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Determination of Effect of Home-Based Oral Chloroquine Treatment on Haematological Indices of *P. falciparum* Malaria in Children under 5 Years in Jos Metropolis

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Abstract

Background: The incidence of *P. falciparum* malaria is characterized by high rates of morbidity and mortality in under 5 children; a trend reportedly prevalent in tropical and subtropical countries including Nigeria, and recently observed in Jos metropolis, has to date defied all constructive, preventive and drug therapy intervention measures and consequently continues to constitute a serious public health problem in this most vulnerable group. **Objective:** The aim of this study was to determine certain haematological indicators of malaria parasite infection; their role in the clinical manifestation of *P. falciparum* malaria and effect of first line oral chloroquine treatment in children under 5 years attending Jos University Teaching hospital and OLA Hospital in Jos metropolis. **Method:** This is a cross-sectional study of 93 malaria and non-malaria children, age 1 - 59 months attending Jos University Teaching Hospital (JUTH), Jos and OLA hospital, Jos, North Central Nigeria. Malaria diagnosis was carried out using microscopical examination of Leishman's stained thick and thin blood films and complete blood count was done using Beckman Coulter Analyzer. **Results:** The mean percentage lymphocyte value of chloroquine treated children (39.28% ± 7.45%) was significantly lower than the control (66.38% ± 2.27%). The mean granulocyte value of chloroquine treated children (51.07% ± 6.40%) was significantly higher than the control (26.69% ± 2.43%). Red Blood Cell (RBC) counts (4.01 ± 0.21 × 10^6/μL), Haemoglobin concentration (9.60 ± 0.51 g/dl) and Haematocrit (30.97% ± 1.43%) of chloroquine treated children were significantly higher than corresponding values in untreated malarious children, but not significantly different from values obtained in non-malaria control children. The RBC counts (2.92 ± 0.39

$\times 10^6/\mu L$), Haemoglobin concentration (7.23 ± 1.01 g/dl) and Haematocrit (23.70% ± 3.37%) obtained for untreated malarious children were significantly lower than corresponding values in the non-malarious control children. **Conclusion:** The pattern of the results obtained in this study suggests that home-based, first-line oral chloroquine treatment 24 hours prior hospital admission decreases the lymphocytes production and elevated production of granulocytes with attendant consequences on their biological functions. The chloroquine treatment seems to protect the red blood cells against the destructive effect of malaria. The haemoglobin concentration of 7.23 ± 1.01 g/dl obtained in untreated malaria children when combined with results of red blood cells; differential analysis indicates a mild, normocytic, normochromic anaemia due to haemolysis. This study demonstrates the beneficial effects of first aid, home-based oral chloroquine use. Rational use of chloroquine needs to be re-evaluated and encouraged in this group of children.

Keywords

Malaria, Chloroquine, Children, Hospital, Treatment

1. Introduction

Plasmodium falciparum malaria is a leading cause of admission of children under 5 years in Nigeria [1] as in many African hospitals and major cause of their death [2] [3] [4] [5]. Despite the existence of effective treatment and protective measures, malaria continues to be of concern, with high mortality in severe malaria [6] [7] [8] [9]. A similar trend is being observed around Jos metropolis of Plateau State, Nigeria [10] [11] [12]. In 2010, prevalence of *Plasmodium falciparum* infection in children in Plateau state was reported to be 36.6%, and *Plasmodium malariae* infection was only 1.4%, while prevalence of anaemia was 57.1%, n = 4209 [13]. Despite the mass Long Lasting Insecticide Nets (LLINs) distribution and utilization campaign by the global malaria action plan in many parts of Nigeria [14], the high prevalence of *P. falciparum* infection and anaemia in Plateau state still persists [15].

Oral chloroquine has long been used for the treatment or prevention of malaria. It is relatively cheap, easy to administer, and widely distributed in most parts of Nigeria. Following the emergence of widespread resistance to chloroquine by malaria parasite *Plasmodium falciparum*, the effectiveness of chloroquine against the parasite has declined [16] [17]. Over the years, many new and effective antimalaria drugs have been used individually or in combinations such as artemisinin-based combination therapy (ACTs) in the treatment of malaria. However, these drugs are expensive for most of the poor population affected and are not readily available in the rural areas where malaria is endemic.

The global malaria action plan and global anti malaria drug policy to date have failed to eliminate the high morbidity and mortality in children under 5

years, with *P. falciparum* malaria. Despite the national policy of ACTs as the first-line treatment of uncomplicated malaria, the Nigeria Malaria Indicator Survey (MIS) 2010 report indicates that over 70% of children treated for malaria in Nigeria received chloroquine.

Recent studies have reported re-emergence of sensitivity of malaria parasite to chloroquine in some areas where resistance was once prevalent, and despite the malaria parasite resistance, chloroquine still has significant influence on many aspects of pathogenesis of malaria [18] [19]. Home-based treatment of children with chloroquine is prevalent in the study area. Therefore, in this work, changes in some selected haematological indices in response to the effect of home-based chloroquine treatment of children infected with *p. falciparum* malaria were assessed with the aim of looking at the suitability of administering chloroquine as a first intervention before presenting the patient at the hospital.

2. Materials and Methods

2.1. Study Design

The study was design to investigate the effect of first aid, home-based oral chloroquine treatment within 24 hours prior to hospital presentation, on the clinical manifestation of malaria in the hospital. To this effect, the work was aimed to determine changes in levels of certain haematological indices of *P. falciparum* malaria in the uncomplicated disease and severe disease state. To achieve these study objectives, assay for red blood cells count, white blood cells count and their respective differential counts were carried out.

The working interval of within 24 hours period between the home-based oral chloroquine administration and hospital presentation is an average time interval needed in the study area for the transfer of the malaria child from home to the hospital in situations where immediate medical attention or access to medical facility is not possible.

2.1.1. Home-Based Chloroquine Treated Malaria Subjects, Chloroquine Dosage and Administration

These are children that were positive for malaria parasite screening on hospital admission. Oral chloroquine was administered to the subjects at home by the mother, following suspected malaria symptoms. The administration of chloroquine treatment was within 24 hours prior to hospital admission and malaria parasite screening. These home treated subjects have no history of any other medication in this particular episode of the sickness. An average dosage of 1 tablet, for oral administration, which contains 250 mg of chloroquine phosphate, USP (equivalent to 150 mg base) in 24 hours was recorded from the mothers of chloroquine treated subjects. All the 16 home-based oral chloroquine treated patients recruited for this study, presents uncomplicated malaria only on admission in the hospital. While, all patients presenting severe malaria on hospital admission did not receive any medication prior to sample collection in the hospital.

2.1.2. Study Area and Location

Jos metropolis, mainly, Jos North local Government area, is the study site. Its geographical coordinates are latitude: 9˚55'42" North and longitude: 8˚54'31" East.

2.2. Study Subjects

The study subjects were under 5 years children malaria patients attending the Emergency Paediatrics Unit (EPU), Paediatrics Department, Jos University Teaching Hospital (JUTH), Jos and OLA hospital, Jos. Non malaria under 5 years patients attending the Child Welfare Center of the Department of Community Health and Paediatrics Outpatient Department (POPD) for immunization, both at JUTH, served as control. The malaria children were recruited consecutively and divided into groups.

2.3. Inclusion Criteria

The criteria used for the selection of patients (under the age of 5 years) with severe malaria were: Fever and presence of *Plasmodium falciparum* in peripheral blood (malaria parasite positive), and at least one of the following conditions; unconsciousness or coma, altered sensorium or inability to sit unaided, repeated convulsion in 24 hour period (meningitis was ruled out, via lumber puncture and Cerebrospinal fluid analysis [lumber puncture-sterile]), and no history of any medication in the particular episode. Whereas selected patients with uncomplicated malaria were children with fever and presence of *Plasmodium falciparum* in blood, without symptoms of other sickness, and no history of any medication in the particular episode. The chloroquine-treated malaria group were children with defined malaria, but were administered oral chloroquine 24 hours prior to sample collection. The control group were children of the same age group range and living in same area, but without fever, negative to malaria parasite test, and were not under any medication.

2.4. Study Population

Blood samples were collected from the various treatment groups. A total of 93 children were recruited for this study. 47 of these children were qualified for the selection of the control group and total children presenting malaria were 46 children. 23 children of the 46 total malaria children (50%) presents untreated uncomplicated malaria, while 7 children (15.22%) presents untreated severe malaria and 16 children (34.78%) were home-based oral chloroquine treated malaria children. The control children were 23 males (48.94%) and 24 females (51.06%). While the total malaria children were 24 males (52.17%) and 22 females (47.83%).

2.5. Clinical Examination of Subjects by Clinician and Data Collection

For the course of recruitment, each subject was examined by a clinician for anthropometric, demographic and other diagnostic indicators of malaria as well as malaria history. The child's age, sex and measurements of weight, height and

temperature were recorded. The weight was measured using a bathroom scale, while height or length was measured using height board or length board respectively depending on whether the child can stand alone or not.

2.6. Equipments, Chemicals and Reagents

Standard laboratory equipments at biochemistry Laboratory University of Jos, and Haematology laboratory, Jos University Teaching Hospital were used and all reagents used were of analytical grade.

2.7. Sample Collection and Preparation

The selection and examination of children for this study and blood sample collection was carried out under the clinical supervision of a pediatrician. Blood samples were collected by the assistance of qualified medical professionals. 2 ml sample of venous blood was collected from each subject by venous puncture, using 5 ml syringe and needle. The collected blood was immediately dispensed into a Z5 tube containing an anticoagulant, Ethylene diamine tetra acetic acid (EDTA) solution. The tube was gently shaken and the portion kept at room temperature pending the haematological analysis, which was carried out within 6 hours of sample collection.

2.8. Malaria Diagnosis

The standard diagnosis of malaria by microscopic determination of Malaria Parasite in the thick and thin blood film on slide using Leishman's stain was carried out as described by Dace & Lewis [20], in all the recruited children malaria diagnosis was based on the presence of asexual stages of *P. falciparum* on the blood films. The determination of complete blood counts was done using Beckman Coulter Analyzer [21].

3. Statistical Analysis

The analysis of the data obtained was carried out using Statistical Package for Social Sciences (SPSS) version 21. Several statistical tools were employed, such as t-test of independence for comparison of two independent groups, and one way analysis of variance (ANOVA) was used to confirm the difference in means of several groups. As a prerequisite to statistical test, an assessment of the normality of data was carried out (using graphical method) as normal data is an underline assumption in parametric testing.

The result of test of normality shows that, the data obtained in this study were normally distributed. Therefore, t-test, ANOVA and Pearson correlation for parametric testing were employed. P-values less or equal to 0.05 ($p \leq 0.05$) was considered significant.

4. Results

The results of clinical examination of demographic and anthropometric para-

meters of age, body weight, height and temperature were summarized in Table 1. Mean age for the 93 subjects was 18.54 ± 1.59 (months) with a wide range of 2 months to 60 months. The control children were 12.47 ± 1.60 (months); while the total malaria children were 24.74 ± 2.46 (months). The lower mean age of the control subjects is typical of the non malaria patients attending the child welfare center of the department of community health for immunization, whereas older children under 5 years presenting with malaria attends the emergency paediatrics unit (EPU) where the samples were respectively taken. The mean age was not significantly different for all the children with malaria. The chloroquine treated children with malaria have significantly ($p < 0.05$) higher mean body weight than the control children, but there was no difference in mean body weight of control children and other children presenting with malaria. The mean height of the control children was significantly lower ($p < 0.05$) than the mean height of chloroquine treated and untreated children with simple malaria. This can be explained by the observed age difference between the groups.

As shown in Table 1, body temperature on admission was significantly lower ($p < 0.05$) in the control group (36.80˚C ± 0.07˚C) than in the untreated children with simple malaria (38.45˚C ± 0.25˚C), chloroquine treated children with malaria (37.94˚C ± 0.30˚C) and untreated children with severe malaria (39.24˚C ± 0.47˚C) respectively. The mean body temperature of chloroquine treated children with malaria was significantly lower ($p < 0.05$) than that of children presenting with severe malaria, but, not significantly different ($p > 0.05$) from the mean temperature of the untreated uncomplicated malaria children, suggesting, a beneficial effect of home-based oral chloroquine treatment. The mean temperature (38.40˚C ± 0.14˚C) of total children presenting with malaria was significantly higher ($p < 0.01$) than the control children (36.86˚C ± 0.07˚C).

Table 1. Anthropometric and demographic parameters of under 5 years subjects attending JUTH and OLA hospital in the Jos metropolis.

Treatment group	Age (months)	Weight (kg)	Height (cm)	Temperature (˚C)
Control	12.47 ± 1.60 (47)	8.42 ± 0.40 (47)	71.27 ± 1.32 (47)	36.80 ± 0.07 (47)
Untreated simple malaria	27.22 ± 4.18[a*] (23)	9.97 ± 0.97 (23)	83.69 ± 3.99[a*] (23)	38.45 ± 0.25[a*] (23)
Untreated severe malaria	19.00 ± 1.48 (7)	8.88 ± 0.44 (7)	75.71 ± 5.20 (7)	39.24 ± 0.47[ab*] (7)
Choloroquine treated malaria	23.69 ± 3.67[a*] (16)	10.68 ± 0.80[a*] (16)	81.96 ± 3.25[a*] (16)	37.94 ± 0.30[a*] (16)
Total	24.74 ± 2.46[a**] (46)	10.05 ± 0.57[a*] (46)	81.88 ± 2.41[a**] (46)	38.40 ± 0.14[a*] (46)

Tabulated values are means $\bar{X}$ ± S.E.M for (n) subjects given in parenthesis. *The mean difference is significant at the $p < 0.05$ level, and **at $p < 0.01$ level. [a]-comparing respective malaria infected group with control. [b]-comparing untreated severe malaria group with chloroquine treated malaria group.

The results of evaluation of the malaria disease status of less than 5 years subjects using haematologic parameters were summarized in Tables 2-4. In the case of white blood cells count and differential count (Table 2), there were significant

Table 2. White blood cells count and differential counts in blood samples of under 5 years children attending hospital in Jos metropolis.

Treatment group	WBC ($\times 10^3/\mu L$)	Lymphocytes (%)	(Monocytes) (%)	Granulocytes (%)
Control	10.35 ± 0.98 (18)	66.38 ± 2.27 (18)	6.93 ± 0.46 (18)	26.69 ± 2.43 (18)
Untreated uncomplicated malaria	12.07 ± 1.99 (6)	51.95 ± 9.27 (6)	6.57 ± 1.16 (6)	41.48 ± 9.92 (6)
Chloroquine treated malaria	11.81 ± 2.08 (9)	39.28 ± 7.45* (9)	5.49 ± 1.39 (9)	51.07 ± 6.40* (9)

Tabulated values are means ± S.E.M for n subjects given in parenthesis. *The mean difference is significant at the ($p < 0.05$) level compared to the control.

Table 3. Red blood cell count, haemoglobin content and haematocrit of under 5 years children attending hospital in Jos metropolis.

Treatment group	RBC count ($\times 10^6/\mu L$)	Haemoglobin concentration (g/dl)	Haematocrit (%)
Control	4.38 ± 0.09 (20)	10.52 ± 0.16 (20)	33.96 ± 0.48 (20)
Untreated uncomplicated malaria	2.92 ± 0.39[a*] (6)	7.23 ± 1.01[a*] (6)	23.70 ± 3.37[a*] (6)
Chloroquine treated malaria	4.01 ± 0.21[b*] (9)	9.60 ± 0.51[b*] (9)	30.97 ± 1.43[b*] (9)

Tabulated values are means ± S.E.M for n subjects given in parenthesis. *The mean difference is significant at the ($p < 0.05$) level. [a]The mean difference is significant ($p < 0.05$) compared to the control. [b]The mean difference is significant ($p < 0.05$) compared to untreated uncomplicated malaria group.

Table 4. Red cell volume, distribution width and haemoglobin content and palatelets count and volume of under 5 years subjects attending hospitals in Jos metropolis.

Treatment group	MCV (femtoliter/cell)	MCH (Picograms/cellg)	MCHC (g/dl)	RDW (%)	PLT ($\times 10^3\mu L$)	MPV (femtoliter/cell)
Control	78.17 ± 21.69 (20)	24.24 ± 0.62 (20)	30.99 ± 0.18 (20)	17.02 ± 0.69 (20)	708.45 ± 127.2 (20)	7.70 ± 0.14 (20)
Untreated uncomplicated malaria	81.42 ± 5.20 (6)	24.90 ± 1.77 (6)	30.50 ± 0.29 (6)	20.27 ± 2.23 (6)	469.83 ± 77.48 (6)	8.00 ± 0.19 (6)
Chloroquine treated malaria	77.90 ± 3.38 (9)	24.22 ± 1.33 (9)	30.97 ± 0.44 (9)	18.98 ± 1.33 (9)	458.13 ± 83.11 (9)	7.63 ± 0.27 (9)

Tabulated values are means ± S.E.M for n subjects given in parenthesis. MCV-Mean Corpusular Volume; MCH-Mean corpusularhaemoglobin; MCHC-Mean corpusulrhaemoglobin concentrations; RDW-Red cell distribution width; MPV-Mean platelets volume.

($p < 0.05$) differences between the control children and malaria presenting patients only with respect to lymphocytes and granulocytes in chloroquine-treated patients. Specifically, the lymphocytes count of the home-based chloroquine treated patients (39.28% ± 7.45%) was significantly ($p < 0.05$) lower than that of the control children (66.38% ± 2.27%). On the other hand, the granulocytes count of the chloroquine treated patients (51.07% ± 6.40%) was significantly ($p < 0.05$) higher than that of the control children (26.69% ± 2.43%). The differences in lymphocytes count and granulocytes count between home-based chloroquine treated patients and untreated uncomplicated malaria patients were not significant ($p > 0.05$). This suggests that home-based oral chloroquine treatment within 24 hours before arriving hospital decreases production of lymphocytes, but elevates production of granulocytes with attendant consequences on their biological functions.

The results of the evaluation of red blood cell counts, haemoglobin concentration, and haematocrit (Table 3) indicates that, in each case, the mean value for untreated uncomplicated malaria children were significantly lower ($p < 0.05$) than that of the control children, a trend which is consistent with the destructive influence of malaria parasite on erythrocytes, causing haemolytic anaemia in the process. However, the corresponding values for chloroquine treated malaria children were significantly higher ($p < 0.05$) than those for untreated malaria children and were generally comparable to the values obtained for the control children, suggesting that home-based firstline treatment with oral chloroquine has a protective role against the destructive effect of malaria parasite on red blood cells. The haemoglobin concentration of 7.23 ± 1.01 g/dl obtained for untreated uncomplicated malaria patients indicates a mild anaemia, whereas chloroquine treated children were not anaemic and were comparable to the control children, with all values obtained within the normal ranges.

In contrast the result of evaluation of red cell volume, width and haemoglobin, platelet count and volume (Table 4) indicates that in each case, the differences between the mean values of the respective malaria presenting-groups of children and the control children were not significant ($p > 0.05$). So also, was the difference between the home-based oral chloroquine-treated malaria children and the untreated malaria children. These suggest that these additional haematological parameters are not sensitive indicators of childhood *P. falciparum* malaria.

5. Discussion

The results of temperature measurements obtained in this study is in agreement with the reports that malaria is always accompanied with fever and it shows that, first line home-based oral chloroquine treatment could significantly reduce body temperature of the subjects within 24 hours of administration, and by that prevent severity of malaria causes by hyperpyrexia. Hyperpyrexia had been implicated in the pathogenesis of severe malaria.

The results of the white blood cells counts in this study suggests that oral chloroquine treatment prior to hospital admission decreases the lymphocytes production and increases production of granulocytes in the chloroquine treated patients. This result seems to be in agreement with the proposed mechanism of action of chloroquine which includes suppression of lymphocytes responses to mitogens, inhibition of TNF-α production by inhibiting T-cell proliferation and interfering with cytokines production [22] [23]. All lymphocytes values obtained in this study were higher than normal adult range. This elevated lymphocytes value is normal for this age range of children developing their immunity. This high level of granulocytes observed in the chloroquine treated patients can be explained in terms of shift in autoimmune response to malaria due to suspected suppressive effect of chloroquine on the lymphocytes production, and resultant compensatory increase in production of granulocytes. This increment in granulocytes in chloroquine treated patients seems to be supported by the reports by Facer [24], and Perrin, *et al.* [25], that eosinophilia occur after initiation of anti malaria treatment. Granulocytes fight infection by their ability to phagocytize bacteria, while lymphocytes fight infection by their role in cell mediated (lymphocyte autoimmune responses) immunity and antibody production. The decreased lymphocyte mediated immune response in chloroquine treated children may be connected with absence of impaired consciousness conditions, and anaemia that result from immune mediated destruction of red blood cells that are usually associated with severe *P. falciparum* malaria; and some clinical manifestation of severe malaria that are attributed to increased activities of cytokines, mostly, the Tumour Necrosis Factor alpha (TNF-α). TNF-α has been reported to have strong correlation with severity of *P. falciparum* malaria, especially in African children [26]. Red blood cells in the untreated uncomplicated malaria children were lower compared to control children and chloroquine treated children. Immune mediated destruction of red blood cells among other factors, have been implicated as causes of acquired haemolytic anaemia in malaria. The observed suppression of lymphocytes in the chloroquine treated children seems to protect against red blood cells destruction and anaemia in this children. Mild anaemia was observed in the untreated uncomplicated malaria children only. Correlation of anaemia with severity of malaria infection had been severally reported [27] [28] [29] [30].

6. Conclusions

The protective effect of home-based oral chloroquine treatment on the red blood cells and its components against the destructive effect of *P. falciparum* had been amply demonstrated in this study. From the results obtained in this study, it can be deduced that the type of anaemia observed in the untreated uncomplicated malaria children under 5 years attending JUTH and OLA hospital in Jos metropolis is the normochromic, normocytics anaemia due to haemolysis.

This study in general demonstrates the beneficial effects of home-based oral

chloroquine treatment as first aid, prior to hospital presentation. Rational use of oral chloroquine needs to be re-evaluated and encouraged in this group of children, living in areas far from immediate medical attention or hospitals.

Study Limitation

Many of these children have histories of non-chloroquine medications before hospital report and as such are not eligible for this study.

Ethical Clearance

The research protocol for this study was approved by the Medical and Health Ethics Committee of Jos University Teaching Hospital, Jos.

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Competing Interest

We hereby declare that we have no conflicting interests on this study.

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