Comparing Serum Haemoglobin Levels of Women who Received Intermittent Preventive Treatment (IPT) with Sulphadoxine Pyrimethamine (SP) and their Controls during Antenatal Care (ANC) in a Malaria Endemic African Community

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Abstract:

Background: The importance of optimal serum Haemoglobin (Hb) levels during antenatal periods need not be further overemphasized as it has been the clinical weapon against the menace of anaemia in pregnancy. Optimal Hb status helps a pregnant woman to enjoy an uneventful pregnancy course as well as to avert the problems of anaemia in pregnancy which may include intrauterine growth retardations (IUGR), preterm births, neonatal anaemias, increased admissions into special care baby units and even neonatal deaths.

AIM: This study compared the serum Haemoglobin levels of women who received Intermittent Preventive Treatment (IPT) with Sulphadoxine Pyrimethamine (SP) and those of their controls during antenatal care (ANC).

Method: This study was conducted at the Federal Medical Centre, Owerri (FMC) Imo State Nigeria. Owerri is in a typical malaria endemic setting in Africa. Ethical clearance and certification was obtained from the ethics committee of FMC, Owerri enabling commencement of longitudinal recruitment of participants after adequate counseling and informed consent involving both groups. It was a laboratory based, cross-sectional descriptive study involving 296 participants who clearly satisfied the criteria for inclusion for either the study or control groups. Recruited participants were followed up through their entire antenatal course till delivery to enable collection of blood samples for Haemoglobin estimation which was done using the Cyanmethemoglobin method as described by Cook in 1985. This method derives its principle from the fact that when blood is mixed with a solution containing potassium ferricyanide and potassium cyanide (Drabkin's solution), the potassium ferricyanide oxidizes iron to form methemoglobin. The potassium cyanide will then combines with methemoglobin to form cyanmethemoglobin (HiCN), which is a stable color pigment read photometrically at a wave length of 540nm.

Data Analysis: The data obtained was computed and analyzed using the computer Software Package for Social Science (SPSS) version 20.0 (SPSS, Inc, 2007, Chicago). Descriptive statistics (mean, standard deviation, range, percentages etc) were determined for continuous variables. P-value less than (<0.05) at 95% confidence interval was considered statistically significant.

Result: The mean haemoglobin value was higher among the study group than the control. Mean Hb of the study group was 14.70 ± 2.34 while the minimum and maximum serum Hb levels were 9.00 and 20.40 respectively. From the control group, the mean Hb was 11.95 ± 2.04 while the minimum and maximum serum Hb levels were 7.20 and 16.70 respectively. From the results above, the mean difference of 2.75 was found to be statistically significant with p value= 0.0001; 95% CI =1.275 – 1.647. This implied that evidence of significant effects was found on the Hb levels between the women that took IPT-SP compared to their counterparts that did not take it.

Keywords: **Haemoglobin, anaemia in pregnancy, Sulphadoxine-Pyrimethamine, antenatal course, malaria endeminicity, Cyanmethemoglobin method, potassium ferricyanide and potassium cyanide (Drabkin's solution).**

I. INTRODUCTION

Malaria is responsible for significant morbidity and mortalities worldwide to about the 40% of the world populace living in the malaria endemic regions of the world. Recorded malaria cases is estimated to be about 300–500 million as recorded annually, it is responsible for about 1.5–2.7 million deaths occurring each year (Abro et al, 2008; Kuthala et al, 2013).

To curtail this menace, the fight against malaria witnessed a major boost with the launching of Roll Back Malaria initiative in April 25, 2000 and the commitment of African leaders to fight the disease which kills over one million children and pregnant women every year (National malaria treatment guideline, 2011).

It is worthy of note that in areas of high or moderate transmission, infected women are hardly symptomatic and so do not present for treatment, prompting the World Health Organization to recommend for in such areas; a three pronged intervention approach aimed at helping to prevent malaria in pregnancy. The interventions include the use of insecticide-treated bed nets (ITNs), intermittent preventive treatment in pregnancy (IPT) and effective case management and treatment of malaria (Nehlen, 2000; WHO malaria prevention & control, 2004; Yeboah et al, 2016; Andrew vallely et al 2007 or http://www.malariajournal.com/content/6/1/16).

From available literature the haematological abnormalities associated with malaria infection include but not exclusive, to anemia, lymphocytosis, thrombocytopenia, and rarely disseminated intravascular coagulation (Facer, 1994; Kuthala et al, 2013), leucocytosis, leucopenia, neutrophilia, neutropenia and eosinophilia, and monocytosis also have been reported (Murphy and Oldfield, 1996; Jandle, 1996; Kuthala et al, 2013). Also in most high transmission areas, malaria is said to be associated with maternal anemia which when severe is potentially responsible for low birth weight (due to prematurity), intrauterine growth retardation and possible maternal deaths (Briand et al, 2007; Yeboah et al, 2016).

While the above reviewed studies aimed at revealing the effect of various artemisinin derivatives on global haematological parameters, this present study tries to elucidate the impact of Sulphadoxine Pyrimethamine (SP) on anemia prevention by assessing the serum haemoglobin (Hb) levels following ingestion of SP during pregnancy.

Asa and colleagues studied the efficacy of intermittent preventive treatment of malaria with SP in the prevention of anaemia in women of low parity in a low socio-economic, in malaria endemic settings. The study was an open randomized control trial which compared the incidence of anaemia among pregnant women on IPT for malaria using SP with those on Chloroquine (O O Asa et al, 2008). This present study is a cross sectional descriptive study aimed at assessing the levels of Hb following ingestion of SP, an intermittent preventive treatment regimen during pregnancy in women of varying parities as well as in a non randomized control trial setting. It is also not meant to compare the effects of SP with that of Chloroquine. Assessing the levels of Hb in women of varying parities is more embracing in knowing the exact effects of Hb in combating anemia in pregnancy. This was done in our present study.

While studying the Quality of Sulfadoxine-Pyrimethamine given as antimalarial prophylaxis to pregnant women in selected health facilities in central region of Ghana, a group of researchers noted that no statistical significant difference existed between the haemoglobin status of pregnant women who had malaria infection and those who did not have malaria. This showed that irrespective of malaria infection, the haemoglobin levels of the pregnant women were generally low. The multifactorial etiology of anaemia in pregnancy was confirmed in the study including iron deficiency, folate deficiency, poor diet, hookworm infections, and malaria itself (WHO Expert Committee on Malaria, 1986; Yeboah et al, 2016). In the study above, both women with malaria infection and those without the disease were recruited. There may be difficulty knowing the exact cause of the anemia necessitating the need for this current study which studied only women adjudged to be free from malaria infestation so as to test the effects of IPT-SP on haemoglobin.

In Uganda, Mbonye and co noted that Intermittent Preventive Treatment increased the mean hemoglobin by 6.7% ($p < 0.0001$) for all parities and by 10.2% among studied primigravids but the prevalence of severe anemia reduced the from 5.7% to 3.1% ($p < 0.04$). The study, as designed tested the community-based delivery system of IPT through traditional birth attendants (TBAs), community reproductive health workers (CRHWs), adolescent peer mobilizers (APMs) and drug-shop vendors (DSVs), to compare these with IPT at health units in an area of high malaria transmission (Mbonye et al, 2008). The use of these TBAs, DSVs CRHWs and APMs in the delivery of drugs to pregnant women may be complicated by a lot of factors and hence we decided to use only trained health professionals in health standard institutions for IPT-SP delivery services in this study.

From the foregoing, it can be deduced that no volume of study can undermine the need for continued evaluation of the relationship between Intermittent Preventive Treatment in pregnancy with Sulphadoxine-Pyrimethamine (SP) and anemia in pregnancy with Hb as the marker. This study hereby affirms that IPT-SP is still capable of curbing certain types of anemia in pregnancy. A lot still need to be done particularly now that SP resistance abound and on the other causes of anemia in pregnancy.

II. METHODS

Study Area:

Federal Medical Centre Owerri served as the study centre for this very research. The tertiary health centre is located in the heart of Owerri which is the capital city of Imo State of Nigeria, a heavy malaria endemic region located in the Sub Saharan part of Africa. Owerri is situated at 5.49^0 North Latitude, 7.03^0 East Longitude & 159 meters elevation above sea level. Owerri is a fairly big town in Nigeria having about 215038 inhabitants (www.maps-streetview.com/nigeria/owerri 2011). Malaria transmission is intense in most parts of the year owing to its geographical disposition. The infection is more from May to October which are the major rainy season months of the year with a seasoned reduction during the dry season months of November to April.

The study was carried out between June, 2015 and December, 2016 (18 months).

Ethical Consideration:

Application for study approval was also sought from the ethics committee of the Federal Medical Centre Owerri to enable commencement of bench work. Thereafter, ethical approval was gotten from the Ethics Review Committee of the same institution. The rationale for the study was explained to the subjects with the assistance of the residents and trained midwives of the institution. Our insistence on voluntary participation and participant anonymity was emphasized and also ensured while a written informed consent from each consenting pregnant woman was sought before sample collection.

Participant Recruitment and Sample Collection:

Participants included pregnant women who patronized Federal Medical Centre, Owerri for antenatal services during the period of the research. The recruited pregnant women had neither signs nor symptoms of malaria infection (from the history and examination) and no **parasitological diagnosis of malaria** as evidenced by the negative malaria parasite tests done at recruitment. Recruited participants who satisfied other aspects of the inclusion criteria were **recruited longitudinally** and must have witnessed quickening from about the 16 week up to 28 weeks of gestation. The sampling method used for the recruitment of participants adopted was the **Purposive Sampling Technique.**

Recruited women were followed up till delivery. Subsequent visits were arranged to coincide with the regular monthly antenatal visits. At such visits, interval history was taken and physical examination done while routine antenatal investigations done included Haemoglobin estimation and Urine analysis. Malaria Parasite test was done for suspected cases of malaria in the women and those who tested positive to malaria were withdrawn from the study. Until the desired sample size was reached, selected candidates who defaulted at any stage of the study despite adequate follow up were discarded and replaced.

Sample Collection:

Approximately, five millilitres (5 ml) of venous blood sample were collected from each participant into waiting ethylene diamine tetra acetic acid (EDTA) containing tubes by the researchers. We were assisted by trained medical laboratory scientists. All collected blood samples were stored on ice and transported to the designated parasitology / haematology research laboratory for analysis.

Laboratory Estimation of Malaria Parasites among Participants:

Giemsa stained thick blood films were prepared. The slides were duly processed and observed under the light microscope using ×100 objective lens (Baker, Silverton, Pallister, 1998; Adefioye et al, 2007; Yeboah et al, 2016). The number of malaria parasites seen were counted against 200 white blood cells (WBCs), then the parasite density was determined. A standard WBC count of 8000 per microlitre (µL) of blood was assumed for each of the participants. Assuming a total of ten (10) malaria parasites were counted against 200 white blood cells (WBCs), counting of the plasmodium malaria parasites was continued until the identification of 500 WBCs was gotten. A negative was concluded only if no malaria parasite was found after counting 500 WBCs (Coulibaly et al, 2007; Yeboah et al, 2016). Catigorization of Parasite density was done as follows:

1. 0 (no parasite),
2. 1–999, 1000–9999, and
3. ≥10,000 (Obonyo, 2006; Yeboah et al, 2016).

The above classification is appropriate since higher parasite densities corresponds to more severe acute phase of malaria infection (Edison et al, 2011; Yeboah et al, 2016).

An alternative way of categorizing malaria parasite density was as follows:

Microscopic blood film examination was done using magnifications of 10x, 40x and 100x objective lens, starting with the 10x and 40x objective lens to identify specific areas of the film to be viewed under the 100x objective lens. We examined for malaria parasites and pigments. The appropriate approximate number of parasites seen on viewing was reported (trophozoites, schizonts, and gametocytes) using the following criteria:

A. 1 – 10 malaria parasites per 100 high power field…… +

B. 11 – 100 malaria parasites per 100 high power field……++

C. 1- 10 malaria parasites in every high power field……. +++

D. More than 10 malaria parasites in every high power field……. ++++ (Baker et al, 1998; Cheesbrough, 2005, Chukwu et al, 2019).

Determination of Haemoglobin among Participants:

Determination of Haemoglobin, Hb was done using the Cyanmethemoglobin method as described by Cook, 1985).

Principle: The principle of this method derives from the fact that when blood is mixed with a solution containing potassium ferricyanide and potassium cyanide (Drabkin's solution), the potassium ferricyanide oxidizes iron to form methemoglobin. The potassium cyanide will then combines with formed methemoglobin to form cyanmethemoglobin (HiCN). This is a stable color pigment read photometrically at a wave length of 540nm.

Procedure: We did pipette 5 mls of Cyanmethemoglobin reagent into each test tube and added 20 µl of the appropriate sample into each test tube. Do not add anything other than the

Cyanmethemoglobin reagent to the waiting reagent BLANK. The test tubes were allowed to stand for about 10 minutes while the Absorbance was read off (A) in the spectrophotometer at 540 nm, zeroing the spectrophotometer with the BLANK solution.

The value of hemoglobin can now be derived from the formula below or from the previously prepared standard graph or table.

$$\text{Hemoglobin in gm/dl} = \frac{\text{Absorbance of the test sample}}{\text{Absorbance of the standard}} \times \text{Concentration of the standard} \times \frac{\text{Dilution factor}}{100}$$

(Cook, 1985).

Drug Availability and Distribution:

The drugs used for the Intermittent Preventive Treatment for malaria, Sulphadoxine-Pyrimethamine was procured by the Principal Researcher directly from the manufacturing Pharmaceutical company and given free of charge to the participants. This was to ensure compliance as well as make sure that the right drugs were used for the research. The SP was given to the participants free of charge and as Directly Observed Treatment Short Course (DOTS) so as to further ensure compliance.

Data Analysis:

The results obtained were presented as mean ±std. deviation and analyzed using the computer Software Package for Social Science (SPSS) version 20.0. (SPSS, Inc, 2007, Chicago). The descriptive statistics (mean, standard deviation, range, percentages etc) were determined for continuous variables. Student's t-test and one-way analysis of variance (ANOVA) was used for comparing mean values of both the study and control groups. The results obtained were presented as tables, histograms and box plots in the next section. All P-value results arrived at that were less than: **<0.05 at 95%** confidence interval were considered statistically significant.

III. RESULTS

A total of 456 antenatal women were assessed for eligibility, 56 women were excluded from the study while 400 questionnaires were eventually administered. A total of 296 finally completed the study comprising of equal numbers (148) each of study (case) and control groups.

The result of the participants recorded serum hemoglobin (Hb) levels indicated that the average Hb level was higher on the women that took IPT compared to the Hb levels recorded from the control group.

The mean haemoglobin level was higher in the study group 14.70 ± 2.34 while the minimum and maximum serum Hb levels were 9.00 and 20.40 respectively. This can be compared to the results gotten from the control group where the recorded mean serum Hb level was 11.95 ± 2.04 while the minimum and maximum serum Hb levels were 7.20 and 16.70 respectively. From the results above, the mean difference of 2.75 was found to be statistically significant with p value= 0.0001; 95% CI =1.275 – 1.647. This implied that evidence of significant effects was found on the Hb levels between the women that took IPT-SP compared to their counterparts that were non Intermittent Preventive Treatment compliant. The IPT drug, SP must have accounted for this difference (see table 1).

Also from figures 1 & 2 below; the comparative Box plot represented the serum haemoglobin status in both the study and the control groups. The mean values were quite different from each other as seen in the study (case) and control groups. The maximum and minimum levels of serum haemoglobin were also noted as the upper and lower class limits. Also two outlier observations were noted from the box plot as well representing values that probably fell outside the expected ranges. In addition to the box plot, the histogram below indicated similar result for the two groups.

IV. DISCUSSION

The mean serum Haemoglobin (Hb) level in the study (case) group was 14.7 while in the control, it was 11.95. The observed difference was found to be statistically significant (p= <0.0001) with odds ratio 1.41 (CI of 95% 1.250-1.579). The results of the serum Hb as determined showed that for the study group, the range of Hb was 9.0 - 20.4 g/dl with a mean of 14.7 ± 2.34 while for the control group, the Hb values ranged from 7.2 - 16.7 g/dl with a mean of 11.95 ± 2.04. The difference in Hb levels between the study and control groups was found to be clearly statistically significant (p= <0.0001) and did compare favourably with the finding by Megnekou and co in Cameroun.

The impact of placental Plasmodium falciparum malaria on the profile of some oxidative stress biomarkers in women living in Yaounde, Cameroon was studied by these scholars. They analyzed the Hb values between malaria infected and malaria non-infected women and noted that the difference between the mean values of the Hb of the two groups was statistically significant (p <0.001). The mean Hb values were 10.4 (7.5-13.6) and 12.8 (9.9-16) for the malaria infected and malaria non-infected women respectively (Megnekou et al., 2015).

Another group of researchers studied the protective responses to sulfadoxine-pyrimethamine (SP), as an intermittent presumptive treatment (IPT) for malaria among pregnant women attending antenatal care at the primary health centre in Sagamu, Lagos State Nigeria. The median packed cell volume at enrolment gotten from the study was similar in the women enrolled in the sulfadoxine-pyrimethamine treated group, SPTG and Non sulfadoxine-pyrimethamine treated group, NSPTG (33% [11.0 g/dl], range 21 - 40, versus 32% [10.7 g/dl], range 17 -43, respectively, P= 0.2) and at follow-up (34% [11.3 g/dl], range 31 - 41, versus 35% [11.7], range 30 -

40, respectively, P= 0.9) (Ahmed et al., 2010). The observed differences in their results were not statistically significant and did not compare with the result of this study.

The efficacies of Intermittent Preventive Treatment for malaria in pregnancy using Sulphadoxine-Pyrimethamine in the prevention of anaemia in pregnancy among women of low parity in a low socio-economic, malaria endemic setting was also evaluated by another study. This study was an open randomized control trial that compared the incidence of anaemia among pregnant women placed on intermittent preventive treatment with Sulphadoxine-Pyrimethamine (IPT-SP) with those placed on Chloroquine (CQ). The primary outcome measure was essentially anaemia (haematocrit <30) at 34 weeks of gestation. Thirty-three (22.6%) and 52 (37.1%) women in the study and control groups respectively, had anaemia (protective efficacy 49.5%, p= 0.01). However, with multivariate analysis, and controlling for the possible confounding effects of education, parity, haemoglobin level at booking and malaria parasitaemia in the peripheral blood, the observed difference in the incidence of anaemia in the two groups remained significant (p= 0.01; odds ratio = 0.5; 95% confidence interval = 0.29-0.85 (Asa et al, 2008). These finding compared favourably with those of this study.

The results from this present study also compared favourably with the findings from the study by Mbonye et al, in Uganda. In their study, IPT was demonstrated to increase the mean hemoglobin by 6.7% ($p < 0.0001$) for all parities and by 10.2% among primigravidae. In that study too, IPT was found to reduce the prevalence of severe anemia from 5.7% to 3.1% with a P value of < 0.04 (Mbonye et al, 2008).

V. CONCLUSION

From the results of this study and supported by the results from other authors/researchers involved in the IPT-SP evaluation, it can be concluded that Intermittent Preventive Treatment regime with sulphadoxine-pyrimethamine was still practically effective in decreasing the risks of anaemia in pregnant women. This is evident from the participants of this study as well as those living in other malaria endemic areas (Falade et al., 2007).

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CONFLICT OF INTERESTS

The authors of this journal article hereby declare that there is no conflicts of interests.

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FIGURE LEGEND SECTION

Table 1: The Hemoglobin concentration of the participant in both the study (treatment/case) and control groups

variable	n	min	max	mean	Std.dev	coef	S.e.	p-value	OR	95% C.I.for OR	
										Lower	Upper
Case	148	9.0	20.4	14.7	2.34						
Control	148	7.2	16.7	11.95	2.04	0.340	0.060	<0.0001	1.41	1.250	1.579

Figure 1 (Box plot): Serum levels of Hemoglobin (HB) of the participants in both the study and control groups

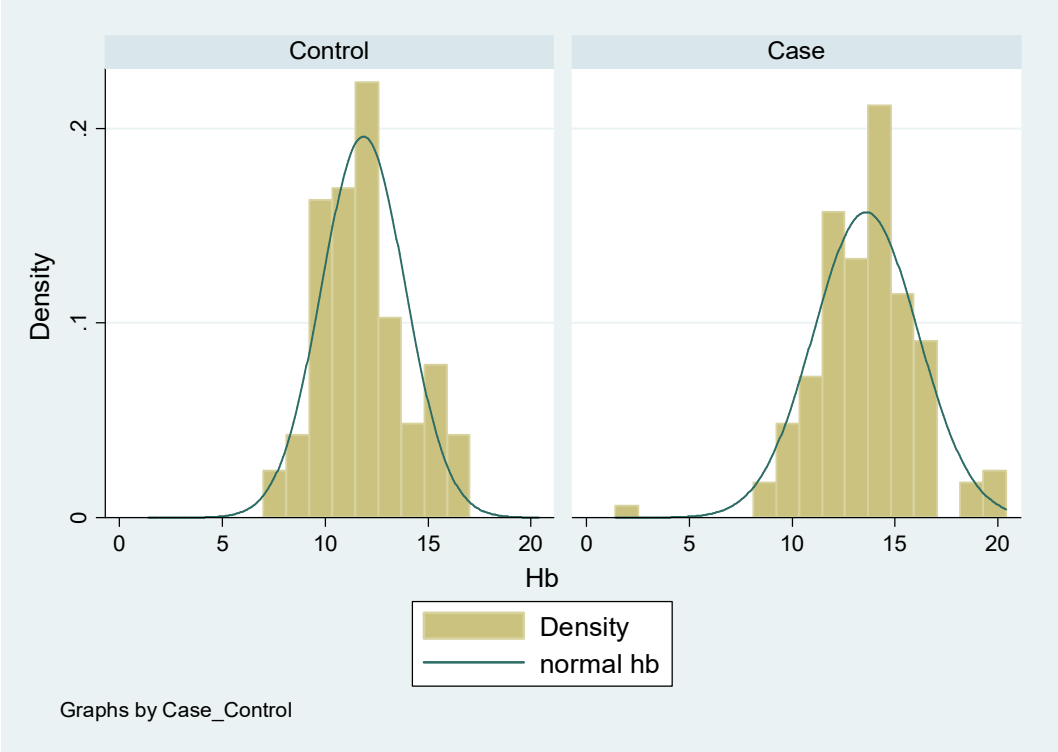

Figure 2 (Histogram): The Hemoglobin (HB) levels of participants in the study /treatment and control groups

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