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*Full Length Research Paper*

# Effect of Quinine therapy on Liver Function Parameters in pregnant women infected with Plasmodium falciparum malaria in Gezira state

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**To examine the role of quinine treatment for *P. falciparum* malaria during pregnancy in alteration of liver function parameters, and correlate the outcome to severity of malaria. The study group included 150 pregnant women with *P.falciparum* malaria, and fifty healthy pregnant women as controls. Serum levels of aminotransferases; albumin, globulin and total protein; direct and indirect bilirubin as well as total bilirubin were tested in the two groups. As part of the correlation, disease severity was assessed, by dividing patients into a pair of subgroups of severe and uncomplicated malaria. The resulted data statistically analyzed. Aminotransferases as well as total bilirubin, direct bilirubin, and indirect bilirubin were significantly increased in malaria group in comparison with control. Albumin, globulin together with total protein in the study group were lower than the control group. Quinine infusions associated with significant decrease in aminotransferases along with total and indirect bilirubin mean levels. *P.falciparum* malaria in Sudanese pregnant women could influence liver parameters and quinine partially reverses this influence. Monitoring of liver function parameters assists in avoiding complications during these circumstances.**

**Keywords:** *P.falciparum* malaria, Pregnancy, Quinine, Liver function parameters

## INTRODUCTION

During pregnancy, the higher serum estrogen and progesterone levels influence liver functions (Bacq et al., 1996). Malaria in pregnancy is a serious health problem in endemic regions (Takem and D'Alessandro, 2013). Quinine is generally safe throughout all trimesters of pregnancy , which makes it widely recommended as a treatment , despite the fact that side effects are common and adherence is poor (McGready et al., 2005). Liver enzymes are increased in malaria parasitemia , to a degree affected by the level of parasitemia (Ignatius et al., 2008). Appropriate interpretation of liver function tests (LFTs) at an early period can result in suitable management as well as minimizing complications in both mother and fetus (Jamjute et al., 2009). In the revised German guidelines on diagnosis and treatment of malaria, parenteral artesunate as well as quinine are regarded as equivalent first-line treatment options (Rolling et al., 2013).

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Quinine is a base and is bound principally to the acute-phase plasma protein a1-acid glycoprotein. Plasma protein binding is increased from approximately 75% to 80% in healthy subjects to over 90% in patients with severe malaria (Nightingale, 2007). Parasitaemia, as a time-varying covariate affecting relative bioavailability, and during acute malaria, quinine plasma concentrations are substantially higher than in the convalescence phase of the treatment (Kloprogge et al., 2014).

The total apparent volume of distribution $V_D$ is diminished during acute malaria, and systemic clearance is dropped in proportion to disease severity. Subsequently, blood concentrations become higher in uncomplicated malaria relative to healthy subjects and highest in patients with severe malaria. In children and pregnant women, the apparent $V_D$ is relatively smaller and elimination is more rapid. The elimination half-life is eleven hours in normal condition, roughly 18 to 20 hours in cerebral malaria and sixteen hours in uncomplicated malaria ( Nightingale, 2007).

The prolonged time to maximum concentration of drug in plasma implies that the rate of absorption is slower in patients compared to healthy people (Auprayoon et al. 1995). Various liver diseases are seen only pregnant women and are reported to be connected with pregnancy (Kondrackiene and Kupcinskas, 2008). Malaria can lead to disastrous outcomes in pregnant women (Jonard and Dewailly, 2004). Quinine is utilized for severe falciparum malaria and uncomplicated P. falciparum (National Guideline, 2015). Hepaticmetabolism is the main elimination route of quinine (80%) (Auprayoon et al., 1995).

Quinine undergoes considerable hepatic biotransformation, initially to 3- and 2-hydroxyquinine; only 20% of the drug is excreted unaffected in urine, and the influence of renal failure on the disposition of quinine does not seem to be significant. Dose reductions are not recommended for patients with severe malaria complicated by either hepatic or renal impairment. In adults with uncomplicated malaria , the elimination half-time of quinine (16 h) is longer than in healthy individuals (11 h); it is even longer in adults with cerebral malaria (18 h) (Winstanley et al., 2004). The systemic clearance of quinine is decreased in acute falciparum malaria, and in severe malaria, it may be as low as one third of that in healthy subjects (Pukrittayakamee et al., 1997).

The aim of our study was to investigate the effect of quinine therapy for malaria, on different biochemical liver function parameters in Sudanese pregnant women.

## PATIENTS AND METHODS

### Study area

This study was carried out at Medani Maternity Teaching Hospital (MMTH), Gezira state, is an area of seasonal mesoendemic malaria transmission (Malik and Khalafalla, 2004). MMTH is the main hospital where all seriously ill patients are referred from health centres and other single-doctor hospitals in the area.

### Study design

This is a prospective, cross-sectional, hospital based, cohort study.

### Patients

A total of 150 patients included in this study were selected from around 2000 pregnant women seen and admitted to the hospital during the period from September to January (the main malaria transmission season) over two years. Pregnant women were included in the study if they had a positive blood film for P. falciparum confirmed microscopically. Patients with diabetes mellitus, and those who used quinine or artemether in the previous three days before the commencement of the study or with intrauterine fetal death or vaginal bleeding were excluded from the study.

The patients or their relatives gave oral consent for recruitment in the study after full explanation of the purpose of the study and its expected risks. The ethical clearance for this study has been obtained from the ethical clearance committee of the college of medicine , university of Gezira.

### Control group

50 healthy pregnant women volunteers selected from the antenatal care clinic as a control group with matched age, gestational age, weight, height, etc.

### Data collection

A full medical and obstetric history and physical examination were performed on the participants and recorded using a questionnaire.

Parasitological diagnosis of malaria was confirmed by thick and thin blood films using Giemsa stain. The parasite was counted against 200 white blood cells and the extent of parasitaemia was calculated using the patients' white blood cells. Haemoglobin was estimated colorimetrically according to *(Lewis and Dacie, 2001*) for each patient immediately on admission.

Blood films for malaria were examined daily until they were negative in two consecutive samples.

### Treatment and follow-up

The women with severe or uncomplicated malaria were treated with quinine (ZMC, ZHEJIANG MEDICINE AND HEALTH PRODUCTS I/E CO. CHINA) at a dose of 10 mg salt/kg 8 hourly per day for 7 days. It was given first

**Table 1.** Clinical and biochemical characteristics of patients and controls.

| Parameter/Group | Healthy Pregnant mean ±SD (N=50) | Pregnant with Malaria mean ± SD (N=150) | P. value |
|---|---|---|---|
| Age (years) | 29 ± 4.6 | 31 ± 4.3 | 0.970 |
| Gestational age (weeks) | 21.8 ± 5.7 | 24.6 ± 7.2 | <0.05 |
| Gravidity | 1.7 ± 1.0 | 2.1 ± 1.4 | <0.01 |
| Parity | 0.7 ± 1.0 | 1.0 ± 1.3 | <0.05 |
| Parasitaemia/200 white blood cells | - | 66574±34329.40 | |
| Hemoglobin g/dl | 11.1±1.3 | 8.7±2.0 | <0.05 |
| Aspartate aminotransferase U/L | 13.02 ± 0.32 | 17.86 ± 0.37 | <0.01 |
| Alanine aminotransferase U/L | 13.22 ± 0.34 | 17.67 ± 0.44 | <0.01 |
| Total protein g/dl | 7.11 ± 0.05 | 5.89 ± 0.06 | <0.01 |
| Albumin g/dl | 3.77 ± 0.03 | 3.11 ± 0.03 | <0.01 |
| Globulin g/dl | 3.32 ± 0.06 | 2.8 ± 0.04 | < 0.01 |
| Total bilirubin mg/dl | 0.9384 ± 0.006 | 1.44 ± 0.05 | <0.05 |
| Direct bilirubin mg/dl | 0.23 ± 0.02 | 0.41 ± 0.04 | <0.05 |
| Indirect bilirubin mg/dl | 0.708 ± 0.05 | 0.98 ± 0.05 | <0.05 |

by intravenous infusion in 5% dextrose solution over 2–4 hours 3 times a day, and when the patient could tolerate it, therapy was continued orally in the form of tablets. The patients were discharged after completing the full dose of quinine on day 8.

### Blood samples collection

Blood samples were collected from each patient in sterile glass container by using sterile syringe, 5 ml of venous blood was drawn. The base line blood sample was taken on day 0 immediately before the commencement of treatment and the second sample was taken on day 2 (2 hours after the 4th dose of treatment with quinine). The third blood sample was taken on day 8 (following the completion of treatment). Blood samples were centrifuged at 4000 rpm for 10 minutes, and the separated sera were kept in the freezer at -70$^0$C till they were required for laboratory examination.

### Laboratory investigations

The stored sera were thawed when required and the following investigations were conducted on day 0, day 2, and day 8 samples:

1. Serum aspartate aminotransferase (AST)
2. Serum alanine aminotransferase (ALT)
3. Serum Total Protein.
4. Serum albumin.
5. Serum globulin.
6. Serum total bilirubin.
7. Serum direct bilirubin.
8. Serum indirect bilirubin.

All investigations were performed in duplicate.

Chemicals:

Kits and chemical reagents were purchased from SpinReact, S.A. Ctra. Santa Coloma, 7 E – 17176 SANT ESTEVE DE BAS (GI) SPAIN.

Albumin was estimated colorimetrically using Bromocresol green method (Dumas et al., 1997) as described by spinreact.

Alanine aminotransferase was estimated spectrophotometrically using NADH. Kinetic UV. IFCC rec. Liquid method (Murray, 1984)

Aspartate aminotransferase was estimated spectrophotometrically using NADH. Kinetic UV. IFCC rec. Liquid method (Bergmeyer et al., 1978).

Bilirubin was estimated colorimetrically using DMSO method (Kaplan et al, 1984 and Malloy et al, 1937).

Total protein was estimated colorimetrically using Biuret method (Burtis et al, 1999).

## RESULTS

In addition to comparing 150 patients with malaria to a group of 50 controls, the malaria group was divided into subgroups of uncomplicated malaria and severe malaria. The clinical and laboratory findings for the women in the study group and the control group are shown in Table 1. The mean levels of AST and ALT were significantly higher ($P < 0.01$) in malaria group when compared to control. The mean levels of total protein including albumin and globulin in the study group were lower ($P < 0.01$) than the control group. Total bilirubin, direct bilirubin, and indirect bilirubin mean levels were significantly higher ($P < 0.05$) in the malaria group. The mean level of parasitemia per 200 white blood cells in the study group, was 66574±34329.40 at presentation. The mean level of hemoglobin concentration was significantly low ($P < 0.05$) in the study group compared to the control group.

**Table 2.** Some Liver function parameters in Quinine – treated patients with severe P.falciparum malaria (means ± standard deviation) on Day 0, Day 2 and Day 8.

| Parameters/Group | | Quinine | Quinine | Significance (2-tailed) | |
|---|---|---|---|---|---|
| | D0 N = 75 | D2 N = 75 | D8 N=75 | A | B |
| Aspartate aminotransferase U/L | 16.0 ± 5.25 | 13.71 ± 4.93 | 12.04 ± 4.64 | S** | S** |
| Alanine aminotransferase U/L | 14.86 ± 6.0 | 12.38 ± 5.29 | 11.36 ± 4.49 | S** | S** |
| Total protein g/dl | 5.93 ± 0.82 | 5.92 ± 0.98 | 5.89 ± 0.77 | NS | NS |
| Albumin g/dl | 3.13 ± 0.49 | 3.15 ± 0.50 | 3.22 ± 0.53 | NS | NS |
| Globulin g/dl | 2.73 ± 0.62 | 2.81 ± 0.55 | 2.64 ± .62 | NS | NS |
| Total bilirubin mg/dl | 1.45 ± 1.0 | 1.18 ± 1.0 | 0.98 ± 0.37 | S** | S** |
| Direct bilirubin mg/dl | 0.23 ± 0.14 | 0.23 ± 0.09 | 0.23 ± 0.03 | NS | NS |
| Indirect bilirubin mg/dl | 1.27 ± 0.96 | 0.96 ± 0.64 | 0.76 ± 0.64 | S** | S** |
| Parasitaemia /200 white blood cells | 110537.333±7161.64282 | - | - | | |

NS: not significant. *Significant at p value < 0.05. **Significant at p value < 0.01.
A: Day 0 vs. Day 2. B: Day 0 vs. Day 8

**Table 3.** Some Liver function parameters in Quinine – treated patients with uncomplicated *P.falciparum* malaria (means ± standard deviation) on Day 0, Day 2 and Day 8.

| Parameters/Group | | Quinine | Quinine | Significance (2-tailed) | |
|---|---|---|---|---|---|
| | D0 N = 75 | D2 N = 75 | D8 N=75 | A | B |
| Aspartate aminotransferase U/L | 19.20 ± 4.24 | 16.22 ± 3.77 | 13.74 ± 3.57 | S** | S** |
| Alanine aminotransferase U/L | 18.80 ± 5.31 | 15.08 ± 4.24 | 12.82 ± 3.78 | S** | S** |
| Total protein g/dl | 5.76 ± 0.60 | 5.60 ± 0.60 | 5.65 ± 0.61 | NS | NS |
| Albumin g/dl | 3.06 ± 0.37 | 2.86 ± 0.39 | 3.0 ± 0.52 | S** | NS |
| Globulin g/dl | 2.70 ± 0.45 | 2.78 ± 0.57 | 2.64 ± 0.32 | NS | NS |
| Total bilirubin mg/dl | 1.41 ± 0.05 | 0.93 ± 0.06 | 0.90 ± 0.09 | S** | S** |
| Direct bilirubin mg/dl | 0.22 ± 0.02 | 0.22 ± 0.024 | 0.22 ± 0.03 | NS | NS |
| Indirect bilirubin mg/dl | 1.23 ± 0.05 | 0.72 ± 0.07 | 0.68 ± 0.09 | S** | S** |
| Parasitaemia /200 white blood cells | 46574±4802.39495 | - | - | | |

NS: not significant. *Significant at p value < 0.05. **Significant at p value < 0.01.
A: Day 0 vs. Day 2. B: Day 0 vs. Day 8

In table 2, comparing day 0 with day 2, and comparing day 0 with day 8 of therapy in patients with severe *P.falciparum* malaria , quinine infusions associated with significant reduction($P < 0.01$) in AST and ALT mean levels as well as significant reduction ($P < 0.01$) in total and indirect bilirubin mean levels. The mean level of parasitemia per 200 white blood cells in the study group with severe malaria, was 110537.333±7161.64282 on admission.

In addition, quinine infusions in patients with uncomplicated *P.falciparum* malaria also showed significant ($P < 0.01$) reduction in AST, ALT, total and indirect bilirubin mean levels, comparing day 0 with day 2 as well as comparing day 0 with day 8 of therapy. Albumin showed transient significant ($P < 0.01$) reduction in day 2. The mean level of parasitemia per 200 white blood cells in the study group with uncomplicated malaria, was 46574±4802.39495 as shown in Table 3.

## DISCUSSION

Disturbances of liver function contribute to the pathogenesis of lactic acidosis, hypoglycaemia, coagulopathyand to the development of jaundice in severe malaria (White and Ho, 1992). Quinine continues to be an essential antimalarial medication. However, the therapeutic window for the unbound drug is comparatively narrow. Negligible side effects such as tinnitus, dysphoria and nausea (cinchonism ) are frequent and hypoglycaemia is a particular issue in later pregnancy (Kloprogge et al., 2014). Quinine is an effective antimalarial for the treatment of chloroquine-resistant falciparum malaria and is the drug of choice for the treatment of severe malaria (Auprayoon et al., 1995). The level of liver function parameters is altered during the course of malaria.

The study showed that aminotransferases levels were

significantly high ($p< 0.01$), as well as total and indirect bilirubin levels ($p< 0.01$) in P.falciparum malaria pregnant patients when compared with pregnant controls. In addition, albumin and globulin levels were significantly low ($p < 0.05$) in P.falciparum malaria pregnant patients when compared with pregnant controls. This findings agree with Premaratna et al (Premaratna et al., 2001) and Sharma et al (Sharma et al., 2012) who documented liver dysfunction in P.falciparum malaria. The positive association found between gestational malaria and liver enzymes, suggest that the latter increased in malarial parasitaemia to an extent dependent on the degree of parasitemia (Bhalla et al., 2006). The findings of high bilirubin (total, direct and indirect) agree with Jha et al (Jha et al., 2014). Low levels of total protein in pregnant women infected with P.falciparum could be explained by reduction in protein synthesis by hepatic cells and to some extent by proteinuria which affirms the report of Fisayo (Fisayo, 2007).

Treatment with quinine in the subgroups of patients with severe P.falciparum malaria resulted in significantly lower ($p< 0.01$) levels of aminotransferases as well as total and indirect bilirubin levels ($p< 0.01$). This supports the study of Kochar et al (Kochar et al., 2003) who have reported a fall in serumbilirubin and regression of signs of hepatic encephalopathy in patients with P.falciparum malaria. The Reduction in aminotransferases levels could be explained partially by the effect of quinine on elimination of parasitaemia. According to Onyesom and Onyemakonor (Onyesom and Onyemakonor, 2011) as well as Ignatius et al (Ignatius et al., 2008), there was a positive correlation between aminotransferases activities and level of parasitaemia.

Treatment with quinine in the subgroup of patients with uncomplicated P.falciparum malaria resulted in a similar significant ($p< 0.01$) reduction in aminotransferases levels and indirect bilirubin level. However, quinine injections associated with reduction on level of albumin on day 2 of treatment in this sub group. The effect of quinine on albumin was transient and albumin level returned to a level insignificantly different from the level at the commencement of treatment. Wanwimolruk et al (Wanwimolruk and Denton, 1992) indicated that quinine is bound primarily to alpha 1-acid glycoprotein (AAG) and albumin, although other plasma proteins such as lipoproteins may be involved. This suggests a correlation between quinine and albumin during initial phase of treatment in pregnant women with uncomplicated P. falciparum malaria. Severity of malaria and parasitaemia affect quinine pharmacokinetics and relative bioavailability. According to Babalola CP et al (Babalola et al., 1998). Malaria affects the pharmacokinetic properties of quinine, resulting in higher total exposures during the acute phase of the disease in proportion to disease severity measured by level of parasitaemia. In addition, drug exposure was only affected during the acute phase when parasitaemia was above the limit of detection (Kloprogge et al., 2014). Kloprogge F et al included additional factors that affect pharmacokinetics of quinine such as estimated gestational age (EGA) and the body temperature on admission. Furthermore, Auprayoon et al (Auprayoon et al., 1995) could not find significant correlation between serum albumin or bilirubin concentrations and the total clearance of quinine in patients with chronic liver disease, which suggests that this correlation may be limited only to acute diseases. However, our study may suggest an effect on quinine pharmacokinetic that could be related to factors other than severity of malaria and parasitaemia.

In summary, malaria in Sudanese pregnant women affects liver parameters by increasing aminotransferases and bilirubin as well as reducing albumin and globulin. Treatment with quinine helps to normalize liver parameters in these women except albumin which increased initially. Monitor of albumin might be advisable and crucial during P. falciparum malaria infection in pregnant women. Additional studies should be carried out to unveil and trace other factors that may affect quinine pharmacokinetics administered during pregnancy.

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