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Comparative study on the efficacy of sulfadoxine-pyrimethamine, amodiaquine and amodiaquine + sulfadoxine-pyrimethamine combination in the treatment of acute uncomplicated malaria in Enugu state, Nigeria

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ABSTRACT

Malaria is a major killer disease affecting one third of the world's population with untold morbidity and mortality especially in under five children in Sub-Saharan Africa. In a randomized controlled trial, involving 180 children aged 6 to 59 months, (M:F, 1:1.37) with clinically characterized malaria; the efficacy of Amodiaquine (AQ) and Sulfadoxine-Pyrimethamine (SP) as monotherapy and in combination as AQ + SP was evaluated. Results revealed that Fever Clearance Time (FCT) of 28.3±2.3 hours in AQ + SP was significantly different (P<0.05) from 51.2±2.3 hours and 74.6±2.5 hours in AQ and SP respectively. Similarly, the Parasite Clearance Time (PCT) in AQ + SP combination differed significantly (P<0.05) from AQ and SP respectively. There was no reported treatment failure in AQ + SP with a Radical Cure Rate (RCR) of 100%. This contrasts with RCR of 83.5±0.34% and 73.8±0.42% reported for AQ and SP respectively in this study. There was no statistically significant difference P>0.05 in the haematocrit and axillary temperatures at pre and post-treatment in the various treatment groups. In conclusion, the AQ+SP combination is strongly recommended for treatment of uncomplicated *P.falciparum* malaria especially in under 5 children in Enugu, Nigeria.

Key words: Combination therapy, efficacy, monotherapy, malaria.

INTRODUCTION

The increasing resistance to Chloroquine (CQ) in extent and severity has necessitated the emergence of alternative cheap and available regimens to control programmes in developing countries, particularly Sulfadoxine-Pyrimethamine (SP) and Amodiaquine (AQ) as monotherapy[1,2,3] or combination of Amodiaquine and Sulfadoxine - Pyrimethamine (AQ + SP) in the treatment of Chloroquine resistant malaria[4]. Since the first proven case of Chloroquine resistance by an African strain of *P.falciparum* was reported from East-Africa[5], there has been a persistent report of increasing rate of resistance all over Sub-Saharan Africa. However, the ever increasing resistance to these cheap and readily available alternative regimens has necessitated the need for regular evaluation of the efficacy of these chemotherapeutic agents in the treatment of acute uncomplicated malaria in children. This study attempts to evaluate the current status in respect of clinical efficacy of SP and AQ as monotherapy or in combination as AQ + SP in the treatment of uncomplicated *P.falciparum* malaria among under 5 children in Enugu, Nigeria.

METHODS

Patients

Patients (n = 180) enrolled in this study were selected by stratified random sampling from children with clinically characterized uncomplicated malaria aged 6 to 59 months (M:F = 1:1.37) who presented at Amafor primary healthcare facility, Ugbawka; a rural farming population with high endemicity of malaria transmission under the Asu Nkanu Local Health Authority of Enugu State. They presented with a history of fever in the preceding 24 to 48 hours or axillary temperature e" 37.5^{0}C and

parasitemia > 2000 asexual forms/mL of blood. Patients with concomitant illness, intense vomiting, recent history of convulsion, lethargic or unconscious state and sickle cell anaemia were excluded. Ethical clearance was obtained and informed consent of the parent or guardian for each child was sought. The patients were subsequently assigned randomly to any of the drug treatment groups: SP, AQ or AQ + SP. Thus, 60 patients were allotted to each treatment group. Drug dosages were computed using the weight of the patients. AQ was given at a dose of 10mg/kg daily for 3 days and SP at 25mg/kg as single dose on Day O. Drugs were administered orally by direct observation and monitored by the clinician to ensure they were not vomited. Drugs were re-administered within 1 hour following initial vomiting but withdrawn from the study with another episode of vomiting. Patients were followed up for two weeks after treatment. Evaluation of response carried out on days 1,2,3,7 and 14 in accordance with WHO criteria[6]. Patients who showed features of treatment failure were salvaged using Artemether-Lumefantrine as rescue drug. Data obtained were statistically analyzed using Student *t*-test and presented in tabular form.

Table 1: Therapeutic response of patients in the SP and AQ + SP treatment groups

	SP (Mean+SEM)	AQ+SP (Mean+SEM)	*P*-Value
Fever Clearance Time (Hrs)	54.6±2.5	28.3±2.3	<0.05
Parasite Clearance Time (Days)	8.3±0.21	3.7±0.15	<0.05
Radical Cure Rate (%)	73.8±0.42	100±0.0	<0.05
Treatment Failure Rate (%)	26.2±0.42	0±0.0	<0.05

Table 2: Therapeutic response of patients in the AQ and AQ + SP treatment groups

	SP (Mean+SEM)	AQ+SP (Mean+SEM)	*P*-Value
Fever Clearance Time (Hrs)	41.2±2.3	28.3±2.3	<0.05
Parasite Clearance Time (Days)	6.1±0.15	3.7±0.15	<0.05
Radical Cure Rate (%)	83.5±0.34	100±0.0	<0.05
Treatment Failure Rate (%)	16.5±0.34	0±0.0	<0.05

RESULTS

Tables 1 and 2, as shown depicted the therapeutic response of patients in the various treatment groups. In the AQ + SP treatment group, mean Fever Clearance Time (FCT) of 28.3±2.3 hours differed significantly (P<0.05) from 41.22.3 hours and 54.6±2.5 hours in Amodiaquine (AQ) and Sulfadoxine-Pyrimethamine (SP) treatment groups respectively. The mean Parasite Clearance Time (PCT) given as 3.7±0.15 days in the AQ + SP group differed significantly (P<0.05) from 6.1±0.15 days and 8.3±0.21 days in AQ and SP respectively. Similarly mean Radical Cure Rate (RCR) in AQ + SP was given as 100% compared to 83.5±0.34% and 73.8±0.44% in AQ and SP groups respectively. There was no reported treatment failure in the AQ + SP group whereas it was given as 26.2±0.44% and 16.5±0.34% in the SP and AQ treatment groups respectively. However, as depicted in tables 3 to 5, there was no statistically significant difference (P>0.05) in the haematocrit and axillary temperature at initial presentation, Day O and post-treatment, Day 14 in the various treatment groups.

DISCUSSION

It is worthy of note that the ideal antimalarial should not only promptly clear parasitemia, fever or other symptoms of malaria, but should also prevent the generation of gametocytes, from asexual forms during treatment[7]. It has been shown in this study that SP is significantly less effective than AQ or AQ + SP in clearing parasitemia or fever in children with acute uncomplicated malaria. Progressive decline in sensitivity of *P.falciparum* to SP has been reported for other similar studies[8,9]. Fever Clearance Time

Table 3: Pre and post–treatment haematocrit and axillary temperature of patients in the SP treatment group

	Pre-Treatment, DO	Post-Treatment, D14	*P* - Value
Haematocrit (%)	27.4±2.2	28.6 ± 2.2	>0.05
Axillary Temp (°C)	38.7±1.6	37.4±1.5	>0.05

Table 4: Pre and post-treatment haematocrit and Axillary temperature of patients in the AQ treatment group

	Pre-Treatment, DO	Post-Treatment, D14	*P* - Value
Haematocrit (%)	28.2±2.5	29.7 ± 2.5	>0.05
Axillary Temp (°C)	38.4±1.6	37.2±1.5	>0.05

Table 5: Pre and post-treatment haematocrit and axillary temperature of patients in the AQ + SP treatment group

	Pre-Treatment, DO	Post-Treatment, D14	*P* - Value
Haematocrit (%)	28.9±2.5	30.1±2.5	>0.05
Axillary Temp (°C)	39.1±1.6	37.0±1.5	>0.05

(FCT) of 54.6±2.5 hours in SP and 41.2±2.3 hours in AQ corroborates findings in other studies. Results clearly showed that AQ + SP combination was significantly ($P<0.05$) more effective than monotherapy with SP or AQ. Sulfadoxine-pyrimethamine selectively inhibits plasmodial dihydrofolate reductase enzyme in folate synthesis. Thus, a treatment regimen combining amodiaquine, a 4-aminoquinoline and effective blood schizonticide with the prolonged parasiticidal effect of SP seems logical; as it takes advantage of the antipyretic and anti-inflammatory effects of the 4-aminoquinoline. The modulating effect of AQ on enhanced production of premature young gametocytes by SP may provide supporting argument for the use of AQ + SP combination therapy[7]. AQ + SP has shown excellent anti-malarial efficacy in most African studies, even in those from regions such as East-Africa, where levels of resistance to each component drug are high[10]. In a study where the monotherapy of AQ and SP was compared with their combinations AQ + SP, a cure rate of 100% was recorded. Also in another comparative study of AQ and SP as monotherapy and combination respectively in Southern Cameroon, a cure rate of 100% was reported for the combination and 83% for the individual monotherapy[11]. The above corroborates findings in this study which reported a cure rate of 100%, 83.5% and 73.8% for the AQ + SP combination, AQ and SP as monotherapy respectively. It has been further suggested that AQ + SP combination might be especially useful in West Africa, where resistance to AQ + SP combination had more than 94% efficacy against uncomplicated malaria in Nigeria, Ghana and Burkina Faso[4,12,13]. Treatment failure of 26.2% reported in this study for SP is low compared to 36.4% in another study in the South-East, Nigeria[14]. This sharply contrasts with treatment failure of 16.5% and 0% reported in this study for AQ and AQ + SP combination. Thus, the treatment failure reported for SP in this study is slightly higher than 25% level recommended for centers in the high endemicity of malaria transmission[15]. In view of the low efficacy of SP reported in this study, associated with treatment failure beyond the acceptable level of 25% given by WHO, it is recommended that SP be withdrawn as anti-malarial drug in use for the study area. The treatment failure of 16.5% reported for AQ as monotherapy is still above the 10% margin recommended for change of first line drug. Thus, its continuous use will create an apparent well-being but engender a tendency to chronic malaria morbidity in the study population. The use of AQ + SP combination should be encouraged as a result of its relatively high cure rate reported as 100% in this study. The combination is safe, highly effective and a viable option that can ensure the therapeutic

lifespan of these drugs. It is, therefore, strongly recommended as the treatment of choice for uncomplicated *P.falciparum* malaria especially in under five children in Enugu, Nigeria.

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