EFFECTIVENESS OF QUININE MONOTHERAPY FOR THE TREATMENT OF PLASMODIUM FALCIPARUM INFECTION IN PREGNANT WOMEN IN LAMBARÉNÉ, GABON

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Abstract. Pregnant women participating in a longitudinal immuno-epidemiologic survey in Lambaréné, Gabon, and presenting with Plasmodium falciparum parasitemia at monthly blood smear examinations were offered treatment with oral 7-day quinine monotherapy according to national health guidelines. A total of 50 pregnant women were offered 7-day oral quinine sulfate 10 mg/kg thrice daily. Clinical examinations and laboratory tests were performed on Days 28 and 56 to assess the effectiveness of this standard regimen. By Day 28, the effectiveness of the 7-day quinine regimen was 60% (95% confidence interval: 46–72%). We conclude that a 7-day course of quinine has a poor effectiveness and that alternative treatment regimens for malaria in pregnant women should be assessed.

INTRODUCTION

Plasmodium falciparum malaria is one of the leading causes of death in tropical countries, taking the highest burden in tropical Africa. It is estimated that 90% of the worldwide falciparum malaria occur in sub-Saharan Africa.1

Pregnant women and newborns are at an elevated risk for P. falciparum infection associated morbidity and mortality. Symptomatic or asymptomatic P. falciparum infection during pregnancy leads to an increased risk for maternal anemia. This is, in conjunction with placental P. falciparum infection, one major predictor for poor birth outcome due to low birth weight and prematurity.2,3

Intermittent preventive treatment, treatment of anemia, and insecticide-treated nets are possible effective control strategies. In the absence of an efficient implementation of the above-mentioned malaria control measures in many African countries, chemotherapeutic treatment of falciparum malaria remains the only viable option against pregnancy-associated malaria for the majority of affected people.

To date, there is a limited choice of approved treatments for chloroquine-resistant P. falciparum malaria in pregnancy in most African countries. In Gabon and many other sub-Saharan African countries, quinine remains the first-line therapy for pregnant women, either administered intravenously in hospitalized patients or orally as a 7-day regimen. Sulfadoxine-pyrimethamine is privileged for intermittent preventive treatment during pregnancy in most malaria endemic areas, however its actual use during pregnancy might in fact be more common.1,4–7 Although quinine monotherapy shows high efficacy in the setting of clinical trials, it also has considerable disadvantages foremost due to its poor tolerability (i.e., cinchonism) and the prolonged treatment course.8

However, whether high efficacy observed under artificial circumstances such as clinical trials translates similarly into real life remains doubtful. The aim of this clinical trial was to assess the actual usefulness of quinine monotherapy when prescribed under routine health care facilities in sub-Saharan Africa.

MATERIALS AND METHODS

The study took place at the Medical Research Unit of the Albert Schweitzer Hospital in the semi-urban setting of Lambaréné, Gabon, from June 2003 to February 2004. The city is characterized by hyperendemic and perennial malaria transmission with an entomological inoculation rate of approximately 50 infective bites/person per year.9,10 The predominant species is Plasmodium falciparum, which has been shown to be highly resistant to chloroquine but sensitive to quinine in vitro and in vivo.11–13 Two mother-child health care centers that are part of the governmental hospital (General Hospital) and the nongovernmental hospital (Albert Schweitzer Hospital) serve the local population.

Pregnant women living in Lambaréné and attending one of the above-mentioned mother-child health care centers in Lambaréné were invited to participate in an immuno-epidemiologic study on the impact of parasitic infections in pregnancy. As part of this study, patients were invited for monthly follow-up visits assessing clinical status and parasitological laboratory diagnostics for malaria, filariasis, and schistosomiasis throughout pregnancy.

This study was designed as an uncontrolled effectiveness study assessing the parasitological cure rate of quinine monotherapy. Women diagnosed with microscopically confirmed P. falciparum monoinfection were considered eligible for this study if the following inclusion criteria were met: 1) absence of signs of severe malaria, 2) ability to tolerate oral therapy, 3) no antimalarial drug intake in the preceding two weeks, and 4) written informed consent.

A study physician examined all patients at enrollment and subsequent follow-up visits assessing vital signs, blood pressure, tympanic temperature, and blood count. A thick blood smear was also done, and each blood film was read by two laboratory technicians following the standard quality controlled procedure.14

Patients who met all entry criteria were assigned to a 7-day weight-adjusted treatment course of thrice-daily quinine sul-
fate (10 mg/kg of body weight per dose). Quinine sulfate was provided as tablets of 300 mg (International Dispensary Association [IDA], Amsterdam, The Netherlands), and the dosage was weight-adjusted by once dividing the tablets if necessary. The first dose was administered under the supervision of the study physician providing at the same time the remaining doses. Patients were counseled about potential side effects and the necessity to comply with the full treatment course. Participants were encouraged to present at the research unit in the case of persistence or reappearance of clinical symptoms. Follow-up visits were scheduled at Days 28 and 56. At delivery, peripheral and placental thick blood smears were taken and examined. The assessment of compliance with the prescribed regimen was omitted due to the lack of active follow-up visits in this trial.

The primary end point for effectiveness was the Day-28 parasitological cure rate. The cure rate was defined as the proportion of patients presenting without asexual Plasmodium falciparum infection on Day 28. Subjects were excluded from statistical analysis in the case of intake of drugs with known antimalarial activity during the follow-up period. The secondary end points were Day 56 effectiveness and the frequency of placental Plasmodium falciparum infections at delivery.

The study protocol was approved by the ethics committee of the International Foundation of the Albert Schweitzer Hospital in Lambaréné. Written informed consent was obtained from all patients or their legal representatives.

The sample size of 50 patients was chosen based on the assumption that a 7-day quinine monotherapy regimen would give 70% efficacy with a 95% confidence interval of 56% to 81%. The first 50 patients fulfilling the inclusion criteria were enrolled in the study.

**Data analysis.** Data were entered from patient record forms into a FileMaker Pro 5.5 database (FileMaker, Inc., Santa Clara, CA) and analyzed using SPSS for Windows 11.5.0 (SPSS Inc., Chicago, IL).

χ² and Fisher’s exact tests were used to analyze differences in proportions. Differences between group means were analyzed using Student’s t test, applying log-transformation when appropriate. Prior to analysis, normality assessment by Kolmogorov-Smirnov and Shapiro-Wilk tests was carried out. Non-normally distributed variables were analyzed using the Mann-Whitney U test. All analysis was carried out at a 5% significance level. P values reported are two-tailed.

**RESULTS**

In total, 50 women presenting with uncomplicated malaria in the ongoing immunology longitudinal study were included in this trial. Figure 1 shows the study flow of all patients and patient characteristics at enrolment are summarized in Table 1. During the first month of follow-up, 20 women presented with peripheral falciparum parasitemia, and 30 had negative thick blood smears. The effectiveness of 7-day quinine monotherapy was therefore 60% (95% CI: 46–72) in our study population by Day 28.

When baseline characteristics of treatment failures were compared with ultimately cured participants, no significant difference was found for gestational age, gravidity, parity, hemoglobin concentration, and body temperature. However, the mean age of participants experiencing reappearing parasitemia during the first month of follow-up was significantly lower compared with cured individuals (20 versus 23 years; \( P = 0.036 \)). Similarly, the mean weight was significantly lower in the failures group (54 versus 61 kg, \( P = 0.001 \)). Initial P. falciparum parasitemia was higher in treatment failures (geometric mean 2,104/μL versus 965/μL; \( P = 0.044 \)). The majority of patients included in this study presented with asymptomatic P. falciparum parasitemia. Twenty percent (6 of 30 cured) and 30% (6 of 20 failures) of the patients in the two groups suffered from malaria symptoms.

Twenty-one women negative during the first 28-day follow-up period were successfully followed up for a second month. Two of them presented with P. falciparum parasitemia. Of the remaining 19 women, data on placental thick smears were available for 12 subjects. Malarial parasites were found in two of these patients.

**DISCUSSION**

In this effectiveness study, we observed a low cure rate of 60% by Day 28 for quinine monotherapy in pregnant women in an area where quinine is still efficacious *in vivo* as well as *in vitro*. Three variables were significantly different between patients experiencing reappearing parasitemia and ultimately cured individuals. Treatment failures tended to be of younger age and lower weight and parasitemia was higher in patients experiencing treatment failure. As semi-immunity is acquired already during childhood in hyperendemic areas and quinine treatment was weight adjusted in this clinical trial, parasitemia might be of particular importance in this context. Women participating in this effectiveness study were recruited from a longitudinal survey with monthly follow-up visits. Therefore, *P. falciparum* infection was diagnosed at an early stage of disease, as reflected by the high rate of asymptomatic infections in our study population. As higher parasit-
Emia was associated with lower cure rate, the actual effectiveness of quinine monotherapy might be even lower in unselected patients presenting with higher parasite burden. Although no statistically significant influence on treatment outcome was observed for parity in this trial, the lower parity in treatment failures also seems to reflect the concept of a parity-dependent increase in immunity against pregnancy-associated malaria strains of \textit{P. falciparum}.\textsuperscript{17}

A potential limitation of this study is the fact that recrudescence was not distinguished from reinfection by genotyping. However, reinfections seem not to account for a major part of treatment failures considering epidemiologic findings at our study site. In a recently conducted survey, the incidence of \textit{P. falciparum} infection was 0.28 per person/year for non-pregnant women.\textsuperscript{18} The relatively low incidence in this age group compared with a crude entomological inoculation rate of 50 might be best explained by a low mosquito exposure of this subgroup and is in concordance with the low rate of reappearing parasitemia during the second month of follow-up in this trial.

Quinine administered under the supervision of a study physician or intravenously for a 7-day period is a highly efficacious treatment in tropical Africa, achieving cure rates of approximately 90\% in our area.\textsuperscript{12} \textit{Plasmodium falciparum in vitro} sensitivity to quinine has not changed over the past decade at our study site as shown recently.\textsuperscript{13,15} Therefore, high efficacy rates of previous clinical trials are in stark contrast to the low effectiveness of quinine monotherapy as observed in our study.

Adherence to the full treatment course may be the main obstacle for effective quinine therapy. Quinine is known to induce substantial side effects particularly in prolonged treatment courses. Adverse events of oral quinine regimens are usually not serious and virtually always self-limiting. Most side effects attributable to quinine are experienced during the initial \textit{P. falciparum} parasitemia\textsuperscript{‡} and usually not serious and virtually always self-limiting. Several studies have shown that the majority of side effects associated with quinine treatment are related to the first 3 days of treatment, when the parasite burden is highest.\textsuperscript{9,21}

\begin{table}
\centering
\caption{Comparison of patients' baseline characteristics comparing individuals with positive and negative thick smears during 28-day follow-up}
\begin{tabular}{lccc}
\hline
 & Positive (\(N = 20\)) & Negative (\(N = 30\)) & \(P\) value \\
\hline
Mean age* (years) (SD, \(N\)) & 20 (4, 20) & 23 (6, 30) & 0.036 \\
Mean weight (kg) (SD, \(N\)) & 54 (6, 18) & 61 (8, 29) & 0.001 \\
Mean EGA\textsuperscript{†} (weeks) (SD, \(N\)) & 25.5 (5.7, 20) & 24.5 (6.3, 30) & NS\textsuperscript{§} \\
Mean gravidity\textsuperscript{†} (range, \(N\)) & 2.2 (1–5, 20) & 3.2 (1–13, 30) & NS\textsuperscript{§} \\
Mean parity\textsuperscript{†} (range, \(N\)) & 0.8 (0–3, 20) & 1.6 (0–9, 30) & NS\textsuperscript{§} \\
Initial \textit{P. falciparum} parasitemia\textsuperscript{‡} (\(\mu L\)) (range, \(N\)) & 2104 (125–240,000, 20) & 695 (12–19, 800, 30) & 0.044 \\
Mean body temperature (\^\circ\textup{C}) (SD, \(N\)) & 36.8 (0.5, 19) & 36.8 (0.4, 27) & NS\textsuperscript{§} \\
Mean hemoglobin (g/dL) (SD, \(N\)) & 9.0 (1.2, 19) & 9.5 (1.1, 29) & NS\textsuperscript{§} \\
Proportion of malaria symptom % (\(N\)) & 30 (20) & 20 (30) & NS\textsuperscript{§} \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*} Normality in Group 2 was rejected by Shapiro-Wilk but not by Kolmogorov-Smirnov test. Nonparametric Mann-Whitney \(U\) test yielded also significant result (\(P = 0.046\)).
\textsuperscript{†} Estimated gestational age by reported last menses date.
\textsuperscript{‡} Number of pregnancies including the current pregnancy.
\textsuperscript{§} Number of births prior to the current pregnancy.
\textsuperscript{‡} Geometric mean, \(t\) test after log-transformation.

7 days in our study population. Besides compliance, immunologic changes in pregnancy and HIV coinfection might also play an important role for the low effectiveness of quinine therapy.\textsuperscript{22} \textit{P. falciparum} infection during pregnancy is a major public health issue posing substantial risks for the health of the mother, the fetus, and the newborn child. Low birth weight and prematurity of newborns due to falciparum malaria in pregnancy are both important contributors to neonatal mortality in endemic regions.\textsuperscript{22,23}

Effective treatment of \textit{P. falciparum} malaria is urgently needed for pregnant women. Nonetheless, data on the efficacy and effectiveness of antimalarial drugs in pregnancy are rare. Despite the fact that pregnant women are particularly vulnerable to malaria, there have been only 12 clinical trials (2.7\% of all clinical trials in malaria) on antimalarials in pregnancy reported in the past decade.\textsuperscript{24} Clinical trials evaluating the efficacy and effectiveness of antimalarials in pregnancy should therefore become a research priority. In the context of the substantial benefits of combining antimalarials in other patient groups, the development of suitable combination regimens for pregnant women seems particularly promising.

Hitherto existing safety and efficacy data suggest combinations of quinine with clindamycin or sulfadoxine-pyrimethamine as potential candidates as well as combinations of artesinin derivatives with slowly acting antimalarials. Due to the failure of the current first-line treatment of uncomplicated malaria in pregnant women, other regimens need to be evaluated for their safety, efficacy, and effectiveness.

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