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Effectiveness of Sulphadoxine Pyrimethamine in Intermittent Preventive Treatment of Malaria in Pregnancy at Federal Medical Centre, Abeokuta

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SOO and DOA designed the study, performed the statistical analysis. Author SOO wrote the protocol and wrote the first draft of the manuscript. Authors DOA, MOA and KIH reviewed and revised the protocol. Author DOA revised and wrote the final draft of the manuscript. Authors SOO and DOA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To determine the effectiveness of sulphadoxine – pyrimethamine (SP) in intermittent preventive treatment of malaria in pregnancy at Federal medical centre, Abeokuta.
Design: Randomized controlled trial.
Setting: Antenatal Clinic, Department of Obstetrics and gynaecology, Federal Medical Centre, Abeokuta.
Population: Pregnant women presenting for antenatal booking that met the inclusion criteria for the study.
Methods: Patients were randomized into two groups. Blood film for malaria parasite was collected from all the patients before administering sulphadoxine – pyrimethamine to the first group. A repeat

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sample for malaria parasite was collected from all the patients after two weeks before administering SP to the second group. The maternal biodata, Pre and Post SP blood film analysis results were compared within the two groups.
Main Outcome Measures: Prevalence of malaria parasitaemia and parasite reduction or clearance rate with use of SP.
Results: The result of 358 patients were analysed; 203 in the case group and 155 in the control group. The prevalence of malaria in pregnancy in the study population was 43.9%. The mean parasite density at booking was 1049.7 parasites/µl in the case group and 1183.4 parasites/µl in control group. Prevalence of parasitaemia in the case group reduced by 67.4% and in the control group by 32.4% (P=0.015). The mean parasite density reduction was 59.3% and 37.9% in the case and control group respectively (P=0.021).
Conclusion: The study findings revealed that sulphadoxine-pyrimethamine is effective for the intermittent preventive treatment of malaria in pregnancy.

Keywords: Sulphadoxine-pyrimethamine; intermittent preventive treatment; malaria parasitaemia, pregnancy.

1. INTRODUCTION

Malaria remains a major challenge in Africa where 45 Countries with the population of about 588 million people are within the endemic zone [1]. Pregnant women are the main adult vulnerable group and in Nigeria 11% of maternal mortality is attributable to malaria [2]. In areas of Africa with stable malaria transmission, *Pasmodium falciparum* infection is estimated to cause as many as 10,000 maternal deaths each year, 8% to 14% of all low birth weight babies, and 3% to 8% of all infant deaths [3].

Each year, approximately 25-30 million African women become pregnant in malaria endemic areas and are at risk of *P. falciparum* infection during pregnancy. Most of these women are in the region of high and moderate(stable) transmission of malaria with majority having asymptomatic parasitaemia, which is associated with maternal anaemia (potentially responsible for maternal death when severe) and low birth weight [4,5].

High and moderate or stable malaria transmission area is characterized by constant predisposition to infection with plasmodium parasite throughout the year. Women in this region acquire immunity to malaria and become partially immune to the infection. There is however a dramatic breakdown of the acquired immunity in pregnancy, especially in primigravida, making pregnant women more susceptible to malaria infection compared to non pregnant women in the same location [6]. Low (unstable) transmission is characterized by sporadic transmission of infection. Women in this region do not acquire immunity to the infection and death may result from direct effect of severe malaria or indirectly from malaria related severe anaemia [7,8].

Nigeria is in the region of stable malaria transmission and has been noted, by the world malaria report, to account for a quarter of all malaria cases in the endemic countries of Africa [1]. This constitutes immense malaria burden with its associated effects on the country. The prevalence of malaria in pregnancy has been quoted by various studies as ranging from 19.7% to 72% [9,10]. The study by Agomo et al. showed a prevalence of 7.7% [11], with increased incidence in primigravida and women less than 20 years of age. The WHO recommends a package of interventions for the prevention and control of malaria during pregnancy. This comprises intermittent preventive treatment (IPT), use of insecticide treated nets (ITN) and access to effective case management of malaria illness and anaemia [12].

The most promising preventive approach using antimalaria drugs is intermittent preventive treatment [12]. IPT is based on the use of antimalaria drugs given in treatment doses at predefined intervals after quickening. WHO recommends that in area of stable transmission IPT with an effective, preferably one dose, antimalaria drug should be provided as part of antenatal care, starting after quickening [12]. Sulphadoxine- pyrimethamine (SP) is currently the most effective single dose antimalaria drug for prevention of malaria during pregnancy in areas of Africa where transmission of *P. falciparum* malaria is stable and where resistance to SP is low. WHO recommends that SP be given during regularly scheduled antenatal

visits after first trimester until time of delivery, provided the doses are given at least 1 month apart [12]. Studies have shown SP to effectively reduce severe anaemia, peripheral and placental malaria and Low Birth Weight [6].

The prospect of this promising result with the use of SP is however being eroded by recent evidence of an increasing incidence of treatment failure with the use of SP in children under the age of five years, thus raising questions about its effectiveness in IPT in the same environment [13,14].

Point mutations in the genes of the two enzymes important in the parasite's folate biosynthetic pathway, Dihydrofolate reductase (*DHFR)* and Dihydropteroate synthetase (*DHPS)* confer resistance to pyrimethamine and sulfadoxine, respectively, with decreasing in vitro *P. falciparum* susceptibility related to the number of mutations in each gene [13]. Quintuple and lately sextuple mutant haplotypes of *P. falciparum* have been described [15,16].

However, recent evidence suggests that IPT with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *P. falciparum* parasites carry quintuple mutations associated with treatment failure. Therefore, IPT with SP should still be administered to women in such areas [12,15,16]. WHO recommends at least 3 doses during each pregnancy [15].

The World Health Organisation has recommended a regular evaluation of the efficiency of the drug in IPT as well as safety of repeated doses of SP to facilitate evidence based practice [12].

This study was aimed at determining the effectiveness of Sulphadoxine – pyrimethamine (SP) in intermittent preventive treatment of malaria in pregnancy using changes in the level of parasitaemia as an indicator of therapeutic response following the administration of a single dose of SP in a cohort of asymptomatic pregnant women presenting at the antenatal clinic of the Federal medical centre, Abeokuta.

2. METHODS

The study is a randomized controlled trial conducted among patients attending the ANC at the FMC, Abeokuta between 1st of August 2011 and 31st of December 2011 (5 months). Ethical approval for the study was obtained from the hospital health research ethics committee. The study involved patients who booked after quickening and before 32 weeks gestation. They had no treatment for malaria within two weeks of presentation and no features of malaria at presentation. Patients who booked at or beyond 32weeks gestation, had malaria illness at presentation or previous treatment for malaria within two weeks of presentation and patients with history of adverse reaction to any of the components of the medication were excluded. Also, patients with immunosuppressive illness such as HIV positive patients were excluded.

All consenting patients were scheduled for blood film for malaria parasite in the first routine ANC clinic and two weeks (day 14) after the first visit. The patients were randomized into two groups using randomly chosen numbers. The first dose of IPT in the two groups was separated by the two weeks study period. The study group (Cases) had IPT at first presentation after the initial blood film for malaria parasite while the second group, the control group, had the first dose of IPT after the Day 14 blood film for malaria parasite had been obtained. All the patients eventually had the recommended minimum of two IPT doses. Feature suggestive of malaria illness within the two week study period were treated and the patients that had such presentation were excluded from the study. The laboratory scientist collecting and analysing the samples was blinded to the grouping of patients.

Thick and thin film for malaria parasite was collected on a slide. Peripheral parasitaemia was determined by the presence of ring form of the *P falciparum* with the reddish chromatin dot and a purple or blue cytoplasm, having been stained with 10% Giemsa stain solution at pH 7.2 and examined using x100 oil immersion objective lens [17].

The proportion of women with peripheral parasitaemia in the two groups was compared using the blood film for malaria parasite at the start of the study and at Day 14. The parasite density was calculated by counting the number of asexual Plasmodium parasites against 200 white blood cells (WBC). Mean parasite densities (MPD) was calculated on the assumption that each subject had 8000 WBC/µl blood.

Analysis of data was performed using SPSS version 17 statistical software package. The

findings focused on the prevalence of malaria parasitaemia which was assessed using the absolute figures, percentages, mean and further assessed using cross tabulation with associated variables and significance determined using the chi-square. The effectiveness of SP in parasite clearance was assessed with the determination of the parasitaemia at booking and at day 14 in the study group which was compared with the control for significance using the t- test.

3. RESULTS

A total of 385 pregnant women were recruited. Twenty patients (5.2%) did not present for follow up visit. Seven patients (1.8%) presented with clinical features of malaria in pregnancy before the follow up appointment and were treated. These 27 patients were excluded from the result analysis.

The result analysis involved a total of 358 patients; 203 patients in the case group and 155 patients in the control group. The two groups had similar socio-demographic characteristics as outlined in Table 1. The mean age of the study population was 30.34 yrs [Case group – 30.37yrs, Control group – 30.31 yrs]. Primiparous patients had the highest percentage in both groups [37.4% in both groups]. Most of the patients in both groups had tertiary education (74.9% in Case group, 79.4% in Control group).

One hundred and fifty seven patients (43.9%) had positive film for malaria parasite at the booking clinic (Table 2). The distribution of parasitaemia in the case and control group was similar at booking (43.8% vs 43.9% respectively) (Table 2). There was a significant reduction in parasitaemia in the case group compared to the control group at the follow up visit (67.4% vs 32.4%, P=0.015) (Table 2). There was also a significant reduction in the mean parasite density between case and control group (59.3% vs 37.9%; P=0.021) (Table 3).

All patients in the case group with initial parasitaemia at booking had either parasite clearance or reduction while 3 patients in the control group had increased parasite density between booking and follow up appointment and all the 7 patients with clinical symptoms of malaria before the follow up visit were in the control group.

Table 1. Socio-demographic characteristics of both case and control groups

	Case - 203 (%)	**Control - 155 (%)**
Mean age [yrs]	30.37	30.31
Age group [n (%)]		
20-24	18(8.9)	18(11.6)
25-29	72(35.5)	60(38.7)
30-34	80(39.4)	49(31.6)
>/= 35	33(16.2)	28(18.1)
Parity [n (%)]		
Nullipara	59 (29.1)	51 (32.9)
Primipara	76 (37.4)	58 (37.4)
Multipara	68 (33.5)	46 (29.7)
Educational status [n (%)]		
Primary	20 (9.9)	6 (3.9)
Secondary	31 (15.2)	26 (16.7)
Tertiary	152 (74.9)	123 (79.4)
Total	**203 (100)**	**155 (100)**

Table 2. Prevalence of malaria parasite at booking clinic

	Positive	**Negative**	**Total**
At booking clinic			
Case [n (%)]	89 (43.8)	114 (56.2)	203 (100)
Control [n (%)]	68 (43.9)	87 (56.1)	155 (100)
Total	157 (43.9)	201 (56.1)	358 (100)
At follow up clinic			
Case [n (%)]	29 (14.3)	174 (85.7)	203 (100)
Control [n (%)]	46 (29.7)	109 (70.3)	155 (100)

Total	75	283	358

Table 3. Mean parasite density [MPD] distribution in case and control group

	MPD at booking [no. parasites/µl]	MPD follow up [no. parasites/µl]	MPD difference [n (%)]
Case	1049.7	427.2	622.5 (59.3%)
Control	1183.4	734.9	448.5 (37.9%)

4. DISCUSSION

The study revealed a prevalence of malaria parasitaemia of 43.9%. This value is higher than the 7.7% observed by Agomo et al in Lagos [11], 29% by Nwonwu et al in Abakaliki [18] and some other studies [19,20]. The prevalence was lower than what was reported by Nnaji et al, among antenatal booking patients at the Nnamdi Azikwe university teaching hospital, Nnewi [21], Adefioye et al in Osogbo [10] and Mockenhaupt et al. in southern Ghana also reported higher prevalence [22]. The prevalence is however comparable to that described by Anorlu et al, among pregnant women at booking in a primary health care facility in a peri-urban community in Lagos [23]. It is slightly higher than the 35.6% described earlier in the same environment by Idowu et al. [24].

There was a significant reduction in parasitaemia in the case group with a 67.4% reduction in prevalence of parasitaemia compared with a 32.4% reduction observed in the control group (P=0.015). This reduced risk of parasitaemia is comparable with the findings of Gies et al. [25]. This response is lower than that described by Kayantao H et al where only 1.8% of the patient who used SP did not have parasite clearance [26]. The parasite density also reduced significantly in the case group showing a reduction of 59.3% from a mean density of 1049.7 parasites/µl to 622.5 parasites/µl compared with the control group showing a parasite reduction of only 37.9% from a mean density of 1183.4 parasites/µl to 734.9 parasites/µl (P=0.021).

During the study period, 7 patients presented with features of malaria in pregnancy and they were all in the control group. This is at variance with the findings by Kayantao et al. who had 14.13% of the patients in the study group (IPTp-SP), compared to 21.7% and 22.5% in the control groups (IPTp with chloroquine and weekly chloroquine respectively) presenting with clinical illness at follow up and were treated [26]. In the study by Kayantao et al., all the patients were followed up at 2 weeks initially and subsequently, at 4 weekly intervals till delivery, whereas in our study, patients were evaluated for clinical malaria within 2 weeks of enrolment into the study.

[26]. Also, 3 patients in the control group showed increase in parasite density at follow up in contrast to the patients in the study group who had no increase in their parasite density at follow up visit. A patient in the study group with negative blood film at the booking clinic had parasitaemia at the follow up clinic compared to 3 patients in the control group. These findings are consistent with a significant difference between the case and control group in parasitaemic parameters and in keeping with an effective intermittent preventive treatment role of sulphadoxine – pyrimethamine. The effectiveness of sulpadoxine – pyremethamine in the intermittent preventive treatment of malaria in pregnancy was also documented by Falade et al in Ibadan [27] and other studies [28,29]. However, the development of parastaemia in a patient that had negative blood film at booking in the study group further highlights the need for repeat doses of SP in IPTp as is currently recommended by WHO and Federal Ministry of Health [15,16].

5. CONCLUSION

Sulphadoxine – pyrimethamine is effective in the intermittent preventive treatment of malaria in pregnancy and its continued use for the purpose is therefore recommended.

CONSENT

All authors declare that written informed consent was obtained from the study participants before they were recruited into the study.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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