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Body Temperature Trends and Fever Risk in the Parasitaemia of Plasmodium Falciparum Treated Children at Lake-Alau, Borno State, North Eastern Nigeria

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Abstract: ***The aim of this study is to assess the relationship between body temperature patterns and fever (≥ 37.5^{0}C) risks in the parasitaemia of uncomplicated Plasmodium falciparum malaria in children (≤59 months). The ever increasing resistance to monotherapies informed the assessment of the combination therapies of Artesunate+Sulphadoxine-Pyrimethamine (AT+SP) and Amodiaquine+ Sulphadoxine-Pyrimethamine (AQ+SP) at the malaria endemic settlements of Lake-alau, Borno State, and North-Eastern Nigeria. The result shows a response of parasitaemia to body temperatures was 55.77% in AT+SP treated children compared to higher response of 64.29% by AQ+SP patients. Similarly, the slope of regression showed a temperature clearance of 0.2071 ^{0}C for AT+SP in contrast to 0.1714 ^{0}C for AQ+SP which relates for each µl of depleted blood parasites there was a higher temperature relief in AT+SP than AQ+SP patients having a mean marginal difference of 0.0357 ^{0}C between the two respective drug groups. In a similar vein, the proportion fever risk was higher (55.75%) in AQ+SP treated children compared to AT+SP (50.69%). Conversely, the rate of fever clearance due to the percentage of each parasite cleared was 12.243% compared to 12.643% for the two respective drugs, with mean terminal parasite clearance of 99.86% and 99.7%, respectively.***

Keywords: Temperature, Trends, Fever risk, Parasitaemia, *Plasmodium falciparum*, children, Lake-Alau

1. Introduction

The disease is one of the greatest challenges to medical experts and parasitologists [35]. It is one of the most important health challenges in sub-Saharan Africa [26]. Globally, it is estimated between 300 - 500 million clinical cases of malaria occur [34] [22], In Africa, malaria is considered a disease of poverty and a cause of poverty [10]; [24]. It has a significant and a measurable direct and indirect cost on children lives with serious constraints to economic development [24]. Malaria has been implicated as one of the major causes of poor childhood development [24]. In Nigeria, almost all of the 170 million people are at risk of malaria infections [7] and further complicated by increasing resistance to hitherto cost-effective antimalarial monotherapies such as Chloroquine, Sulphadoxine-Pyrimethamine and Amodiaquine [2]; [16]; [1] . Efforts to combat this predominant Apicomplexan protozoan of tropical parasitic disease is also constrained by high degree of poverty, ignorance on its pathology and life cycles [21] ; [3] and weaker health infrastructures at national, State and Local Government levels [27]; [28]; [20]. Antimalarial drugs have varying effects on the stages of the malaria parasite's life cycle [29] ; [13] like the antifolates, quinine and mefloquine which exerts little or no effect on the parasites during the first 24 hours of their life cycles [30] however, effects are only on the actively dividing forms (Schizonts) [15] ; [17] ; [19]; [1] . Chloroquine, artemesinin, and other drugs act on early ring stages and could enhance faster parasites clearance shortly after administration which potentially prevents further development of susceptible parasites and the worsening of clinical expressions like fever [32]; [5] . Thus, the assasment of the body temperature pattern and fever risks tendencies in malaria positive patients on course of treatment are reliable indicators for the prevention and control of malaria transmission [34] .

2. Literature Survey

Fever is the most apparent sign in an acute malaria attack and can be accompanied by other non specific symptoms such as headache, diarrhea, abdominal pain, vomiting, and nausea. One of the possible therapeutic strategies for prolonging the clinical efficacy of an antimalarial drug and reducing the risk of selecting drug-resistant malaria parasites is to use drug combinations [17] . The physiological role of fever in malaria and other infectious diseases remains important [1]. Current options for the treatment of acute uncomplicated chloroquine-resistant *P. falciparum* infections in Africa includes the use of drugs such as Amodiaquine (AQ), Artesunate (AT), Sulfadoxine–Pyrimethamine (SP) and in combinations (ACT) with any two.The choice of these drugs is based not only on their clinical efficacy but also on their affordability, good tolerance, safety for young children, and low toxicity risk. Their high clinical efficacy when used separately has been demonstrated in recent clinical trials conducted in Chloroquine-resistant zones of Africa [2]. The side-effects are well known and documented [6]. For exam[ple, the fever clearance time in the treatment of *Plasmodium falciparum* malaria in children was significantly faster in the AQ and AQ+SP groups than in the SP group ($P < 0.05$). The therapeutic efficacy of the three regimens were similar when the clinical and parasitological responses were evaluated on day 14($P>0.05$) [28].

3. Materials and Methods

3.1. Study Site

Lake-Alau settlement is in Konduga Local Government Area of Borno State Nigeria, it is located at (Lat: 12^0N and 13^0N; Long: 11^0E and 13^0E) (Fig. 1). Malaria transmission was intense and continuous throughout the year in the study area. The lake and other water bodies surrounding the settlements made a malaria holo-endemic environment which disposes the inhabitants to incessant malaria epidemics all the year round. The peak of transmission was during the rainy season (June - October) typically characterized of stagnant water bodies all year round. Thus, making malaria the major health challenge of the area. The major vectors are *Anopheles gambiae* and *Anopheles funestus*. Malaria incidence has increased in recent years in the study area, due to loss of efficacies of commonly used anti-malarial drugs that are usually monotherapies (Molta *et al*., 2004). The health records of the study area indicated that malaria accounts for 65% of consultations, 60% of hospitalized patients, and 30% of mortality among hospitalized children.

3.2 Ethical clearance and randomization for treatment allocation

Before the commencement of the study, ethical clearance was sought from the Borno State Ministry of Health Authorities in accordance with [34]). The study patients were assigned study numbers at enrollment and referred to the study nurses for the treatment as were randomly assigned to either Artesunate + Sulphadoxine-Pyrimethamine or Amodiaquine +Sulphadoxine-Pyrimethamine treatment groups. This was conducted according to a predetermined randomization list and treatment. While allocation and administration of the drugs was performed by trained study nurses not involved in the assessment of treatment outcomes, while the other members of the team were blinded to the treatment regimen in order to remove bias [37]

3.3 Body temperature assessment

A digitalized electronic clinical thermometer was used to record the body temperatures on days 1, 2, 3, 4, 7, 14 and 28 during study. Children with body temperature ≥ 37.5 °C (fever) at enrolment were recruited for the study [33].

3.4 Laboratory and follow-up procedures

3. 4.1. Blood Sampling

The blood was sampled using the techniques outlined by [36]. The Finger prick and venipuncture (syringe) methods were employed by pricking the lateral side of the third phalanx with a sharp sterile needle after thorough cleaning with spirit-moistened cotton. The first drop of blood was cleaned with cotton while subsequent drops were obtained by gently squeezing the finger, and blood droplets were collected on a glass slide on days 0, 1, 2, 3, 4, 7, 14 and 28 for the assessment of parasite density.

3.4.2. Blood smear preparation

3.4.2.1. Thin film: The protocols on thin film preparations by [36] was employed. A drop of blood sample equivalent to 1.5 µl and 3 - 4 mm in diameter was collected on one end of the slide. The edge of a second slide was held at an angle of 45^0 with the first slide and then spread the blood on the other slide for rapid diagnosis at the field[11] .

3.4.2.2. Thick film: The procedures by [11] was adopted in the preparation of thick blood film. Three drops (4.0 µl) of blood sample was used for the preparation of the thick film. Three triangular blood drops were placed on the slide and gently mixed for 20-30 seconds using the corner of a second slide to defibrinate the blood to obtain a round smear of about 1 cm in diameter.

3.4.2.3. Staining procedures

Giemsa staining solution was prepared by diluting Giemsa powder with buffered water in the ratio of 1:10 and 1:20 for thin and thick films, respectively. This was achieved by putting 1 drop (thin film) and 2 drops (thick film) of Giemsa per ml of distilled water buffered to pH 7.2. The slides were then immersed in the staining trough for 30 - 40 minutes in 3% stain, for laboratory analysis. About 5 ml of the stain solution was used for each slide. Thick film was allowed to dry completely and then a drop of oil immersion was applied to a stained portion and then examined for malaria parasites density assessments on days 0, 1, 2, 3, 7, 14 and 28 while thin film was used for parasite morphological studies and species identification [33.

3.4.2.4. Parasite density counts (per µl):

The slides were examined under x100 objectives of a research microscope and asexual parasites were counted alongside with 200 leukocytes. In an event the parasite count was < 10 parasites/200 leukocytes, the count was continued per 500 leucocytes. The parasite density was expressed as the number of asexual parasites per ml of blood by assuming a mean normal leukocyte count of 8000/µl of blood [36] .

3.5 Statistical Analysis

Data collected were subjected to descriptive statistical analysis, using the analytical software the Staistix Version 8.0 (Microsoft, 2003) and the regression analysis was conducted on the relationship between the rates of parasite (µl) and temperature (fever) (°c) clearance in respect to the two tested drugs (AT+SP and AQ+SP) on days 0,1,3,14 and 28 in children with *Plasmodium falciparum* malaria.

4. Results

Table 1, shows an initial mean body temperature range of 37.0 - 39.6 ^{0}C among the infected children by *Plasmodium falcifarum* summarized within the mean range of 38.15 $\pm$ 0.47 ^{0}C. The mean parasite count on admission was highly dispersed (2304 - 36800/µl) from the mean range of 20820 $\pm$ 5277.7/µl. Fig. 1a and b relates parasite density to body temperature among children with *Plasmodium falciparum* infections subsequent to AT+SP and AQ+SP treatments. Results showsl that parasitaemia influenced body

temperature by 55.77% in children treated with AT+SP compared to a relatively higher influence of 64.29% in AQ+SP treated children. Fig. 2 a and b matches percentage febrile to parasite clearance which almost concurred to each other by 50.69% and 55.75% for AT+SP and AQ+SP, respectively. However, the b-value/ coefficient of regression shows 0.2071 ^{0}C for rate of body temperature clearance for AT+SP as compared to 0.1714 ^{0}C for AQ+SP showing for each µl of blood depleted parasites, higher temperature relief in AT+SP was observed as compared to AQ+SP patients on course of treatment. In a similar vein the proportion of fever clearance due to the percentage parasite cleared was 12.243% compared to 12.643% showing a marginal difference of 0.4% in favor of AQ+SP for the two respective drugs, similarly, there was a terminal parasite clearance of 99.86% and 99.7%, between the two respective drugs.

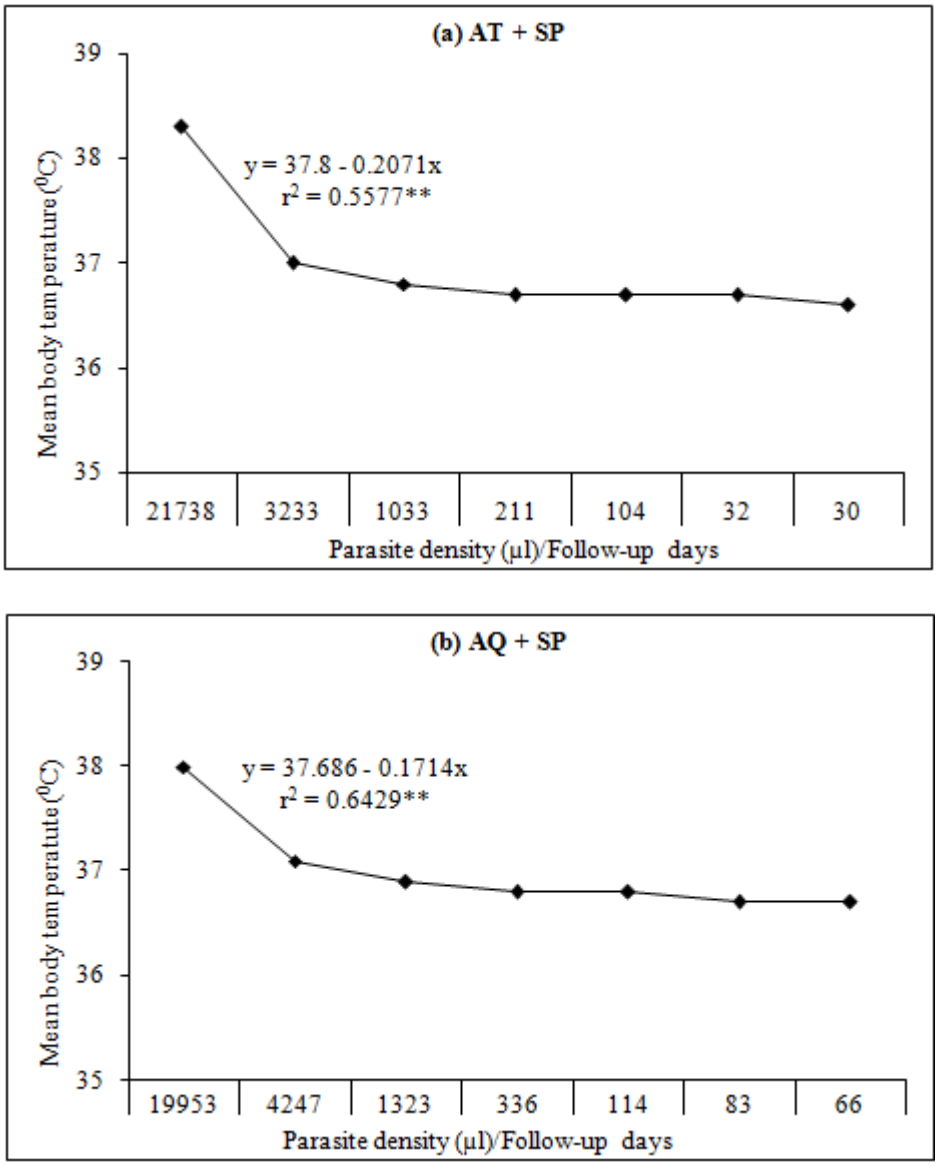

Figure 1: Relationship between parasite densities and body temperature pattern in children administered (a) AT+SPand (b) AQ+SP in P. falcifarum treated at Lake-Alau, North Eastern Nigeria

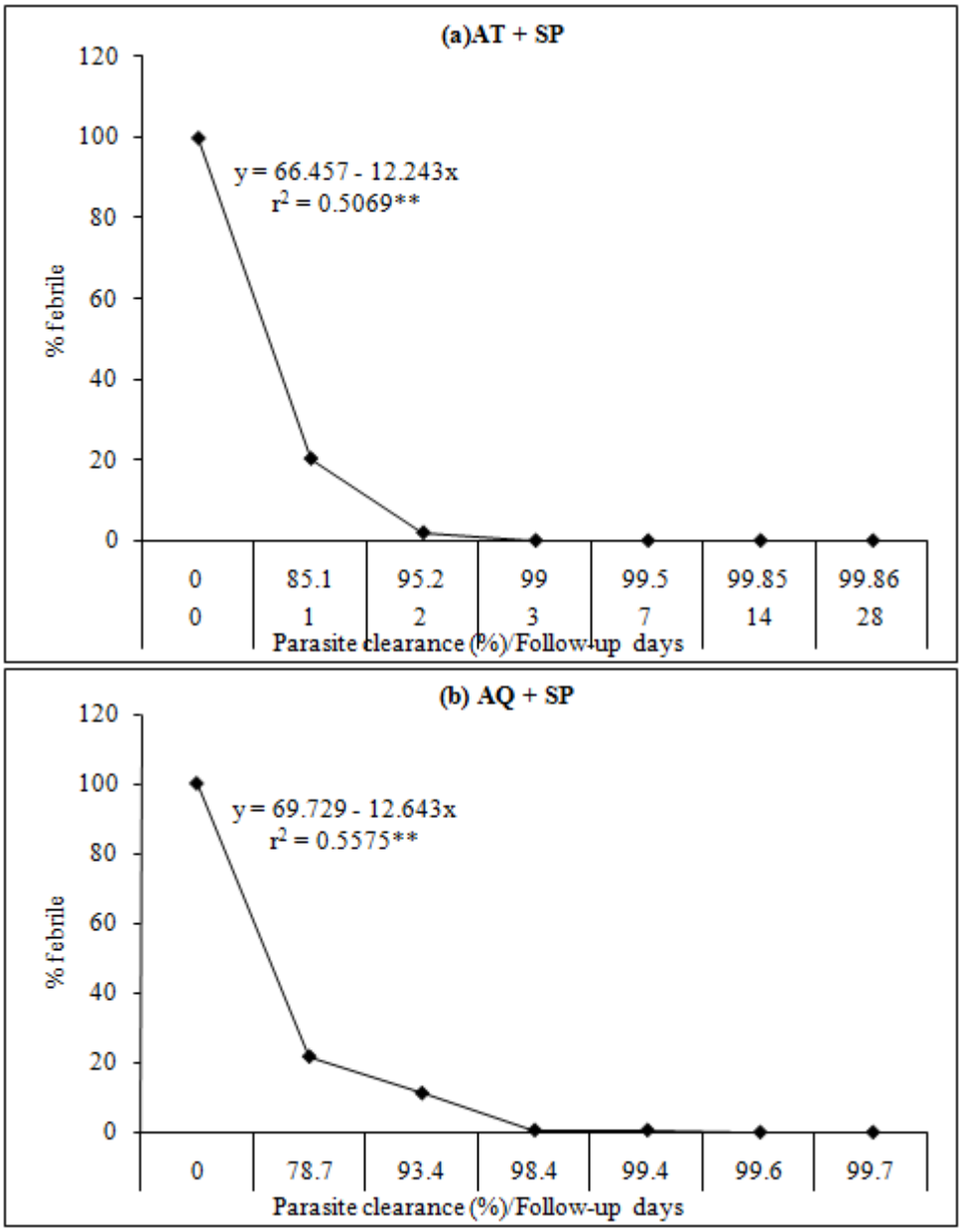

Figure 2: Relationship between parasite clearance and percentage febrile in children administered (a) AT+SP and (b) AQ+SP in P. falcifarum treated at Lake-Alau, North Eastern Nigeria

5. Discussions

The body temperature and fever ($\geq 37.5^0$C) pattern in children is often considered as one of the most important clinical determinants for malaria positive diagnosis [9], while level of transmissions serves a predominant predictor for either fever or its risk in patients [34]. The fever frequencies of the two tested drugs favored a downward trends in either case during the follow-up periods [35]. The fever risk and body temperature frequencies were simultaneous in malaria positive patients in the present study, and are linked because of the relationship between the patho- physiology of Plasmodium infections with fever developments [12]. This is because the infected erythrocytes by *Plasmodium falciparum* adhere to the endothelial lining of the small blood vessels which likely results in blockages that gives rise to a decrease in tissue perfusion and ends up in metabolic acidosis [12] . The resultant lysis of erythrocytes and the release of merozoites could cause an immune response and its effects on the production of cytokines (TNF- alpha), these finally develops into characteristic fever ($\geq 37.5^0$C) of malaria [14], The results of the present study is characterized of a sharp parasite clearance phase between days 0 to 3 after treatment and a more stable clearance phase from days 7 to 28 after drug administration, irrespective of the two drug combinations used (fig 2 a and b.). The study consistently expressed rapid temperature (fig 1 a and b) and fever (fig 2 a and b) ($\geq 37.5^0$C) clearance in the early phases of the treatment (days 0-3), this is because combinations of AT+SP, having Artesunate as an active component is known to be rapid in the clearance of the bulk of the parasites within the first three days, left low parasites concentrations to reach the later phase of the parasite clearance, and this is linked to the corresponding rapid fever clearance in the first three days of post drug administration and faster in AT+SP compared to AQ+SP. These results corresponds with [23] .. Similarly, the drug combination of AT+SP was ahead of AQ+SP in the clearance of fever in both early and late follow-up days, which similarly concurs with findings by [8

] and [2] who ascribed Artesunate and Amodiaquine arms in combination with Sulphadoxine – Pyrimethamine effectas significant reduction of high proportion in body temperatures and fever frequencies in patients with documented parasitaemia in early follow-up days, but AT+SP was faster than AQ+SP [6] . Conversely, the parasite clearance accompanied by concomitant temperature clearance implies higher quantum of temperature relief from each cleared parasite in AT+SP compared to AQ+SP patients.

The result also indicated that for each µl of blood parasites depleted there was a clearance of temperature by 0.2071 ^{0}C and 0.1714 ^{0}C in the two respective drug groups, with a marginal difference of 0.0331 ^{0}C between the two administered drugs which is in favor of AT+SP [1] . Similarly other reports indicated that both AT + SP and AQ + SP run neck to neck during follow up days [18]. In a similar vein, [25] observed a prolonged fever clearance time in Sulphadoxine-Pyrimethamine and higher febrile frequencies and significantly lower with AT + SP and AQ + SP treatment in the first two days [18]. The result further revealed that despite the body temperature margin between the two drug combinations at enrollment, AT + SP had cleared fever by 79.6% as against 78.3% by AQ + SP on the first day of follow-up. The results on fever clearance rates are in concordance with [4] compared to AT + SP (83%) as reported by [31] . In a similar vein, AT + SP completely resolved fever in three days (72 hours) compared to fourteen days as reported by [4] for AQ + SP, and a complete fever clearance in 30 hours with AT +SP [31] . These findings have important implications for determining relationship between malaria parasite densities and fever risk in children.

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