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APPRAISAL OF THE EFFICACY OF SP-IPTP IN AMINU KANO TEACHING HOSPITAL – IMPACT ON MATERNAL ANAEMIA, MALARIA PARASITAEMIA AND CLINICAL MALARIA IN PREGNANCY.

Omole-Ohonsi A. Attah R. Umoru JU. Habib UR.

Department of Obstetrics and Gynaecology, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria.

ABSTRACT

Background: Sulphadoxine-pyrimethamine (SP) intermittent preventive treatment in pregnancy (IPTp), is the malaria prophylaxis that is recommended in malaria endemic areas. Increasing reports of resistance to SP across the globe, make appraisal of its efficacy to be necessary in health facilities that use it.

Objective: To determine the efficacy of SP – IPTp in the prevention of malaria in pregnancy using Proguanil chemoprophylaxis as the gold standard, in Aminu Kano Teaching Hospital, Kano, Nigeria.

Methods: In this prospective study, 300 primigravid women were enrolled and assigned by block randomization to SP – IPTp (cases) or proguanil chemoprophylaxis (control) group. Each group consisted of 150 women. Study variables of interest were packed cell volume (PCV) at recruitment and at 34 weeks gestation, peripheral malaria parasitaemia, severe anaemia at 34 weeks gestation, and the frequency of clinical malaria during the study period in the two groups. The data obtained were recorded using tables. Students't-test, Z-test and chi-square test were used to compare means and proportions respectively for statistically significant differences, setting the level of significance at $P < 0.05$.

Results: There was statistically significant increase in the PCV between recruitment and at 34 weeks in each group ($P < 0.05$), but there was no statistically significant difference in the PCV, peripheral malaria parasitaemia and frequency of clinical malaria between the two groups at 34 weeks gestation ($P > 0.05$).

Conclusion: SP-IPTp has similar effectiveness as proguanil chemoprophlaxis. SP-IPTp is still effective in the prevention of malaria in pregnancy at Aminu Kano Teaching Hospital.

Keywords ; Sulphadoxine-pyrimethamine, proguanil, malaria, pregnancy.

INTRODUCTION

Malaria infestation in pregnancy is a global health concern because half of the world's population is at risk of malaria, with majority of them in Africa, where it is a major public health concern and cause of death[1,2]. Although the continent is home to about 15.2 percent of the world's population, 500 million people are infested by malaria annually, while 1 million of these die from malaria, about 24 million pregnancies are threatened, and 75,000 to 200,000 infant deaths are associated with malaria infestation in pregnancy[2-4].

Falciparum malaria is an important cause of maternal, perinatal and neonatal morbidity in high transmission settings in sub-Saharan Africa[2]. Besides the number of people at risk in sub-Saharan Africa, malaria in pregnancy

Correspondence: **Dr Omole-Ohonsi A,**
P.O.Box 14578, General Post Office, Kano, Nigeria. Tel no.: +234 807870540.
Email: aomohonsi@yahoo.com

commonly co-exist with conditions that alter the acquired maternal partial immunity against malaria infestation, like haemoglobimopathies, Human Immunodeficiency Virus infection/Acquired Immunodeficiency Syndrome (HIV/AIDS), poverty and poor nutrition with micronutrient imbalances, pre-existing anaemia, Tuberculosis, diarrhoeal diseases, septicaemia, and Tropical Splenomegaly Syndrome (TSS), which exacerbate the impact of pregnancy-associated malaria. [5-9]. In addition, early pregnancy losses and perinatal mortality from increased risk of vertical transmission, low birth weight babies from prematurity and intrauterine growth restriction, and intrauterine fetal death have been documented[9-12].

The integration into the antenatal programs of effective antimalarial interventions like $IPT_{p,}$ use of long lasting insecticide treated bed nets (ITNs), advise to rid their environments of breeding places for mosquitoes, indoor spraying of insecticides and where possible fumigation of their surroundings, together with the use of artemisinin-based combination therapy for the treatment of cases with clinical malaria[13], presents a new opportunity for large scale malaria control, and progress towards targets set by Roll Back Malaria Partnership within the framework of the Millennium Development Goals[12].

In many countries in sub-Saharan Africa, SP-IPTp has proven efficacious in reducing the burden of pregnancy associated malaria[13,14], and two doses of SP were found to be enough to significantly reduce the prevalence of peripheral and placental malaria parasitaemia[15], but its effectiveness is being threatened by increasing levels of parasite resistance to SP across Africa and in South East Asia [15-19]. This may seriously undermine the benefits of national SP-IPTp programs in this region[16]. Hence there is an urgent need for on-going appraisal of the efficacy SP for IPTp, in health facilities that use the drug for prevention of malaria in pregnancy, in order to detect early development of resistance to the drug, in event of which alternative drug regimens for IPTp can be introduced, and failure of preventive therapy can be avoided[16].

It is against this background that an appraisal of the efficacy of the antimalarial intervention using SP - IPTp in Aminu Kano Teaching Hospital, Kano, Nigeria, was carried out using proguanil chemoprophylaxis as the gold standard, so that recommendations can be made on whether to continue the use of SP for IPTp or to develop alternative drug regimens.

METHODOLOGY

This is a prospect study to determine the efficacy of SP-IPTp in the prevention of malaria in pregnancy among primigravida who attended the antenatal clinic in Aminu Kano Teaching Hospital, Kano, Nigeria, and consented to be included in this study between January and June 2011, using proguanil chemoprophylaxis as the gold standard, which was based on the findings of Flemin et al[17] in Zaria, Nigeria, which attested to the efficacy of proguanil, with the findings that resistance to proguanil is infinitely minimal. Only primigravidae were recruited for uniformity, and because they have lower immunity to malaria than women of higher parity[14], and will be more representative of the effect of malaria prevention in pregnancy.

The women were recruited at the booking clinic. The inclusion criteria were primigravidae with certain dates (last menstrual period confirmed with ultrasound scan), who were carrying

singleton gestation between 16 and 24 weeks of pregnancy, who gave informed consent to participate in the study, while the exclusion criteria were women with severe anaemia (PCV < 24%), sickle cell anaemia, multiple pregnancies, urinary tract infection (acute pyelonephritis), HIV/AIDS, and previous adverse reaction to Sulphonamides – pyrimethamine, proguanil or Artemisinin-Lumefantrine combination. Participants who developed clinical malaria during the study period in the two groups were excluded from follow-up.

In this prospective study, 300 primigravid women were enrolled and assigned by block randomization to the SP – IPTp (cases) or Proguanil chemoprophylaxis (control) groups. Each group consisted of 150 women.

All participating clients who fulfilled the inclusion criteria were given Artemisinine combination therapy (ACT) at recruitment in the booking clinic to clear initial parasitaemia, before SP and proguanil hydrochloride tablets were given to their respective groups at the next clinic visit a week later. ACT that was used was Artemether-lumefantrine, 4 tablets twice daily for 3 days, each tablet contained artemether 80mg and lumefantrine 480mg, with the first dose given as directly observed therapy (DOT) at recruitment in the booking clinic.

Participants in the SP-IPTp group received two adult doses of S-P at 4 weeks interval between 16 and 24 weeks of gestation (3 tablets at once, each tablet containing 500mg Sulphadoxine, and 25mg pyrimethamine) as directly observed therapy during the clinic visits, while participants in the proguanil chemoprophylaxis group received 100mg oral proguanil daily, with doses that coincided with clinic visits taken under directly observed therapy, and other doses were double checked for compliance by looking at the remaining proguanil tablets in the container, to ascertain the quantity that have been used before clinic visits. Subjects in both groups continued with routine antenatal visits/care, and were all on routine haematinics. The participants were counseled on the need to strictly comply with medication

Study variables of interest were socio-demographic characteristics of the women, the use of ITNs, maternal packed cell volume (PCV) at recruitment and at 34 weeks gestation, peripheral malaria parasitaemia and the frequency of severe anaemia at 34 weeks gestation, and the frequency of clinical malaria during the study period in the two groups.

The data obtained were recorded using tables. Statistical analysis was done using computer software SPSS Version 11.0, Illinois, USA. Qualitative data were presented using percentages and frequencies, while quantitative data were presented using mean and standard deviation. Chi-square test and Fisher exact test were used to compare qualitative variables, while Students'-test and Z-test were used to compare quantitative variables for statistical significance. A P-value of less than 0.05 was considered significant.

Sample Size Determination

Nahlen et al,[18] in a study done in Ilorin Nigeria, found a 29.7%(11/37) parasitologic failure rate with antimalarial intervention in pregnancy. Using the result obtained in this study, and accepting a study power of 80%, confidence interval of 90%, study to control ratio of 1:1, and an acceptable dropout rate of 10%, the sample size for each group was then determined using the statistical formula for comparison of proportions as follows:-

$$n = \frac{1}{(1 - f)} \times \left\{ 2 \times \frac{(Z\alpha + Z\beta)^2 \times P \times (1 - P)}{(P_O - P_1)^2} \right\}$$

Where n = minimum sample size

Po = the proportion of participants that are expected to have parasitaemia at 34 weeks gestation = 0.297.

P_1 = the efficacy of SP-IPTp among the participants would be determined if the parasitaemia rate among them at 34 weeks gestation is reduced by 50%.

$$= \frac{50}{100} \times 0.297$$

$$= 0.149$$

P = is the pooled value. $P = \frac{Po + P_1}{2} = 0.223$

Zα = 1.96; for the significance level of 0.05, that is used in this study.

Zβ = 0.84; for the power of the test of 80% that was used in this study to compare between the 2 groups.

f = the proportion of study participants who are expected to be lost to follow up in this study (attrition) = 10% (0.1).

Therefore, the minimum sample size required for each study group for it to be statistically significant was:

$$n = \frac{1}{(1 - 0.1)} \times \frac{(2 \times (1.96 + 0.84)2 \times 0.223 \times (1 - 0.223)}{(0.297 - 0.149)^2}$$

$$= 1.1 \times \frac{2 \times 7.84 \times 0.223 \times 0.777}{0.219}$$

$$= 1.1 \times 123.7$$

= 136 subjects per group approximately + 10% attrition

= 150 subjects per group approximately.

RESULTS

A total of 300 clients, who fulfilled the inclusion criteria were recruited into this study, and using block randomization, they were divided into two groups of 150 participants each. Twelve participants were lost to follow up (7 from the SP group, and 5 from the proguanil group). Nine participants (5 (3.5%) from SP group, and 4 (2.8%) from proguanil group) developed clinical malaria during the study and were excluded from follow-up, which left a total of 279 participants at the end of the study, with 138 participants in the SP group and 141 participants in the proguanil group. Occurrence of clinical malaria among the participants during the study period did not show statistically significant difference between the two groups (Fisher exact = 0.47). They were all treated with oral arthemeter-lumefantrine on outpatient basis, with complete clinical remission. There was no case of severe anaemia in the two groups at 34 weeks gestation. The use of insecticide treated bednets in the SP was 2.7% and 3.0% for proguanil group, with no statistically significant difference between the two groups (X^2 = 0.07, P = 0.788).

Table 1 shows the socio-demographic characteristics of the participants in the two groups. The mean age (Z = 1.62, P = 0.115), mean gestational age at recruitment (Z= 0.67, P = 0.502), occupation (X^2 = 1.44, P = 0.837), educational status (X^2 = 1.18, P = 0.757) and tribe (X^2 = 0.55, P = 0.908) of the participants did not show statistically significant difference between the two groups.

Table 2 shows the mean packed cell volume between the two groups at recruitment and at 34 weeks gestation. The mean PCV in the SP and proguanil groups at recruitment were 32.1 ± 3.1% and 32.2 ± 2.85% respectively, which did

not show any statistically significant difference between the two groups (Z = 0.39, P= 0.731). The mean PCV at 34 weeks gestation was 35.0 ± 2.5% and 35.4 ± 3.2% for SP and proguanil groups respectively, which also did not show statistically significant difference between the two groups (Z = 1.85, P= 0.074), but there was statistically significant increase between recruitment and at 34weeks gestation in the SP group (Z = 2.40, P = 0.021), and the proguanil group (Z = 9.14, P < 0.001).

Table 3 shows the number of participants with malaria parasitaemia at 34 weeks gestation in the two groups. Among the SP group, 9 participants (6.3%) had malaria parasitaemia, while 5 (5.7%) had in the proguanil group at 34 weeks gestation. There was no statistically significant difference in the number of participants with malaria parasitaemia in the two groups at 34 weeks gestation (X^2 = 0.75, P = 0.388).

DISCUSSION

In this study, there was no significant difference in the socio-demographic characteristics of the participants as well as the use of ITNs in the two groups. This would have eliminated any bias which could originate from these variables that could affect the frequency of malaria parasitaemia and occurrence of clinical malaria in pregnancy in the two groups during the study period.

The low frequency of use of ITNs of 2.7% and 3.0% for SP and proguanil groups respectively, is similar to the Nigerian National average of 4.8%,[20], and has been attributed to the low level of awareness and poor distribution of the free insecticide treated bed nets provided by the Federal Government of Nigeria[20-24].

The incidence of peripheral malaria parasitaemia at 34 weeks gestation of 6.3%, among the participants in the SP group, is lower than 8.7% from southern Mozambique[15], 11.9% from Benin city[22], and 10.4% from Ibadan[26], and may probably be because only primigravida were used in this study, which was not the case in these studies from southern Mozambique, Benin City and Ibadan, where multigravid pregnant women were also involved. This may be explained by the findings of Gies et al in Burkina Faso[27], where it was found that SP is more effective in preventing malaria parasitaemia among primigravida than among women of higher parity.

In this study, there was significant increase in the mean packed cell volume between recruitment and at 34 weeks gestation in each group, but there was no significant difference in the mean packed cell volume and number of participants who had malaria parasitaemia at 34 weeks gestation, and those who had severe anaemia and clinical malaria during the study period between the two groups, which agrees with the findings of other studies.[10,12,26]. This showed that the effectiveness of SP-IPTp in preventing malaria in pregnancy is similar to that of proguanil, which shows that SP-IPTp, is still effective in the prevention of malaria in pregnancy in Aminu Kano Teaching Hospital, despite reported cases of resistance in southern Asia and some part of Africa[15-19]. The similar mean packed cell volume between the two groups at recruitment showed that the base line PCV at recruitment did not contribute any bias in the final PCV at 34 weeks gestation.

The low incidence of peripheral malaria parasitaemia at 34 weeks gestation in the two groups in this study, was also the finding of Ojo et al[24], where it was said that women on SP-IPT with low peripheral malaria parasitaemia at 34 weeks gestation, are most likely to have reduced

incidence of placental malaria parasitaemia and low birth weight babies, as well as favorable pregnancy outcome if followed to delivery. Also Flemin et al[17], Aimaku et al[28], Steer[29], and Rana et al[30] found that pregnant women with normal PCV are likely to have favorable pregnancy outcome.

Haven confirmed in this study, that SP-IPTp is still effective in the prevention of malaria in pregnancy, with its sequel of anaemia, malaria parasitaemia and clinical malaria at Aminu Kano hospital, future studies on the efficacy of SP-IPTp in the prevention of placental malaria and low birth weight babies are recommended.

Limitations of the study: Patients in the Proguanil group used most of their tablets at home not as directly observed therapy, and the use of ITNs was also not directly observed.

Conclusion:

This study has showed that SP-IPTp is still effective in the prevention of malaria in pregnancy at Aminu Kano hospital. It has also showed that the use of two treatment doses of SP-IPTp, is associated with significant increase in the packed cell volume, significantly lower incidence of peripheral malarial parasitaemia and clinical malaria, and prevention of severe anaemia in pregnancy, which will go a long way in the realization of Millennium Development Goals 4 and 5.

Recommendations

The continued use of SP- IPTp is advocated for the prevention of malaria in pregnancy at Aminu Kano Teaching Hospital, in order to reduce maternal and fetal morbidity and mortality like maternal anaemia, congential malaria, low birthweight babies from intrauterine growth restriction (IUGR) and pretem delivery as well as the risk of Mother to Child Transmission of Human Immunodeficiency Virus.

Health facilities that use SP for IPTp, should carry out periodic surveillance on the efficacy of SP- IPTp, in order to detect early the occurrence of resistance to the drug, so that appropriate intervention can be instituted.

It is hoped that malaria vaccine that is being developed in the United States of America, which will address whatever lacuna there is in the national malaria control programs, will soon be made available in our hospital and communities in malaria endemic areas.

Conflict of interest – None.

Source of funding - None

Table 1: Shows the Socio-Demographic Characteristics of the Participants in the Two Groups

Variable	SP n=150	Proguanil n=150	Test	P-value
Mean Age ± SD (years)	23.6±4.0	23.1±3.4	Z= 1.62	P= 0.115
Mean gestational Age ± SD (Weeks)At recruitment	21.0±2.8	21.2±2.3	Z= 0.67	P= 0.502
Occupation				
Student	5(3.3%)	6(4.12%)		
Petty trader	10(6.7%)	13(8.8%)	X^2= 1.44	P= 0.837
Civil Servant	25(16.7%)	22(14.4%)		
Business	5(3.3%)	8(5.7%)		
Housewife	105(70.0%)	101 (67.0%)		
Educational status				
Quranic Education	2(1.1%)	4(3.1%)		
Primary Education	5(3.0%)	3(2.0%)		
Secondary Education	45(30.1%)	44(29.5%)	X^2= 1.18	P= 0.757
Tertiary Education	98(66.0%)	99(6.61%)		
Tribe				
Hausa/Fulani	90(60.1%)	96(63.8%)		
Igbo	19(13.2%)	18(12.3%)	X^2= 0.55	P= 0.908
Yoruba	15(10.0%)	13(8.4%)		
Others	26(17.0%)	23(15.5%)		

Table 2: Shows Mean Packed Cell Volume (PCV) Of The Participants In The Two Groups At Recruitment And At 34 Weeks Gestational.

	Mean PCV (%)			
Variable	**SP**	**Proguanil**	**Test**	**P- Value**
	n= 150	**n= 150**		
At Recruitment	32.1±3.1	32.2±2.8	Z= 0.39	0.731
	n= 135	**n= 141**		
At 34 weeks Gestation	35.0±2.5	35.4±3.2	Z= 1.85	0.074
Test	Z= 2.40	Z= 9.14		
P=Value	0.021	< 0.001		

Table3: Shows The Number Of Participants With Malaria Parasitaemia At 34 Weeks Gestational In The Two Group.

Malaria Parasitemia	**SP n= 138 (%)**	**Proguanil n= 141 (%)**	**Test**	**p- value**
Positive	9 (6.3)	5 (5.7)	X^2= 0.75	0.388
Negative	129 (93.7)	136 (94.3)		

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