MONTHLY SULPHADOXINE-PYRIMETHAMINE COMBINATION VERSUS DAILY PROGUANIL FOR MALARIA CHEMOPROPHYLAXIS IN SICKLE CELL DISEASE: A RANDOMIZED CONTROLLED STUDY AT THE JOS UNIVERSITY TEACHING HOSPITAL.

[1]Dawam JA, [2]Madaki JKA, [1]Gambazai AA, [3]Okpe ES, [1]Lar-ndam N, [4]Onu A, [2]Gyang M.

[1.]Department of Family Medicine, Jos University Teaching Hospital (JUTH) Jos, Plateau State, Nigeria.
[2.]Department of Family Medicine, University of Jos, Plateau State, Nigeria
[3.]Department of Paediatrics, University of Jos, Plateau State, Nigeria
[4.]Department of Family Medicine, Garki Hospital, Abuja, Nigeria

ABSTRACT

BACKGROUND:
Malaria carries a high case fatality among patients with sickle cell disease. In Jos University Teaching Hospital, at the time of this study, the use of Proguanil was the acceptable mode of chemoprophylaxis for preventing malaria in these patients. Intermittent Preventive Treatment (IPT) with Sulphadoxine-Pyrimethamine [SP] has shown great potential for reducing the prevalence of malaria and anaemia among pregnant women, infants and travellers. We hypothesised that monthly SP was superior to daily Proguanil in reducing malaria parasitaemia, clinical malaria attacks and sickle cell crises in such patients.

OBJECTIVE:
To assess the efficacy and affordability of monthly SP versus daily Proguanil for malaria chemoprophylaxis in patients attending Sickle Cell Clinic at Jos University Teaching Hospital, Plateau State, Nigeria.
Methods: One hundred and fifty four patients [114 children and 40 adults] with Sickle Cell Disease in their steady state were randomized to monthly SP or daily Proguanil for malaria chemoprophylaxis. Active detection of malaria parasite in the peripheral blood and packed cell volumes were done at each monthly visit to the clinic over a period of three months. The primary outcome measure was the proportion of patients with malaria parasite in the peripheral blood at the end of 3 months. The secondary outcome measures included episodes of clinical malaria attacks, frequency and type of sickle cell crises and adverse effects of the medication.

RESULTS:
Ninety four percent [72/77] of patients in the SP group and 91% [70/77] in the Proguanil group respectively completed three months of follow up. SP reduced the prevalence of malaria parasitaemia by 25% [(14%) 10/72] compared to 6.4% [(30%) 21/70] in the proguanil group. [X^2 54; p = 0.01]. Seventeen percent [12/72] of the patients receiving monthly SP had malaria attacks compared to 57% [40/70] on prophylaxis with Proguanil. [X^2=25; p< 0.0003]. Thirty three percent [24/72] of the patients receiving SP had at least an episode of bone pain crises compared to 69% [48/70] of the patients receiving Proguanil. [X^2 =17.6; p<0.0001]. SP was 8 times cheaper than Proguanil.

CONCLUSION:
Monthly chemoprophylaxis with SP was more efficacious than daily Proguanil in reducing the prevalence of asymptomatic malaria parasitaemia, clinical malaria attack and sickle cell crises in patients with sickle cell disease. SP was 8 times cheaper than Proguanil. No significant side effect was recorded in both groups. The current practice of routinely prescribing daily Proguanil to SCD patients for malaria chemoprophylaxis needs to be reviewed.

Key Words: Sickle Cell Disease, Malaria Chemoprophylaxis, sickle cell crisis

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INTRODUCTION

Sickle cell disease, a condition resulting from the inheritance of two abnormal Hb genes in which at least one is the sickle haemoglobin, has become one of the most important scourges of our time.[1]

Sickle cell disease was first observed by Dr JB Herrick in 1904 in the blood of an anaemic West Indian medical student as described in a paper published in 1910.[2] Thus the disease is occasionally called "Herrick's syndrome." The disease was later named "Sickle cell anaemia" by Vernon Mason in 1922.[3] Since then giant strides have been made in our understanding and knowledge of the disease.[1]

Correspondence: Dr Madaki JKA,
Department of Family Medicine, Jos University Teaching Hospital.
E-mail: wankarani62@gmail.com

The highest frequency of sickle cell disease remains in tropical regions, particularly sub-Saharan Africa, India and the Middle East. About 120,000 infants are born each year with sickle cell disease in Africa. The majority have sickle cell anaemia (Hb SS), but Hb SC and sickle cell β-thalassaemia (Hb S/B+ -thal) are also relatively common in West Africa.[4]

It has been reported that the prevalence of sickle cell disease (SCD) rises from the time of birth until about five years of age, after which there is no further change.[1] This is because most of diagnoses of SCD are made before the age of 5 years.

It is estimated that in Nigeria alone, about 30,000 children are born each year with sickle cell disease while one in 375 blacks in America has Hb SS.[5] The prevalence of SCD in Nigeria is about 3% of the population.[1,3,5,6]

Nigeria, with a population of about 140 million, is the most populous country in Africa. It has the largest concentration of patients with sickle cell disease in the whole world.[8]

Malaria is one of the commonest precipitating factors in sickle cell disease crises in malaria endemic countries of sub-Saharan Africa and Southeast Asia.[1,4]

The prevention of malaria among those who are at high risk of death or serious morbidity such as pregnant women is practiced in many parts of the world where malaria is common.[9,10]

One group at high risk of malaria is those with SCD and although malaria prevention is widely used among this group, there is little evidence base for the current practices in Nigeria.[5,10]

The increased mortality and morbidity among SCD individuals that are attributable to malaria are potentially preventable with available tools such as insecticide treated bed nets (ITNs), chemoprophylaxis and/ or intermittent preventive treatment (IPT).[10]

SCD individuals can have crises precipitated by malaria and bacterial infections such as pneumococcus and Haemophilus influenzae, to which they are susceptible due to impaired immune function and functional asplenia. These factors are perhaps the most important ones in many developing countries where the S gene is highly prevalent.[3,10]

Evidence suggests that malaria probably due to fever and dehydration is one of the most common cause of SCD crises in malaria endemic areas such as Africa and Nigeria in particular. It has been implicated in many cases of hyper-haemolytic anaemia.[10]

Between 25 and 50% of fever among homozygous SCD patients in some part of Africa is caused by malaria, while about 20% of severe anaemia is also due to malaria.[10,11]

While it is agreed that the mortality and morbidity is increased in homozygous SCD individuals if they are infected with malaria, there is ample evidence that the S trait accounts for increased survival of children in early life in malaria endemic areas.[10,12]

This necessitates life long recommendation of malaria chemoprophylaxis for SCD individuals living in malaria endemic zones by health professionals.[1,13]

Randomized, open label controlled studies to evaluate the effect of pyrimethamine versus proguanil in preventing malaria in children with sickle cell disease have shown that chemoprophylaxis against malaria is beneficial to sickle cell disease patients through reduction in the frequency of clinical malaria attacks, anaemia and other forms of sickle cell crises.[13,14]

These studies also showed that both proguanil and pyrimethamine protect children with sickle cell disease from the complications of Plasmodium falciparum infection, despite persistent parasitaemia. The use of proguanil was more potent than pyrimethamine in preventing bone pain crisis in the same studies.[13,14]

The current practice is to give all affected individuals a daily dose of 1.5mg/kg of proguanil. Proguanil-resistant strains of P. falciparum had been identified in Nigeria as far back as 1949.[1] It appears this has been on the increase leading to reduced effectiveness of proguanil prophylaxis.[10]

A recent study conducted by Kitola et al in Ibadan, Nigeria and published in 2007 evaluated the prevalence of asymptomatic malaria parasitaemia in sickle cell disease patients. They found a prevalence of asymptomatic malaria parasitaemia to be 24% among sickle cell disease patients on malaria prophylaxis with proguanil which was the same prevalence amongst those not taking prophylaxis. Another study conducted in Enugu by Juwah AI et al found 17.4% prevalence of malaria parasitaemia among children presenting with anaemic crises even though they were on routine proguanil prophylaxis.[12] This suggest some degree of inadequate prophylaxis by proguanil at the applied dose level (1.5mg/kg to a maximum of 200mg).[1]

Despite these earlier observations, no recent attempt has been made to evaluate the impact of a daily regimen of proguanil on compliance, affordability and efficacy.[1,10]

The long-term use of malaria chemoprophylaxis by sickle cell disease patients confers loss of immunity to malaria; hence the consequence of non-compliance may be as grave as that of acute severe Plasmodium falciparum infection and its complications.[1]

With the increasing incidence of chloroquine resistant strains of plasmodium species, chemoprophylaxis with chloroquine is no longer advisable.[16,17]

Sulphadoxine-pyrimethamine (SP) combination for malaria chemoprophylaxis has been shown to be effective and more potent in pregnant women, travellers, under five children and infants.[18,19,20,21]

A randomised double blinded controlled trial by Nakibuuka V, et al carried out in Uganda and published in 2010 showed that SP reduced prevalence of malaria by 50% compared to chloroquine. Six percent (7/122) of the children receiving weekly chloroquine had malaria related admissions compared to 2.5% (3/120) on presumptive treatment with SP. There were no serious drug site effects reported in both treatment groups.[22]

There are no published studies in Nigeria evaluating the efficacy, compliance, affordability and the tolerability of this drug in sickle cell patients. Its single monthly dosing may promote adherence as well as reduce cost and the pill burden on sickle cell disease patients.

Presently, one month adult course of daily proguanil (200mg) cost about six hundred Naira (N 600), while an adult dose of SP cost between thirty and seventy Naira (N 30 - N 70) per month depending on the brand.

METHODS.

This study was carried out at the Jos University Teaching Hospital [JUTH] which is a 525 bed hospital. It offers primary, secondary and tertiary medical services to Plateau state and the neighbouring states.

The study was carried out between August and December 2009. It was commenced at the peak of the rainy season when malaria transmission was high.

One hundred and fifty four patients [114 children and 40 adults] with Sickle Cell patients were needed to detect a 20% reduction in malaria parasite between the two groups.

Exclusion.

1. Those with known history of hypersensitivity to sulphonamide group of drugs or proguanil.
2. Sickle cell disease patients with reported history or diagnoses of G-6PD deficiency.
3. Sickle cell disease patients whose illness required admission.

Ethical consideration

An approval was obtained from the JUTH Ethical Committee and a signed consent was obtained from eligible consenting patients or care givers for subjects less than 18years.

Recruitment and allocation.

Consecutive patients attending the SCD clinics were assessed and those that met the study criteria were recruited and randomised into two groups. Randomisation was done using Open Epi generated random numbers which were placed separately in opaque envelopes. All patients picked numbers from these envelopes and those with odd numbers were allocated to a group while those with even numbers were allocated to the second group. The randomisation was done in blocks of 30 for children and blocks of 10 for adults. The ratio of SCD patients seen on each clinic day in children and adult clinics was 3:1 (60 versus 20) respectively which informed the decision of the investigator to recruit 3 children to 1 adult.

The participants were recruited over a month. The sickle cell clinic visits were every Wednesdays and Fridays for children and adult respectively.

Data collection.

Semi-structured, pre-tested questionnaires were administered to eligible consenting patients/parents at the beginning, during follow up and at the end of the study by the investigator.

Information was collected on socio-demographic factors including the educational level of patient/parents, employment status, income of patient/parents (both parents), age at first diagnosis of sickle cell disease and symptoms that led to first diagnosis. Other documentation included study number, hospital number and age of patient, sex, telephone number of patient or parents in the case of children.

Further information was collected on frequency of crisis, type of crisis, the use and frequency of malaria prevention drugs, use of folic acid supplementation, use of untreated and insecticide treated bed nets, symptoms of malaria and tolerability of malaria prevention medication. Further information was

collected on body temperature, weight, height, packed cell volume, malaria parasite and splenic size.

Group health talks on the importance of adhering to prophylactic medications, the use of insecticide-treated bed nets and environmental sanitations were given to patients and their relations that accompanied them to the hospital. This was re-enforced at the time of administering the questionnaire and at each follow up visit.

Each patient was then sent to an intern pharmacist for his/her folic acid and malaria prevention drug before seeing their managing Physician who only prescribes any additional treatment the patient may need. These procedures were repeated at each follow up visit which was every 4 weeks for three months.

3.2.0. Interventions.
Eligible consenting patients were randomised to:
1) Monthly sulphadoxine-pyrimethamine (experimental) arm.
2) Daily proguanil (control) arm.

Treatment allocations was prepared in a series of opaque envelopes and administered by a third party (the Pharmacist).

The investigator was blinded on which drug each patient was taking until data collection was completed. Adherence to medication was ensured by patient swallowing their monthly medication in the presence of the pharmacist [SP group], the same applies to the first dose of proguanil. Further adherence to proguanil was evaluated by checking the pill boxes of patients during their next follow up visits. Children who could not swallow tablets were administered crushed tablets dissolved in clean water.

Drug dosages.
1. Daily proguanil (1.5mg/kg) to a maximum of 200mg (manufactured by Mancare Pharmaceuticals).
2. Monthly sulphadoxine-pyrimethamine at dosages of 25mg/kg of sulphadoxine and 1.25mg/kg of pyrimethamine manufactured by Swipha (up to a maximum dose of 3 tablets).

Statistical methods.
Data was analysed after it was entered into Epi info version 3.5.1 (CDC, Atlanta, Georgia, USA.). Analysis was by intention to treat. Chi-square was used to compare the proportions of patients with asymptomatic parasitaemia, acute clinical malaria attacks and frequency of sickle cell crisis in the two groups.

Students''t' test was used to compare the mean values of PCV, PCV change, mean temperature, mean weight and mean height in the two groups. Univariate analyses was used to determine the influence of parents income/mother's educational level, the use of insecticide treated bed nets, and the two interventions on risk of asymptomatic parasitaemia, clinical malaria attacks and frequency of crises. $p< 0.05$ was considered statistically significant.

RESULTS.
Ninety four percent [72/77] of patients in the SP group and 91% [70/77] in the Proguanil group respectively completed three months of follow up. Table 2 shows that the prevalence of asymptomatic malaria parasitaemia was 37.7% (58/154) at recruitment [30 patients (39%) from the SP arm and 28 patients (36.4%) from the proguanil arm].

Figure 3 shows that 16.7% (12/72) of participants in the intervention group had at least 1 episode of clinical malaria attack compared to 57.1% (40/70) of participants in the control group (Chi-square 25.1); $P<0.0003$. At the end of the study, 33.3% (24/72) of the participants had at least one episode of bone pain crises in the intervention group compared to 68.6% (48/70) participants in the control group (chi-square 17.6); $p<0.0001$ (figure 4)

The mean packed cell volume (PCV) of the control group and the intervention groups at recruitment were 22.96 ± 3% and 23.0 ± 2% respectively. At the end of the study, the mean PCV was 23.1 ± 3% and 24.0 ± 2.9% in the control and intervention groups respectively. ('t' test = 1.9); P-value = 0.29. The PCV range was 16-38% (table 3).

Although there was a statistically significant increase in mean PCV change (PCV 3 months-PCV day1) in both study groups at the end of the study, there was no statistically significant change in the mean PCV between the two groups (table 4).

The average cost of purchasing malaria prevention drugs was fifty eight naira (N58.00) per person for a month in the intervention group (N7.50k- N100.00k), and four hundred and fifty naira (N450.00) per person for a month in the control group (N150.00k-N750.00k).This means that proguanil was 8 times more expensive than SP.

Discussion
There was a 25% reduction in malaria parasitaemia in the peripheral blood in the intervention group [14% (10/72)] compared to 6.4% in the control [30% (21/70)], Chi-square=54; p=0.01

This is similar to the result of Nakibuuka et al from Uganda, even though their study compared weekly chloroquine and monthly SP for malaria prophylaxis in sickle cell disease patients.[22]

Although there was 6.4% drop in the prevalence of asymptomatic malaria from the base line in the Proguanil group, this could be attributed to the adherence counselling given to all patients at recruitment and follow up visits. Adherence was further re-enforced by counting the pill boxes at subsequent follow up visits for the Proguanil group which improved the adherence from 16% at base line to about 98% at the end of the study although it was not possible to ascertain whether they were really taking the drug or just bringing empty pill boxes to the clinics. There was a statistically significant reduction in the episodes of sickle cell disease crises in the intervention group (33%) as compared to the control group (69%). Chi-square=17.6; p<0.0001.

There was also 41% reduction in the episodes of clinical malaria attack in the intervention group (16%) compared to the control group (57%). Chi-square=25; P<0.0003, which was statistically significant. These findings are similar to the 40% reduction in malaria attacks by SP compared to chloroquine documented by Nakibuuka et al in Uganda.[22]

This difference in efficacy between the two drugs could be explained by the fact that resistance to prophylactic dose of proguanil is higher probably due to poor adherence[5] compared to SP.

The other reason is that SP has a longer half life and its terminal elimination phase normally exceeds the minimum parasiticidal concentrations which is the lowest concentrations that give maximum effect]. In contrast this does not occur in proguanil.

While SP may have failed as a mono therapeutic agent, it is still effective for prophylaxis. Several studies from Nigeria, Ghana, Mozambique and Tanzania have documented its usefulness in prophylaxis and particularly in reducing malaria episodes even in areas where resistance is high.

There was a statistically significant increase in mean PCV change (PCV 3 months-PCV day1) in both study groups at the end of the study. This could be due to the reduction in malaria parasitaemia documented in the two groups at the end of this study probably due to improved adherence mentioned earlier.

There was no statistically significant change in the mean packed cell volume (PCV) between the intervention group and the control group at the end of 12 weeks (23.1 ± 3% versus 24.0 ± 2.9%, p = 0.97). This is probably due to the anti- folate activity of both drugs.

Although forgetfulness rather than cost was the major reason for poor adherence to proguanil in this study, the cost of proguanil per person per month was about eight (8) times that of SP (N58.00k for SP versus N450.00k for proguanil). In Nigeria where poverty is endemic, a less expensive but effective drug like SP will be of economic advantage in reducing the financial burden of these patients and their family.

In addition to the potential to reduce the financial burden of most families with SCD patients, SP as a monthly medication can reduce the problem of adherence to malaria prevention drugs in sickle cell disease patients. Adherence could further be strengthened by making the administration of this drug a form of directly observed therapy (DOT) in a four weekly follow up visit.

Conclusion

SP prophylaxis in SCD has demonstrated superior efficacy and similar tolerability compared to Proguanil by significantly reducing the prevalence of malaria parasitaemia, episodes of clinical malaria attacks and much of SCD crises. SP is 8 times cheaper than Proguanil. No significant side effect was recorded in both groups.

This study has shown that adherence is very poor with a daily malaria prevention drug like Proguanil, however this can be improved by giving adherence counselling at each clinic visit as was done in this study (adherence improved from 16% at base line to 98% at the end of the study).

There was no significant change in the mean packed cell volume and drug side effects between the groups.

Competing Interest: we the authors hereby declare that we have no competing interest.

Table 1: Physical and Socio-demographic characteristics of participants at recruitment

Variable	SP	Proguanil	p value
Sex			
Male	40	39	0.74 ‡
Female	37	38	
Mean age(months)	129.9±91.9	149.8±113.7	0.27*
Mean wt(kg)	31.7±17.8	35.5±18.2	0.39 *
Mean ht(cm)	119.2±36.2	121.6±37.6	0.27 *
Mean parent income[N]	37798.0±2496.5	37221.±24139.6	0.89*
Mean age at Diagnosis (months)	15.40.89±18.6	18.2±22.0	0.30*

‡Chi-square test, * 'T' test

Table.2. Laboratory characteristics of patients at recruitment

Variable	SP	proguanil	p value
MP			
positive	30	28	0.86‡
Negative	47	49	
Mean PCV (%)	23.0	22.96	0.26*
Prevalence of Mp	39%	36.4%	

*** 'T' test, ‡Chi-square test**

Figure 1

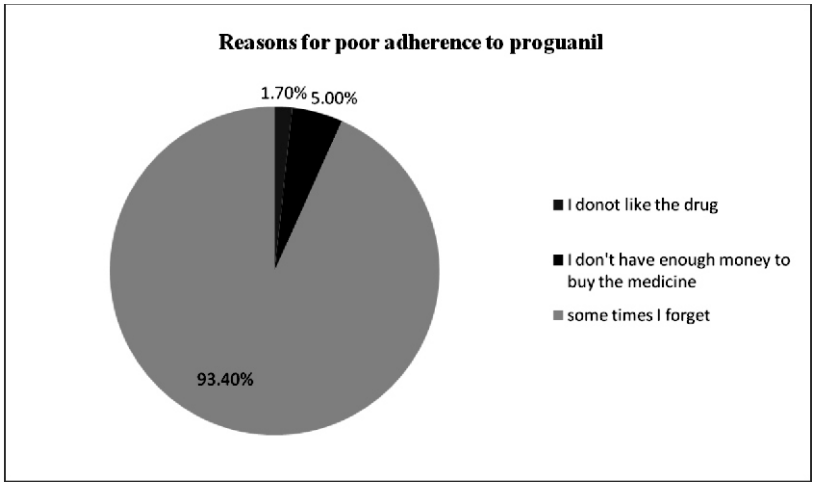

Figure 2

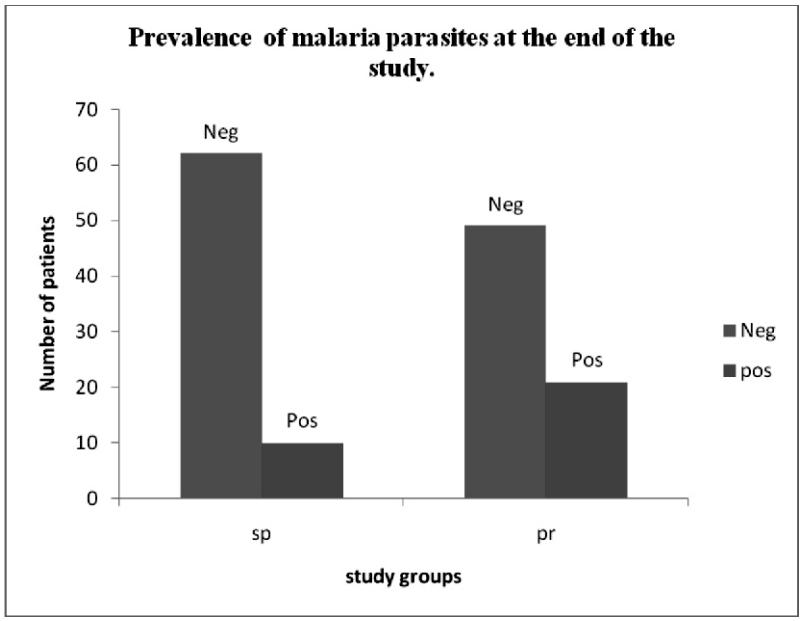

Figure 3

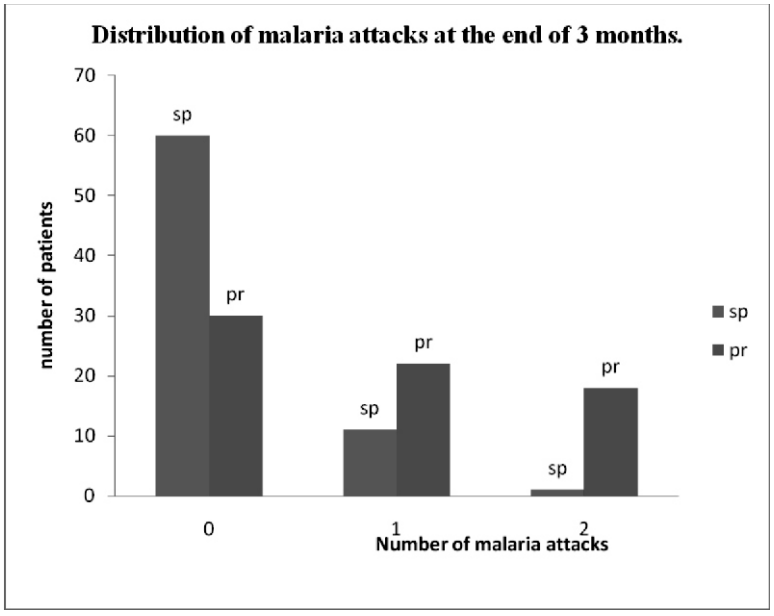

Figure 4

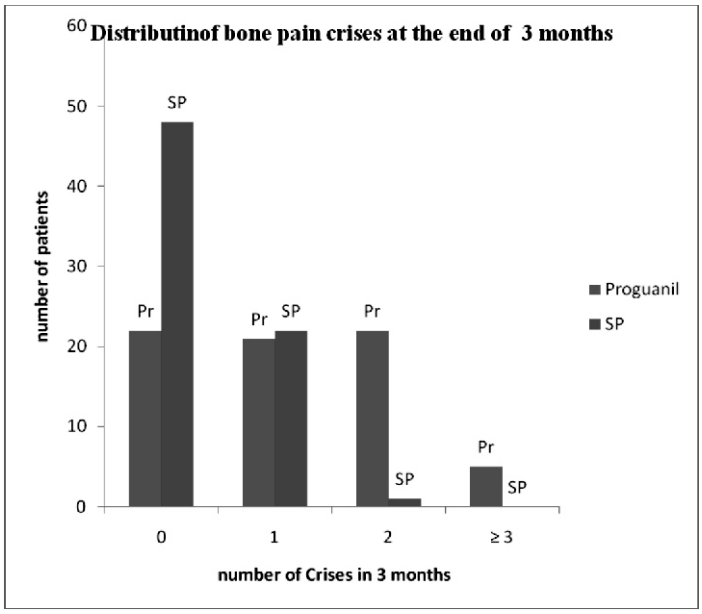

Table 3. Mean PCV of patients in the 2 groups at recruitment, follow up and 3 months.

Mean PCV	SP	Proguanil
Day1	23.0±2%	22.963%
1 month	23. **1** ±3%	22.9±4%
2 months	23.1±**2%**	22.3±3%
3 months	24.0±**3%**	23.1±**3%**

Table 4. Mean PCV change (PCV 3 months - PCV day1) in the two groups

	Mean PCV difference	p-value	CI
SP	0.86	<0.001 *	[0.71, 1. 37]
Proguanil	0.79	<0.001 *	[0.32, 1.32]

*** paired 'T' test.**

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