

A comparison of the efficacy of sulphadoxine-pyrimethamine with azithromycin versus sulphadoxine-pyrimethamine alone for malaria chemoprophylaxis in pregnancy: a triple-blind randomized controlled trial

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ABSTRACT

INTRODUCTION: Sulphadoxine-pyrimethamine (SP) is the recommended drug for malaria chemoprophylaxis in pregnancy. However, there are growing reports of resistance to its use. This study compared the efficacy of Sulphadoxine-pyrimethamine with azithromycin (SPAZ) versus Sulphadoxine-pyrimethamine as chemoprophylactic agents against malaria in pregnancy.

METHODS: A triple-blind randomized trial was conducted among women presenting for antenatal services between February and November 2023. One hundred women were randomized into two groups: those who received SP and a placebo (Group I) and those who received SPAZ (Group II). The collected data were coded and analyzed using Statistical Product and Service Solutions (SPSS) version 26, and $p < 0.05$ was considered significant.

RESULTS: There was no statistically significant difference between the two groups regarding the clearance of maternal parasites, maternal packed cell volume (PCV), cord blood parasites, fetal PCV, fetal birth weight, and placental parasitaemia despite having reduced incidences of anaemia and malaria parasitaemia in the SPAZ group.

CONCLUSION: The results of this study suggest that SPAZ is as efficacious as SP for malaria chemoprophylaxis in pregnancy and can be used in place of SP in areas with established resistance to SP.

Keywords: Sulphadoxine-pyrimethamine, Sulphadoxine-pyrimethamine with Azithromycin, Efficacy, Malaria, Pregnancy, Randomized controlled trial

INTRODUCTION

Malaria remains a serious global health threat according to the World Health Organization (WHO) [1], and the burden of malaria lies more

in countries with a high poverty index, including sub-Saharan Africa. According to the WHO's latest world malaria report, there were an estimated 263 million cases and 597,000 malaria deaths worldwide in 2023. Approximately 95% of these

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deaths occurred in the WHO African region, where many who are at risk of the disease still lack access to the services, they need to either prevent, detect or treat the disease [1]. Nigeria has the highest burden of malaria globally, accounting for nearly 27% of the global Malaria burden [2]. Pregnant women are particularly at great risk of malaria due to the altered immunity to malaria during pregnancy [3].

Omang et al. highlight the fact that as many as 10,000 women and 200,000 babies die annually because of malaria in pregnancy, which is responsible for 20% of stillbirths and 11% of maternal deaths [4]. The review by Omang et al. goes further to point out that sub-Saharan Africa bears the burden of global disease, with one-fifth of pregnant women accessing antenatal care testing positive for *Plasmodium falciparum* parasitaemia [4]. As many as nearly three-quarters of pregnant women are affected with the malaria parasite without being aware of it [5]. Fetal complications of malaria include intra-uterine growth restrictions, low birth weight and prematurity [5]. Congenital malaria can occur in the newborn from malaria in pregnancy [6].

Several antimalarial agents have been used for chemoprophylaxis since the 90s when the WHO first introduced it [7]. These changes have moved from a single agent to the present combination agent (Sulphadoxine-pyrimethamine). However, current evidence shows that *Plasmodium falciparum* resistance to Sulphadoxine-pyrimethamine is emerging, with the resulting failure of SP as an intermittent preventive treatment of malaria in pregnancy (IPTp). A study by Quan et al. in Lagos, Nigeria, reported a high prevalence of dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHFS) mutant allele in *Plasmodium falciparum* [8]. Another study conducted in Calabar, Nigeria, revealed that the efficacy of SP as IPTp may be severely threatened and that there may be a need to evaluate alternative preventive treatment strategies and drug options for preventing malaria in pregnancy [9]. In a multi-centre study undertaken in Ibadan, Enugu, Benin, and Maiduguri, the authors observed a novel dhps mutation at codon 431, and this mutation was widespread throughout Nigeria. They concluded that it was crucial to evaluate the impact of this mutation in IPTp since the mutation was on the increase [10]. A systematic review across Africa analysed nationwide standardized levels of

Plasmodium falciparum resistance. The systematic review concluded that under the WHO protocols, SP is no longer effective for intermittent preventive treatment in pregnancy in most of Eastern Africa and parts of Central Africa [11].

In a study by Unger et al., in Papua New Guinea, the authors compared SPAZ versus Sulphadoxine-pyrimethamine plus Chloroquine as IPTp. The study found that SPAZ may protect against adverse pregnancy outcomes by reducing inflammation and preventing its deleterious consequences, including dysregulation of placental angiogenesis in women with or without malaria infection [12]. In another study by Luntamol et al., they observed that adding Azithromycin to the IPTp SP regimen offered further benefits in improving fetal well-being [13]. Unger et al. also noted that SPAZ was efficacious and safe in pregnancy, reducing the incidence of low birth weight by possibly acting through multiple mechanisms, including the effect on malaria and sexually transmitted infections [14].

This study was a triple-blind randomized controlled trial that compared the efficacy of Sulphadoxine-pyrimethamine with Azithromycin versus Sulphadoxine-pyrimethamine alone for malaria chemoprophylaxis in pregnancy:

METHODS

Study design

A triple-blind randomized controlled trial (parallel design) was used for this study. Also, the Consolidated Standards of Reporting Trials (CONSORT) were followed [15], it was registered on the Pan African Clinical Trials Registry (PACTR) (No: PACTR202305696485090).

Study area

FMC Asaba is a 350-bedded tertiary hospital located in Asaba, the capital of the oil-rich Delta State in Nigeria. It also receives referrals from primary, secondary, and even tertiary hospitals in Delta State and neighbouring Anambra and Edo states.

Study population

These included all consenting patients who booked for antenatal care services in the study centre between February and November 2023.

Inclusion criteria: All consenting booked patients

with a gestational age ≥16 weeks.

Exclusion criteria: Sickle cell disease, multiple gestation, retroviral infection, clinical or laboratory evidence of malaria infection, anaemic patients, patients with known drug allergies to Sulphadoxine-pyrimethamine or Azithromycin or any of its components.

Sample size determination

The sample size was calculated using the formula below [16].

$$n = \frac{2(Z_{\alpha/2} + Z_p)^2 P(1-p)}{(P_1 - P_2)^2}$$

Where $Z_{\alpha/2} = 1.96$ at a type 1 error of 5%

$Z_p = 0.842$ at 80% power

$P_1 =$ Prevalence in group 1 (27.9%) [17]

$P_2 =$ Prevalence in control group 2 (57%) [14]

$P =$ prevalence in group 1 + prevalence in group 2
2

$$\text{Sample size} = \frac{15.702 \times 0.4245 \times 0.5755}{0.084681} = 45$$

This formula determined a sample size of 45 participants per study group. Allowance was made for a 10% loss to follow up by giving a final size of 50 per group and a total of 100 participants for the study.

Outcome measure

The primary outcome measures for this study were the presence of malaria parasites at delivery in the mother, the presence of malaria parasites histopathologically in placental tissue, and the presence of cord blood malaria parasites in the newborn in either arm of the study, while the secondary outcome measures included maternal packed cell volume, fetal packed cell volume and fetal birth weight.

Data collection

A study proforma was used to obtain data from the

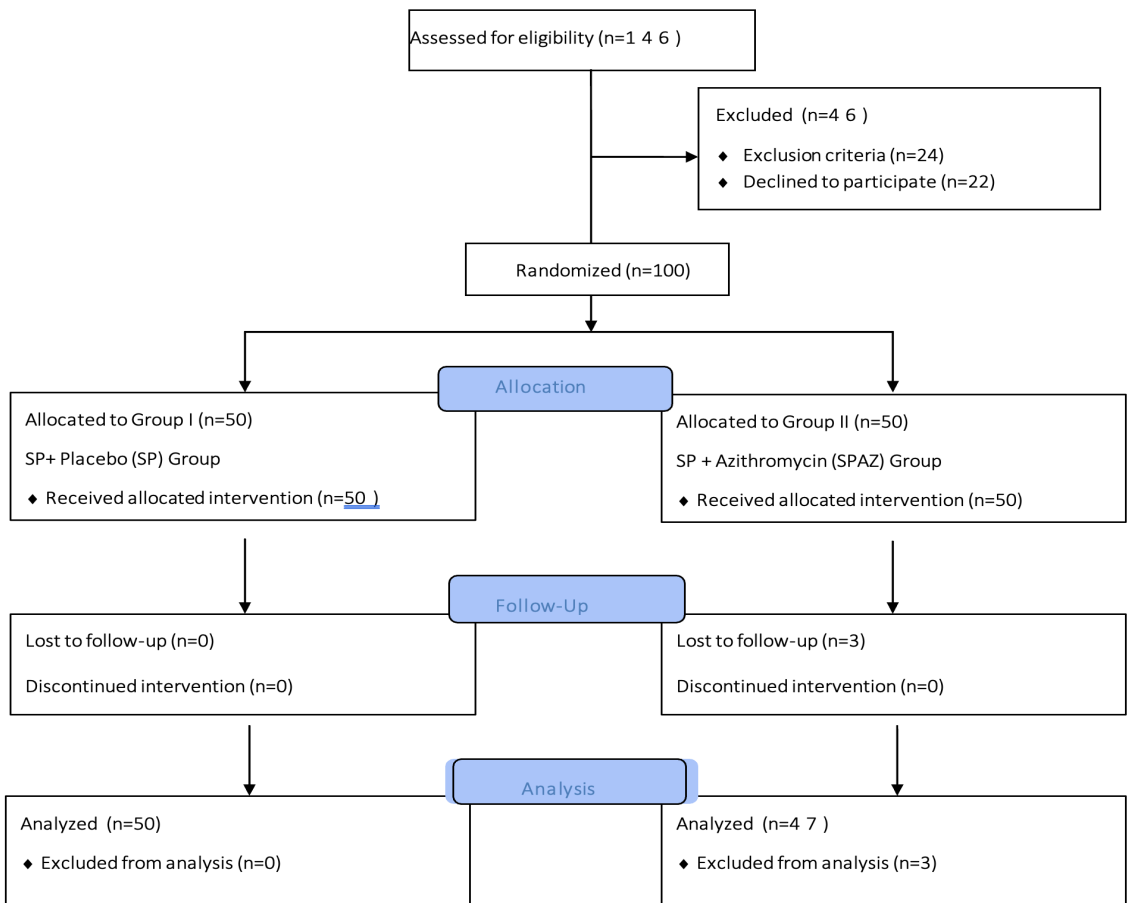


Figure 1: Consort flow diagram showing the selection of study participants

patients recruited for this study after randomizing the study participants using computer-generated random numbers from the research randomization application. The research randomization application was used to generate two sets of numbers with fifty for each group: those who received SP with a placebo (Group I) and those who received SPAZ (Group II). Each patient had four tablets in all. The placebo had similar features to azithromycin tablets.

A Hospital Pharmacist who was not part of the study assigned the randomly generated numbers to the hospital folders of the participants after participants had chosen sealed envelopes containing the randomly generated numbers. The pharmacist also was in charge of the drugs used for this study and gave the drugs to participants according to the respective groups. The study

participants, the outcome assessor and the data analyst were blinded as to the group allocation and intervention participants received. The participants were followed up till delivery. At delivery, blood samples were collected from the participants, cord blood of the newborn, and the weight of the newborn were recorded. Placental tissue was also collected for histopathological analysis.

Data analysis

Data was subsequently analysed using IBM Statistical Product and Service Solutions (SPSS) version 26. Categorical variables were expressed in frequencies and percentages, while continuous variables were expressed as mean and standard deviation. The test of association between the categorical variables was via the chi-square and Fisher's exact test, where necessary, while the

Table 1: Socio-demographic features of the participants

| Variables | Group I (n=50) | Group II (n=47) | χ^2 | P-value |
|---------------------------|----------------|-----------------|----------|---------|
| Age Group | | | 8.66 | 0.0702 |
| 20 – 24 | 9 (18.0) | 6 (12.8) | | |
| 25 – 29 | 16 (32.0) | 7 (14.9) | | |
| 30 – 34 | 19 (38.0) | 18 (38.2) | | |
| 35 – 39 | 5 (10.0) | 14 (29.8) | | |
| 40 – 44 | 1 (2.0) | 2 (4.3) | | |
| Marital Status | | | 0.600 | 0.439 |
| Single | 8 (16.0) | 5 (10.6) | | |
| Married | 42 (84.0) | 42 (89.4) | | |
| Level of Education | | | 4.18 | 0.242 |
| None | 0 (0.0) | 1 (2.1) | | |
| Pry | 2 (4.0) | 0 (0.0) | | |
| Sec | 18 (36.0) | 15 (31.9) | | |
| Ter | 30 (60.0) | 31 (66.0) | | |
| Occupation | | | 2.23 | 0.135 |
| Informal | 34 (68.0) | 25 (53.2) | | |
| Formal | 16 (32.0) | 22 (46.8) | | |
| Ethnicity | | | 10.4 | 0.106 |
| Ibo | 30 (60.0) | 24 (51.0) | | |
| Isoko | 5 (10.0) | 2 (4.3) | | |
| Urhobo | 9 (18.0) | 7 (14.9) | | |
| Ijaw | 0 (0.0) | 4 (8.5) | | |
| Itsekiri | 3 (6.0) | 2 (4.3) | | |
| Yoruba | 3 (6.0) | 4 (8.5) | | |
| Hausa | 0 (0.0) | 4 (8.5) | | |

t-test was used for continuous variables, with a P value of < 0.05 considered statistically significant.

Ethical considerations: Ethical approval was obtained from the Health Research Ethics Committee (HREC) of the hospital with approval number FMC/ASB/A81 VOL. XII/293 before the commencement of the study in conformity with the Helsinki Declaration [18], on research involving human subjects with emphasis on the core ethical principles of autonomy, beneficence, non-maleficence and justice [19].

RESULTS

The study participants' randomization, allocation, follow-up, and analysis are displayed in the

CONSORT flow chart below (Figure 1). The socio-demographic and obstetric characteristics of the study participants are shown in Tables 1 and 2 respectively. The tables show that there were no statistically significant differences between the distribution of the study populations in both groups in terms of age, marital status, level of education, occupation, ethnicity, parity, estimated gestational age, and mode of delivery.

Figure 2 below shows that most of the participants in Group I took 5 to 6 doses 29 (58.0%) of IPTp while in Group II most of the participants 27(57.4%) took 3 to 4 doses of the drug. The difference was not statistically significant (P= 0.13).

Table 3 below shows no statistically significant

Table 2: Maternal obstetric characteristics

| Variables | Group I (n=50) | Group II (n=47) | χ^2 | P-value |
|------------------------------|----------------|-----------------|----------|---------|
| Parity | | | 0.0277 | 0.98627 |
| 0- 2 | 21(20.62) | 19(19.38) | | |
| 3- 4 | 25(25.26) | 24(23.74) | | |
| 5- 6 | 4(4.12) | 4(3.88) | | |
| EGA | | | 3.118 | 0.210 |
| Pre-Term | 6(12.0) | 5(10.6) | | |
| Term | 43(86.0) | 37(78.7) | | |
| Post Date | 1(2.0) | 5(10.6) | | |
| Mode of Delivery | | | 1.254 | 0.263 |
| Spontaneous vaginal delivery | 42(84.0) | 43(91.5) | | |
| Cesarian section | 8(16.0) | 4(8.5) | | |

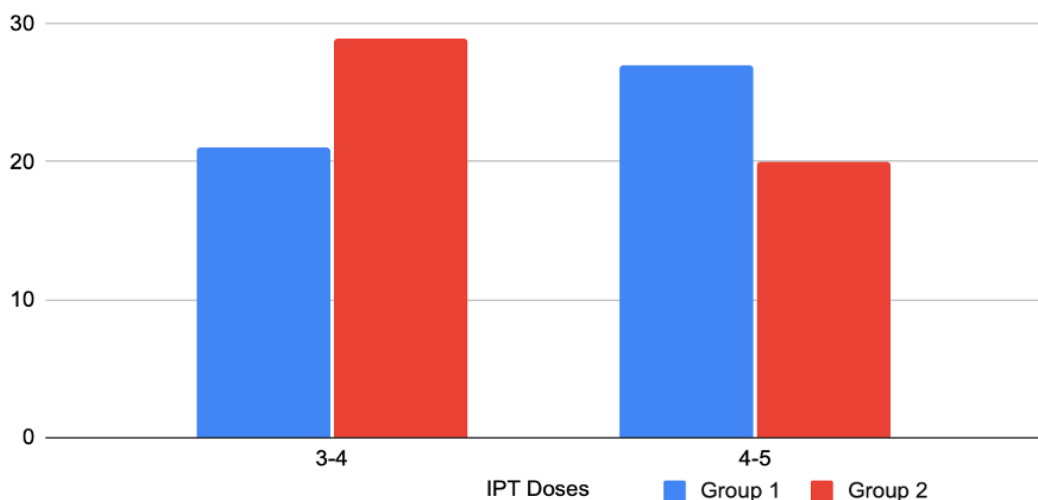


Figure 2: Maternal uptake of Intermittent Preventive Treatment for Malaria in Pregnancy (IPTp)

Table 3: Maternal outcome variables, Fetal outcome variables and Placental Histopathological outcomes

| Variables | Group I (n=50) | Group II (n=47) | χ^2 | P-value |
|---|----------------|-----------------|----------|---------|
| Maternal Anaemia (PCV less than 30%) | | | 2.590 | 0.108 |
| Anaemic (PCV less 30%) | 10(20.0) | 4(8.5) | | |
| Not Anaemic | 40(80.0) | 43(91.5) | | |
| Fetal Anaemia (PCV less than 45%) | | | 0.419 | 0.518 |
| Anaemic (PCV less than 45%) | 5 (10.0) | 3 (6.4) | | |
| Not Anaemic | 45 (90.0) | 44 (93.6) | | |
| Maternal Malaria Parasitaemia | | | 0.142 | 0.706 |
| Malaria Parasite Present | 10(20.0) | 8(17.0) | | |
| No Malaria Parasite | 40 (80.0) | 39(83.3) | | |
| Cord Blood Malaria Parasitaemia | | | 1.276 | 0.259 |
| Malaria Parasite Present | 12 (24.0) | 7 (14.9) | | |
| No Malaria Parasite | 38 (76.0) | 40(85.1) | | |
| Placenta Tissue Malaria Parasitaemia | | | 0.381 | 0.537 |
| Malaria Parasite Present | 11(22.0) | 8(17.0) | | |
| No Malaria Parasite | 39(78.0) | 39(83.0) | | |
| Fetal Birth Weight | | | 0.102 | 0.749 |
| Low Birth weight (less than 2.5kg) | 12 (24.0) | 10 (21.3) | | |
| Normal Birth weight 2.5kg and above | 38 (76.0) | 37 (78.7) | | |

difference in the incidence of maternal and fetal anaemia in the two groups studied. There was also no significant difference concerning maternal malaria parasitaemia, cord blood malaria parasitaemia, placenta tissue parasitaemia, and fetal birth weight in either of the groups studied. The SPAZ group, however, recorded lower incidences of anaemia, malaria parasitaemia burden, and low birth weight.

DISCUSSION

This study was a triple-blind randomized controlled trial that compared the efficacy of Sulphadoxine-pyrimethamine with Azithromycin to Sulphadoxine-pyrimethamine alone for chemoprophylaxis against malaria in pregnancy. The results showed that there was no statistically significant difference

in the socio-demographic variables between the two groups. This suggests that the randomization process was effective in ensuring that both groups had a similar distribution of probable confounders. Effective randomization of study participants into the comparison groups is considered the most effective way to eliminate the effects of confounding variables involving human subjects, which is critical to the validity of the study's findings [20]. The triple blinding employed in this study helped to prevent response or placebo-effect bias, selection bias, and ascertainment bias. Blinding has been adjudged as an effective method of reducing bias in clinical trials [21].

The findings from this study showed that there was no statistically significant difference between the two groups on the impact of malaria on the women studied, namely the levels of maternal

parasitaemia and maternal anaemia. This finding is different from that of Unger et al. [12], who conducted a randomized controlled trial comparing the effects of Sulphadoxine-pyrimethamine plus Azithromycin to Sulphadoxine-pyrimethamine plus Chloroquine. The difference between the two studies may be due to the different doses of azithromycin administered in their study, alongside the addition of chloroquine to SP in the other arm of the study by the authors. In the study by Unger et al., the women in the SPAZ group received a higher dose of Azithromycin 1g twice daily for two days, in addition to the standard dose of Sulphadoxine-pyrimethamine (1500mg/75mg), as opposed to the 500mg of Azithromycin used in this study. There were no other accessible randomized controlled trials with the same drugs and doses in both arms of the study for comparison with the findings of this study.

Similarly, the results of this study showed no statistically significant differences in the outcome measures used to compare the effects of malaria on the fetuses delivered. These outcome measures include placental parasitaemia, cord parasitaemia, fetal anaemia, and low birth weight. The findings of this study are in agreement with those of Hallamaa et al. [22], Lingani et al. [23], and Kimani et al. [24], who also reported no statistically significant differences in fetal outcomes, including low birth weight. However, the findings of this study differ from those of Unger et al. [14,25], and Luntamo et al. [26], who reported a statistically significant difference in placental parasitaemia and birth weight. These differences may be attributable to the different dosages of azithromycin used in the studies cited and the addition of other agents to SP. No untoward adverse effects were noted in either arm of the study, demonstrating the safety of the drugs administered in both arms.

The findings from this study showed no statistically significant difference between the two groups in the outcome measures of the impact of malaria on both the mothers and their fetuses. The clinical significance of the findings of this study is that Sulphadoxine-pyrimethamine with Azithromycin (SPAZ) is as efficacious and safe a chemoprophylactic agent for malaria in pregnancy as Sulphadoxine-pyrimethamine alone (SP) and hence may be used in place of SP as IPTp in areas with established resistance to SP.

The demonstrated effectiveness of the randomization process in this study, the triple

binding carried out to minimize the possible influence of bias and the measures instituted to minimize the effects of the anticipated limitations of this study make it most likely that the results and conclusions of this study are valid and generalizable to similar clinical settings in Nigeria and other countries where malaria in pregnancy remains endemic.

CONCLUSION

This study found no statistically significant difference in the efficacy and safety of Sulphadoxine-pyrimethamine with Azithromycin (SPAZ) and Sulphadoxine-pyrimethamine alone as chemoprophylaxis for malaria in pregnancy. It is concluded that Sulphadoxine-pyrimethamine with Azithromycin (SPAZ) is as efficacious and safe a chemoprophylactic agent for malaria in pregnancy as Sulphadoxine-pyrimethamine alone (SP) and hence may be used in place of SP as IPTp in areas with established resistance to SP.

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