in Zaria, Northern Nigeria. The Survey in Zaria[4] showed 18 percent R1 and R2 resistance to sulphadoxine/pyrimethamine *in vivo*. It has therefore, become necessary that other effective drugs be introduced to enhance the chemotherapy of malaria control. Halofantrine is an antimalarial drug that was previously introduced into the Nigerian market, It is devoid of any significant activity against the exoerythrocytic stages or gametocytes of malaria parasites, and studies had revealed high sensitivity of malaria parasites to the drug in the south-eastern parts.[5] Recently, the oral preparations of the artemisinin derivatives have been introduced into the

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Nigerian market. These damage the mitochondria-like organelles and alkylate parasite proteins.[6] The success of the parenteral form of this drug in the management of severe and complicated malaria calls for appropriate clinical trials of the oral derivatives such as artesunate as a possible alternative drug in the treatment of uncomplicated malaria. This is of importance in view of the current emphasis on malaria treatment at primary care centres and homes. There is also a need for continuous monitoring of the efficacy of these oral preparations. Artesunate, a derivative of the Chinese woodworm plant, is a peroxidic antimalarial with a unique mode of action which involves intra-parasitic haem catalyzed production of carbon centered free radical. Halofantrine is a phenanthrenemethanol which is schizonticidal with a high degree of activity against the asexual erythrocytic stage of malaria parasites.

This study was designed to compare the clinical efficacy of artesunate and halofantrine in the treatment of uncomplicated malaria in children.

Patients and Methods

The study was carried out at the paediatric outpatient clinic of the Park Lane General Hospital, Enugu. This is a second level state-owned hospital, which serves Enugu metropolis as well as the surrounding local government areas in the state. It has a sixteen-bed paediatric ward. There is a daily paediatric outpatient clinic, which is run by a consultant paediatrician and medical officers. All paediatric age groups are seen in the clinic with an attendance rate of 30-50 patients daily giving an annual rate of about 10,000. Enugu has an area of 72.8 square kilometres and lies on an altitude of 232.6m above sea level. The projected population (from the 1991 census) is 667,994. The temperature in the area ranges between 22.4°C and 30.8°C with an annual rainfall of 1520mm and 2030 mm. The vegetation is tropical rain forest and there are two major seasons namely, dry (November to April) and wet (May to October). Malaria transmission in the area is stable and the illness is said to be holoendemic.

This was an open comparative clinical trial of oral artesunate and halofantrine in which 56 children aged two years to eleven years who presented at the children's outpatient clinic of the hospital, between October 2000 and January 2001 were selected by simple convenience method. Patients who fulfilled the following inclusion criteria were randomly assigned to either of the test groups using a randomization table whereby all patients with odd numbers were assigned to the artesunate group while those with even numbers were assigned to the halofantrine group. The criteria included informed consent from parents/caregiver, age 2-11 years, parasite count e"1000/ul, fever e" 37.5°C, and pure *Plasmodium falciparum* parasitaemia. On recruitment, personal data such as name, age, sex, place of abode and history of complaints were obtained from the parent(s)/caregivers. Physical and laboratory examinations were carried out to exclude patients with features of renal impairment, liver disease, cardiac disease, hyperparasitaemia or parasite density >250,000 parasites/μl, prostration, and excessive vomiting. Also excluded were patients who received quinine or artemisinin within 3days, sulphadoxine /pyrimethamine and mefloquine or 4-amino-quinoline derivatives within 7days and 14 days respectively, of presentation. The temperature, pulse, blood pressure, and weight of each child were determined and recorded.

Blood specimens from finger prick, were obtained from each patient on the first day, for packed cell volume, thick and thin films for malaria parasite density counts and specie identification. This procedure was repeated on days 2, 3, 4, 5, 7 and 14. The parasite density was obtained after staining the thick film with five percent Giemsa solution. The stained slides were viewed with a microscope using x100 oil immersion lens. Malaria diagnosis was based on identification of trophozoites of plasmodium on the thick blood film. Specie identification was made using the thin blood smears which were stained with Leishmann stain. The parasite density was determined from the number of parasites counted against 200 leukocytes (or 500 white blood cells (wbc) if no parasite is found) on the thick blood film and calculated using the formula:[7]

$$\frac{\text{No of parasites x 8000 wbc}}{\text{200 wbc}} = \text{parasite/ml}$$

If there were no parasites seen after viewing 500 wbc, such slides were declared negative. White blood cell counts, and packed cell volume were determined on days 1 and 7. Liver function tests, serum electrolytes, urea and creatinine and full blood count were obtained in patients who had adverse reactions.

Dosage Schedules

Halofantrine was given at a dose of 8mg/kg body weight /dose every 8hrs for three doses, while artesunate at a dose of 2mg/kg of body weight, was given at 12-hourly intervals for two doses on Day 1, then 2mg/kg once daily from Day 2 to Day 5. The drugs were administered by the direct observation method, whereby each patient took the drug in the presence of the investigators and was observed for one hour. If the child vomited the drug within one hour of ingestion, the same dose was repeated.

Follow-up

Patients were reviewed on Day 2, and subsequently

on Days 3, 4, 5, 7, and 14. On each of these occasions, physical and laboratory examinations were carried out, and any complaints recorded. Those who failed to report were, where possible, traced to their respective homes where the procedures were carried out. The following evaluation criteria were applied:

Assessment of responses to treatment

Cure Rate: The percentage of patients who were cleared of parasites within seven days.

Fever Clearance Time: The time it took for the individual's body temperature to fall below 37. 5°C and remain so for more than 48 hours.

Parasite Clearance Time: The time it took for parasite to clear from the blood following drug administration without reappearance during the following 48 hours.

Recrudescence Rate: The proportion of patients who, having been cleared of parasites within seven days, again developed parasitaemia within fourteen days.

Study Days: For the purpose of the study, the date of enrolment and drug administration were taken as Day 1, and the subsequent days of follow-ups as Days 2, 3, 4, 5, 7, 14.

Early Treatment Failure[8] : Subjects presenting with persistent fever who were positive on Day 3 with parasite densities higher than Day 1 and/or with parasite density > 25 percent of Day 1 density on Day 4, as well as those whose clinical condition/parasitaemia had worsened before Day 4.

Statistical analysis

This was carried out using Epi info 6.04d and Graphpad prism softwares to evaluate the variables. Analysis was 'per protocol'[8] in which data from patients lost to follow up was excluded from the analysis. The Student's 't' test was used to evaluate continuous outcome variables such as age, and weight ,while non-parametric tests were used for categorical variables like and sex to determine the test of significance of observed differences. Fischer exact test and Chi squared test were used for test of proportions. Analysis of variance of the means of outcome variables, parasite density, and temperature were performed to determine the statistical significance of the effects of the drugs. Correlation and linear regression tests were also conducted to compare outcome, fever clearance and parasite densities of the two treatment groups. The p value of < 0.05 was the determinant level of significance.

Ethical Clearance

Ethical clearance was obtained from the Ethical Committee of the University of Nigeria Teaching Hospital, Enugu. Informed verbal consent was obtained from each child's parent(s)/caregiver prior to the commencement of the study.

Results

A total of 56 children were recruited for the study. Although the patients were randomized on odd and even fashion, this was, not done consecutively due to the pattern of block randomization used whereby 5 consecutive odd numbers receive one drug while the consecutive 3 even numbers receive the alternative drug. .The presenting features except fever are presented in table-1— Thus, with time limitation of the study, there was a slight lopsided distribution of the patients (30 artesunate and 26 halofantrine). Of the 56, 40 (71.4 percent) completed the study while sixteen were lost to follow up, resulting in a default rate of 28.6 percent. This was believed to be due to the fact that the study centre was located in an urban area where follow up is

Table 1

Frequency of Symptoms at Presentation

Symptoms	*Arsumax*		*Halfan*		*Total*	
	No	*%*	*No*	*%*	*No*	*%*
Headache	7	23.3	5	19.2	12	21.4
Myalgia	3	10.0	0	-	3	5.4
Abdominal discomfort	2	6.7	1	3.8	3	5.4
Cough	3	10.0	0	-	3	5.4
Digestive problems	0	-	0	-	0	0
Difficulty in breathing	0	-	1	3.8	1	1.8
Malaise	3	10.0	2	7.7	5	8.9
Total	30	100.0	26	100.0	56	100.0

rather difficult. Majority (81%) of patients gave wrong addresses, parents of one patient withdrew consent and were quite hostile when visited, reason being that patient had recovered and they objected to the frequent pin-pricks. The remaining 2 patients had travelled with their parents. Seven out of the sixteen patients received halofantrine. Twenty-one (52.5 percent) of the 40 children who completed the studywere those assigned to artesunate, while the remaining 19 received halofantrine.. Among the number that completed the study there were 25 males and 15 females, a ratio of 1.7:1. The age range was 24 months to 132 months with a mean age of 57 (± 31) months.

Clinical Characteristics

Halofantrine

On day 4, 18 of the 19 children in this group had parasite densities more than 25 percent of the count on day 1, signifying early treatment failure, but all had temperatures < 37.5°C. Nine patients showed good therapeutic response with total parasite clearance by day 7, thus giving a cure rate of 47.4 percent. There were ten children with parasitaemia beyond the seventh day. However, the mean parasite clearance time was six days6.7±3.6days (Fig 1). While the fever clearance time was 2.6±0.7 days two days (Fig 2). There was no recrudescence in this group. There was a 3.64 difference in the mean haematocrit values of patients on days 1and 7, which were 32.42± .16 (range 25-40 percent) and 36.06±3.59 (range18-41 percent), respectively; a difference that was not significant ($p > 0.05$).

Artesunate

On day 4, 19(90.5 percent) of the 21 patients in this group had a parasite density count which was more than 25 percent of the count on day 1; but, all except one had temperatures less than 37. 5°C. Fifteen children had negative parasitaemia on day 7, giving a parasite cure

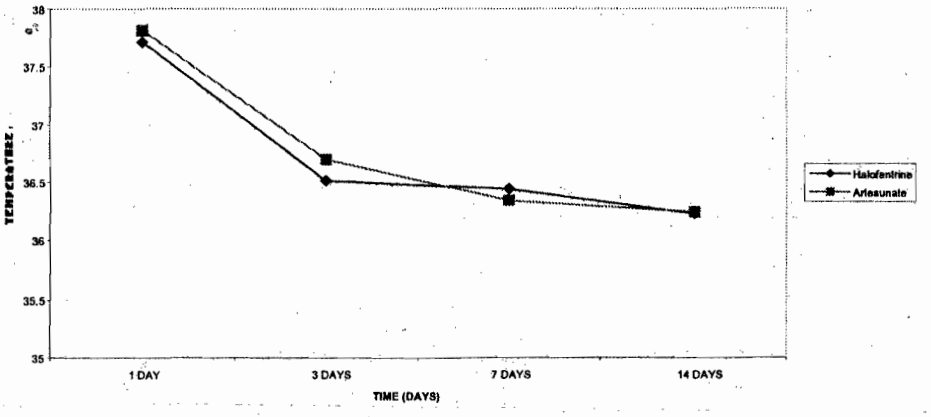

Figure 1: Fever Clearance Time

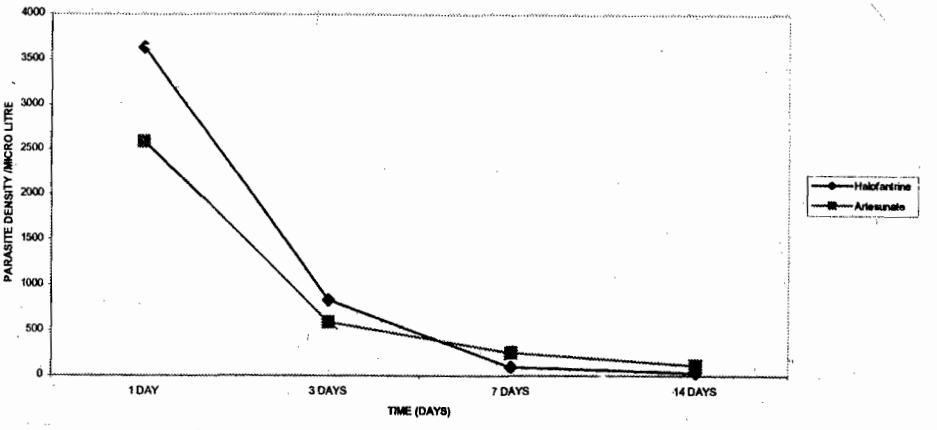

Figure 2: Parasite Clearance Rate:

Table II

Clinical and Parasitological Response to Artesunate and Halofantrine

Parameter	*Artesunate*	*Halofantrine*
Cure rate (%)	71. 40	47. 40
Parasite clearance time (days)	5	6
Fever clearance time (days)	2	2
Hematological recovery by Day 7	3.67%	3. 64%

p values > 0. 05

rate of 71.4 percent. The mean parasite clearance time in this group was five days with a mean fever clearance time of two days. There was a single case of recrudescence. The mean haematocrit for the patients treated with artesunate on day 1 was 33.3 ± 4.00 percent (range 17- 42 percent), while at the end of treatment (Day 7), it was 36.97 ± 3.69 percent (range 16- 41 percent), a difference of 3.67 (p > 0. 05; Table 1).

Other Observations

There were no significant drug reactions among the patients in both groups. One child who was on artesunate had generalized maculopapular rash within 24 hours of drug intake; this however, cleared within 72 hours of chlorpheniramine therapy, and liver function tests showed no derangement in liver enzymes.

Discussion

The results showed that artesunate nominally had better cure, parasite, and fever clearance rateswhen compared with halofantrine. The differences were however, not statistically significant and although both drugs showed good clinical efficacy on days 3 and 7, the parasitological efficacy for halofantrine was poor. The presence of recrudescence observed with artesunate is an important factor in the use of the drug and with its prolonged dosage schedule which might increase parasite pressure on the drug in the course of time.

There were minor differences in PCV values on days 1 and 7 for each of the treatment groups, and the PCV levels on day 7 when compared, showed haematological recovery for each drug but this was not statistically significant. This is an encouraging outcome for both drugs and might be related to the parasite clearance observed with each drug in this study; an effect that was previously documented.[9] The relatively mild reactions will suggest a good tolerance to both drugs. The maculopapular reaction, although in a single patient, should be noted for further observation, as this has not been reported previously.

The significant number of defaulters noticed, may be attributed to ignorance and patients' resistance. The quick resolution of symptoms might have contributed to this default rate, especially among the halofantrine group who probably saw no need to continue the visits after the initial few days. Some parents were averse to the daily bleeding of their wards, and in spite of pleadings still kept away. A mother declined participation on the grounds that since the drugs were free, theywould probably be of no benefit. These factors are impediments to the follow up assessment in therapeutic efficacy trials. The factors correspondingly affected the recruitment and assignment of patients during the study, thus limiting the number of patients enrolled. It is however, envisaged that in subsequent studies, these factors will be accommodated and larger numbers recruited to enable a better evaluation of the outcome.

The observations in this study have been noted in earlier studies. For example, Ojuawo *et al* [10] reported a cure rate of 83.8 percent on day 7 and noted a 21 percent recrudescent rate on day 21 with artemether, which is much higher compared with 4.76 percent after 14 days in this study. Their study was conducted on cases of complicated malaria and patients were observed for a longer period (27days). Ezedinachi [5] and Kerbwang *et al* [11] have reported at various times declining sensitivity of artemisinin-based drugs in Nigeria and Thailand. Similarly, a decline in halofantrine efficacyagainst malaria has also been demonstrated in Nigeria[12] and Kenya.[13] These findings as well as those of the present study do not portend a bright future for continued use of these drugs as a single agent for the treatment of uncomplicated malaria.

It may be concluded that although both drugs showed a high level of early treatment failures, artesunate seems to have an apparent edge in terms of efficacy over halofantrine. Both drugs were safe and well tolerated. In view of the small sample size in this study we recommend further multi-centre studies on a larger scale, to validate the findings. In addition there is a need for periodic sensitivity studies to monitor efficacy of these drugs.

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