EVALUATION OF THE EFFICACY OF INDIGENOUS HERBAL REMEDY, LISAMOS™, IN THE TREATMENT OF MALARIA INFECTION

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ABSTRACT

The use of chemical or synthetic drugs to treat plasmodial infections has been currently highlighted. The treatment of wide range of human diseases with herbal remedies, in recent time, is a novel approach that needs to be further elucidated. The absence of efficient public healthcare facilities in most developing countries, particularly in Sub-Saharan Africa, coupled with financial constraints places traditional medicine as the mainstay of treatment for malaria. In this study, the efficacy and effectiveness of the herbal antimalarial, Lisamos™, in the treatment of plasmodial infection was evaluated. A total of 125 subjects were screened, out of which 31 subjects met the inclusion criteria. Parasitaemia and body temperature were recorded three times a day in the 31 subjects throughout the study period. Patients treatment outcome profiles revealed that thirteen (41.9%) of the total number of patients studied had negative blood smear for malaria parasitaemia by day 14 while eighteen (58.1%) of the patients still had positive blood smear for malaria parasitaemia by day 14. Mean fever clearance time calculated was given as 10.1±4.39 days. Twenty-one (67.7%) of the patients studied had complete clinical resolution between days 3 and 14 (temperature≤37⁰C). The above, therefore, is suggestive that Lisamos™ has anti-malarial effect though relatively poor. In conclusion, the poor performance of Lisamos™ in this study could be attributed to the highly resistant strains of Plasmodium falciparum found in the study region.
KEYWORDS: Drug-herbal interaction, efficacy, lisamos\textsuperscript{TM}, malaria, Plasmodium falciparum, poly-herbal remedy.

INTRODUCTION

Malaria continues to exert unacceptably high death toll in Sub-Saharan Africa, accounting for about 90\% of the worldwide malaria burden due to decline in public health systems and drug resistance.\textsuperscript{[1]} The World Health Organisation (WHO) has reported that 40\% of the world’s population was at risk of malaria and \textit{Plasmodium falciparum} was implicated in 95\% of the mortality associated with malaria worldwide.\textsuperscript{[2,3]} Malaria is the commonest cause of outpatient hospital attendance among all age groups in Nigeria and hospital admission especially among children. The disease is more severe among the rural than urban dwellers with death often occurring before access to any healthcare personnel or facility.\textsuperscript{[4]} The precise magnitude of the economic burden of malaria on Nigeria is not known, but it has been estimated that the economic burden of the disease on Africa is about $8 billion dollars annually.\textsuperscript{[5]} The use of herbal medicine in the treatment of malaria dates back to thousands of years ago. Indeed, the two major antimalarial drugs, artesunate (from \textit{Artemisia annua}) and quinine (from bark of Cinchona tree), currently used in orthodox medicine are derived from traditional sources. The use of currently available drugs for the treatment of malaria are limited by development of resistance and prohibitive cost. The rise in parasitological resistance and the drastic increase in the prices of conventional chemical drugs, in the background of financial crises in African countries, have brought about a growing interest in the use of medicinal plants in the past ten years. The growing interest in the use of herbal medicines to treat a wide range of medical conditions ranging from insomnia, anxiety, obesity, bronchial asthma, constipation, gingivitis, Vincent's infection, malaria to acquired immunodeficiency syndrome has been reported.\textsuperscript{[6]} Hence, there is need to study the safety, tolerability and efficacy of herbal medicin as a first step to possible deployment of herbal remedy in sub-Saharan Africa due to \textit{Plasmodium falciparum} resistance to many conventional chemical drugs. This is to encourage the deployment of traditional antimalarial remedies in view of the prohibitive costs and increasing resistance of chemical drugs militating against the combat of malaria. The present study, therefore, sought to evaluate the efficacy of lisamos\textsuperscript{TM}, a polyherbal antimalarial remedy, in a parallel group clinical trial in the treatment of uncomplicated \textit{Plasmodium falciparum} malaria in Enugu, South-East Nigeria.
MATERIALS AND METHODS

Study Site and Population
The study was conducted between August and September, 2005 at Achi Primary Health Centre, a government facility serving a rural population of approximately 600,000 people in Enugu State, South-East Nigeria. The area is predominantly rural and the subjects from this area are primarily farmers at subsistence level and petty traders. The rainfall is seasonal and lasts between the months of March and October with the greatest intensity at the middle of the year. The area has intense *Plasmodium falciparum* transmission running throughout the year with peak transmission occurring at the beginning and end of the rainy season.

Patient Screening and Recruitment
Patients between the ages 1 and 50 who presented at the outpatient department of the health facility with a history of fever were referred to the study team for evaluation. They were eligible for enrolment in the study if they met the following inclusion criteria:

- Age range: 1 - 50 years and presented at the study centre with a recent febrile illness and a geometric parasite density of 200/µL to 100,000/µL.
- Uncomplicated *Plasmodium falciparum* malaria without evidence of hepatic, neurological involvement, haemolysis, renal impairment or vomiting.
- Has not taken any anti-malarial drug in the past two weeks preceding presentation.
- Haemoglobin level greater than 7g/dL.
- Ability to take drug orally.
- Evidence of informed written consent to participate in the study.

Exclusion criteria included

- Age less than 1 year.
- Complicated malaria with evidence of vomiting, haemolysis, dehydration, cerebral, hepatic or renal involvement.
- Severe underlying disease requiring specific therapeutic intervention.
- Haemoglobin level less than 7g/dL.
- Parasitaemia greater than 100,000/µL.
- Pregnancy or lactation
- No informed written consent to participate in the study.
A standard medical history was taken and a clinical examination performed by a medical officer on admission. The patients were weighed, axillary temperature, pulse and respiratory rate were also taken and capillary blood samples obtained for malaria films. These were repeated on days 3, 7 and 14 after enrolment.

**Study Design, Randomization and Treatment**

A total of 31 patients participated in the study. They received either tablets or syrup of \textit{Lisamos}™ depending on the age. \textit{Lisamos}™ (formulated by Iris Medicals, Lagos-Nigeria) is a polyherbal product comprising of four different indigenous plants of African origin namely: \textit{(Tonacetum parthenium, Gentiana lutea, Hydrastis canadensis and Anacardium accidentale)} marketed for the treatment of malaria. \textit{Lisamos}™ was given at a dose of 25mg/kg body weight daily for 3 days by a nurse at the health centre. Children were observed for 30 minutes following drug administration for vomiting. Patients with axillary temperature more than 38°C were tepid sponged.

**Assessment of Treatment and Follow-up**

Patients were followed-up for 14 days. They returned every other day to the hospital for 3 days for drug administration, assessment of symptoms and adverse drug reactions. Evaluations for parasite clearance and physical examinations for temperature, pulse, body weight and respiratory rate assessment were done on days 3, 7 and 14. Patients who failed treatment were rescued with Artemether-Lumefantrine (\textit{Coartem}™ from Novartis Pharma) and withdrawn from the study. Treatment failure was defined as development of any of the following: danger signs of severe malaria on D1-D3 in the presence of parasitemia (early) or development of the danger signs of severe malaria after D3 in the presence of parasitemia, without previously meeting any of the criteria of early treatment failure (late).

**Laboratory Procedures**

Thick and thin blood films were stained with 3% Giemsa's stain for 30 minutes, dried and read by two independent microscopists using x100 objective. Parasite density was calculated per 200 white blood cell (WBC) count on a thick film assuming a mean WBC count of 8000/µL. \textit{Plasmodium falciparum} gametocyte count was done per 1000 leucocytes.

**RESULTS AND DISCUSSION**

Baseline characteristics of the study participants is displayed in Table 1. The patients were monitored parasitologically and clinically for 14 days as depicted in Table 2. Thirteen
(41.9%) of the total patients studied were cured, that is, had negative blood smear for malaria parasitaemia by day 14. Eighteen (58.1%) of the patients were not cured, that is, still had positive blood smear for malaria parasitaemia by day 14; only 4 of these were children under 5 years of age. Mean fever clearance time on follow-up are as shown in Figure 1. The individual parasitological outcomes observed in the study population are presented in Figure 2. Twenty-one (67.7%) of the total patients studied had complete clinical resolution between days 3 and 14.

The high cost of conventional medicines has forced many indigent people of sub-Saharan Africa to look for alternative medicines for the treatment of a common illness like malaria. The use of herbal medicine in the treatment of malaria in Nigeria varies from one locality to another.[7,8] However, over-dependence on herbal medicines could lead to parasitological resistance and complications. There is a general belief that herbal preparations, being natural are intrinsically harmless. Their effects are generally due to the pharmacological characteristics and dose levels of their active constituents. However, herbal medicines can be potentially toxic if used incorrectly or concomitantly with conventional medicines. It is generally assumed that traditional medicines are safe, probably due to usage by indigent population over the years, though scientific evidence has revealed that herbal medicines may be potentially toxic, carcinogenic and mutagenic.[9] It is well known in several countries like Asia and Africa where herbal medicines are commonly used, that certain plants must be used with caution because they may be toxic to the liver, kidney, skin and other tissues.[10,11] Herbal medicine has contributed immensely to the discovery of a number of pharmacologically active substances in plants currently used in orthodox medicine.[12,13] Plants may help in shifting the drug discovery paradigm from providing new molecules to combining existing agents, and not only in the provision of valuable clues for finding new drugs.[14,15] Treatment of malaria traditionally with use of decoctions or infusions from bitter plants has been reported.[16] The present study showed that the use of Lisamos\textsuperscript{TM} for treating malaria, in this area of intense transmission and emerging \textit{Plasmodium falciparum} strains resistant to many antimalarials, was associated with high rates of parasitological resistance. Lisamos\textsuperscript{TM} was found to be safe and well tolerated. Safety of herbal medicine is of particular importance since most of these products are self-prescribed and patients usually do not inform their medical practitioners of their use. Many of these products are sold as dietary supplements but scientific information about their safety and efficacy are hard to find due to limited toxicological data available on herbal
remedies and lack of rigorous clinical studies. A study reported the efficacy of herbal remedy for treatment of malaria stressing the need for further studies into their efficacy, possible toxic effects and effective lifespan.\(^{[17]}\) Herbal medicines can reduce or potentiate the efficacy of concurrently used conventional medicine, hence studies on the interaction between herbal and conventional medicines are highly desirable. The objective is to find out adverse effects that could occur and the influence of factors such as age, sex, pathophysiological conditions and genetic factors.

The present study found high rates of parasitological resistance to Lisamos\(^{TM}\) during the 14 day follow-up period. Moreover, patients treated with Lisamos\(^{TM}\) remained parasitaemic and febrile for a longer period and were more likely to be gametocytaemic. The level of parasitological resistance to lisamos\(^{TM}\) on day 14 was as shown in Table 2 and Figure 2. Lisamos\(^{TM}\) known to exhibit therapeutic efficacies on wide range of parasitic and bacterial ailments, however, demonstrated poor anti-malarial activity in the current study. Previous reports on the traditional uses of these plants showed that the plants have more antibacterial than anti-parasitic effect; although the therapeutic efficacy of herbal medicines is not influenced by a single group of compounds. The efficacy and safety of herbal medicine depend not only on the remedy and its dosage but also on consumer-related parameters such as age, genetics, concomitant diseases and concurrent use of other drugs. Conclusively, the poor performance of Lisamos in this study could be attributed to the highly resistant strains of Plasmodium falciparum found in the study region.

![Figure 1: Temperature Reduction on Specified Follow-up Days](image-url)
Day 0
125 subjects screened. 1st blood smear collected and examined. 31 subjects found positive for malaria parasitaemia. The 1st standard dose of Lisamos™ administered according to body weight

Day 1
2nd standard dose of Lisamos administered according to body weight

Day 2
3rd standard dose of Lisamos administered according to body weight

Day 3
2nd blood smear taken for quantitating parasite density.

Parasitaemia
<25% 5(16.1%)
Parasitaemia >25%
26 (83.9%)

Follow-up to day 7

Parasitaemia <25% 10 (32.3%)
Parasitaemia >25%
21 (67.7%)

Follow-up to day 14

Parasitaemia <25% 13 (41.9%)
Parasitaemia >25% 18 (58.1%)

Figure 2: Flow-Chart Depicting Parasitological Outcome in the Study Population
Table 1: Baseline Characteristics of Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number Enrolled</td>
<td>31</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.9 ± 20.28 (1-60)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>41.8 ± 21.93 (12.7-88.1)</td>
</tr>
<tr>
<td>Male:Female Ratio</td>
<td>1:2</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>85.4 ±15.32 (60.5-117.8)</td>
</tr>
<tr>
<td>Presenting Body Temperature</td>
<td>37.8 ±2.7 (37.6-38.5)</td>
</tr>
</tbody>
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Table 2: Parasitological and Clinical Response Post-Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Geometric Parasite Density (/uL)</td>
<td>1267 ± 389 (652-7185)</td>
</tr>
<tr>
<td>Fever Clearance Time (days)</td>
<td>10.2 ± 4.39 (6.8-14.1)</td>
</tr>
<tr>
<td>Parasite Clearance Time (days)</td>
<td>7.1 ± 4.35 (5.3-12.8)</td>
</tr>
<tr>
<td>Cure Rate on Days (%)</td>
<td>3: 16.1  7: 32.3  14: 41.9</td>
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REFERENCES