

**Original Article.****BIOCHEMICAL STUDY IN SUDANESE CHILDREN WITH CEREBRAL MALARIA DURING ANTIMALARIAL TREATMENT (ARTEMETHER vs. QUININE)**

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**ABSTRACT**

**Background** Malaria is an important neglected disease and one of the most important global health problems, potentially affecting more than one third of the world's population. Cerebral malaria (CM) is a deadly complication of *Plasmodium falciparum* infection, associated with a 15-30% mortality rate and approximately 1-2 million annual deaths among young children predominantly in sub-Saharan Africa and Southeast Asia.

**Objectives** The objective of this study was to examine the effect of artemether on some biochemical parameters and compare it with that of quinine in Sudanese children with cerebral malaria.

**Methods** This is a comparative randomized controlled antimalarial treatment trial of intramuscular artemether in cerebral *falciparum* malaria in children. Forty one children of age 3 months to 15 years with cerebral malaria were divided into artemether group (24 patients) and quinine group (17 patients) they received treatment as recommended. Blood samples of each group were collected on day 0 and day 2. Serum levels of glucose, creatinine, urea, total protein, albumin, globulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were measured and results compared.

**Results** In quinine treated group there was significant decrease in blood glucose, even when compared with the Artemether treated group ( $P=0.01$ ). Additionally, the ALT was significantly elevated in the quinine treated patients ( $P=0.03$ ). No significant differences in levels of other parameters were observed between the two groups during the study. Comparing the Artemether treated group with the quinine treated group, both groups were completely treated from cerebral malaria.

**Conclusions** Artemether is as effective as quinine in the treatment of cerebral malaria in children. It is safe, well tolerated and easy to administer.

**Key words:** artemether, cerebral malaria, children, *falciparum* malaria, quinine,

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## الخلاصة

الملاريا من الأمراض المهمة وأحد أهم المشكلات الصحية العالمية وتصيب أكثر من ثلث سكان العالم. الملاريا الدماغية من المضاعفات المميتة للبلازموديوم فالسبارم وتتراوح نسبة الوفيات الناجمة عنها 15-30%. وقد تصل حوالي 1-2 مليون حالة وفاة سنويا بالأخص صغار الأطفال في إفريقيا وجنوب شرق آسيا.

هدفت هذه الدراسة لمعرفة تأثير عقار الأرتيميثير على بعض القياسات الكيموحيوية والمقارنة مع عقار الكينين في الأطفال السودانيين المصابين بالملاريا الدماغية. تعتبر هذه دراسة عشوائية للمقارنة العلاجية، ويقارن فيها الأرتيميثير مع الكينين في علاج الملاريا الدماغية عند الأطفال. شملت الدراسة 41 طفلاً في الأعمار من 3 أشهر - 15 عاماً تم تشخيصهم بالملاريا الدماغية، قسموا الي مجموعتين، مجموعة الأرتيميثير (24 مريضاً) ومجموعة الكينين (17 مريضاً) تلقياً العلاج على النحو الموصى به. جُمعت عينات الدم من كل مجموعة قبل العلاج واليوم الثاني للعلاج لقياس مستويات الجلوكوز، الكرياتينين، اليوريا، البروتين الكلي والألبومين، الجلوبيولين، إنزيم الانين أمينوتراسفيريز (ALT)، إنزيم اسبارتيت أمينوتراسفيريز (AST) و إنزيم الفوسفاتاز القلوي (ALP)، تم قياس ومقارنة النتائج.

أظهرت مجموعة الكينين انخفاض ملحوظ في نسبة جلوكوز الدم بعد العلاج وحتى عند مقارنتها مع مجموعة الأرتيميثير ( $P=0.01$ ). بالإضافة إلى ذلك زيادة مستوى إنزيم الانين أمينوتراسفيريز في المجموعة المعالجة بالكينين مقارنة بمجموعة الأرتيميثير ( $P=0.03$ ) ولم يلاحظ اختلاف في القياسات الأخرى أثناء الدراسة. تم علاج جميع الأطفال المصابين في مجموعتي الأرتيميثير والكينين مما يستنتج من ذلك أن عقار الأرتيميثير علاج فعال مماثل لعقار الكينين في علاج الملاريا الدماغية لدى الأطفال.

## Introduction

Malaria continues to be a major health problem in sub-Saharan Africa. In general, the disease is endemic in more than 90 countries and is responsible for about 500 million cases and more than 1 million deaths each year<sup>1</sup>. Cerebral malaria (CM) is a serious complication of *Plasmodium falciparum* infection and contributes significantly to the morbidity and mortality of this pandemic. Primarily young children develop a diffuse potentially rapidly reversible encephalopathy associated with loss of consciousness, seizures, and few localizing neurologic signs; other complications as severe anemia or respiratory distress increase the

tragic outcome<sup>2</sup>. CM is estimated to affect more than 785000 children who are younger than 9 years in sub-Saharan Africa every year, the case fatality rate even with optimal therapy, is 15-30%<sup>3</sup>. Children who survive CM may be left with permanent neurological sequelae, including seizures, acquired language disorders, motor deficits, and problems with memory and attention<sup>4, 5</sup>. Recent studies have shown that mechanical blockage caused by sequestration of parasitized red blood cells (pRBCs), leukocytes and platelets, secretion of cytokines and chemokines, increased levels of matrix metalloproteinases, angiogenic failure, immune status, the genetic background of the host, and parasite factors are involved in the pathogenesis of CM<sup>6,7</sup>.

Of increasing concern, a sub-patent parasitemia which may occur in CM, high fatality rate among quinine-treated patients and the declining efficacy of quinine in parts of Southeast Asia, a trend that could prove disastrous if it spreads to Africa, are the most challenges in diagnosis and treatment alternatives<sup>8, 9</sup>. One of the potential alternatives to quinine, the artemisinin (qinghaosu, *Artemisi annua*); artemether, the methyl ether of dihydroartemisinin (the active metabolite of artemisinin) has shown marked therapeutic effects<sup>10</sup>. In addition, studies in Kenya, Malawi, Nigeria, Sudan and Uganda reported that children with cerebral malaria recovered more quickly from coma when treated with artemether than when treated with quinine, and the use of artemether represents an important option in the management of cerebral malaria especially in rural areas where facilities for intravenous administration may not yet be optimal<sup>11-15</sup>. Information on the use of artemether in children is limited; therefore we studied the biochemical status of children with CM during treatment with artemether in reference to quinine.

## Methods

**Study Population** The study was conducted in Khartoum, the capital of Sudan. Recruitment began at the Khartoum Pediatric Hospital and Ahmed Gasim Pediatric Hospital, forty one patients with clinical symptoms of CM, asexual forms of *P. falciparum* were identified on a thick blood film, aged between 3 months to 15 years were enrolled in this study. Patients with diseases other than CM at the time of admission were excluded, as those with evidence or history of head trauma, bacterial meningitis, drug toxicity, administration of anti-malarial, sepsis, typhoid fever, diabetic coma, or epilepsy.

**Study Design** This study is randomized controlled antimalarial treatment trial of intramuscular artemether versus standard quinine

in cerebral falciparum malaria in Sudanese children. A sequence of randomly drug assignments were kept in sealed envelopes, and opened as each subject was entered, this procedure should minimize biased group assignment. Rational of the study was clarified to all patients' parents/ guardians to obtain their consent. The ethical clearance to carry out this trial was granted by the ministry of health and medical council for research, Sudan.

**Drug schedule** Patients were hospitalized for at least 7 days during which antimalarial treatment was completed, became a parasitemic and able to function independently. Patients assigned to the artemether group (24 patients) received intramuscular injections of artemether for four days, in an initial dose of 3.2 mg/kg, followed by daily doses of 1.6 mg/kg for five days. Those assigned to the quinine group (17 patients) received intravenous infusion of quinine 20 mg/kg of quinine dihydrochloride dissolved in 5% dextrose as initial dose followed by 10 mg/kg every 8 hours for 7 days.

**Clinical assessment and laboratory investigations** On admission, the patient's history and clinical findings were recorded on standardized questionnaire. A venous blood samples were obtained for estimation of glucose, creatinine, urea, total protein, albumin, globulin, ALT, AST and ALP in serum on day 0 (prior treatment) and day 2 (during treatment). All surviving children were asked to return on days 14, 21 and 28 of admission, for a further detailed assessment by a clinical investigator.

**Statistical Analysis** Values were presented as mean  $\pm$  standard deviation (SD), comparison between variables was analyzed by Student's t-test using SPSS, version 12.0 (SPSS Inc, Chicago, IL 60606, USA). Statistical significance for each parameter was set at a two tailed  $P < 0.05$ .

## Results

A total of 41 children were randomly assigned to receive artemether or quinine. The clinical features on admission were similar in the two groups (Table 1). On admission, 75.61% had past history of malaria, 9.76% had past history of CM. More than two thirds of children (68.29%) were from low socio-economic status.

The blood glucose was significantly decreased on day 2 after administration of quinine ( $P = 0.01$ , Table 2). The other biochemical parameters showed no significant differences before and after quinine treatment. Laboratory findings in the Artemether treated group are presented in Table 3; admission laboratory data were generally similar. Table 4 summarizes the changes in the

biochemical parameters levels in quinine and Artemether treated groups on Day 2, the levels of creatinine, urea, total protein, albumin, globulin, AST and ALP did not show statistically significant differences between the 2 treated groups. However, changes in levels of glucose and ALT were associated with quinine treatment. The level of glucose was significantly lower in children treated with quinine compared with those treated with artemether ( $P= 0.01$ ), while the ALT level was significantly higher in the quinine treated group ( $P= 0.03$ ).

### Discussion

Intramuscular artemether is effective and well tolerated and could be used to treat cerebral malaria. There were no major adverse effects observed with any of the two treatment regimens. With all regimens, all of the patients survived, the clinical and biochemical outcomes of artemether and quinine were similar. In the present study, evidence is provided indicating that the serum levels of blood glucose and the ALT, were altered in the quinine treated group. The changes in the other measured parameters creatinine, urea, total protein, albumin, globulin, AST and ALP were not significant.

Hypoglycemia is a common complication of severe falciparum malaria, occurring in 8–30% of individuals affected with this disease. It is frequently seen in children with severe malaria, particularly in those with cerebral malaria and often correlated to quinine and quinidine therapy<sup>16</sup>. Disorders of carbohydrate metabolism, including hypoglycaemia and lactic acidosis, are amongst the most important markers of disease severity both in adults and children infected with *Plasmodium falciparum*. Hypoglycemia occurring during management in patients of severe malaria is often overlooked, which can be associated with higher morbidity and mortality rates. In this study the difference in glucose concentration was significantly decreased on day 2 in quinine treated group. The mean of blood glucose concentrations before treatment was similar in both groups; so the significant fall in glucose levels has been attributed to quinine hyperinsulinemic effect<sup>17</sup>. In addition to quinine-induced hyperinsulinemia acutely ill patients with malaria are prone to development of hypoglycemia that is usually ascribed to increased glucose consumption (by malarial parasites) and impaired glucose production caused by the inhibition of gluconeogenesis<sup>18</sup>. Several trials conducted in Bangladesh, India, Indonesia, and Myanmar showed that treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia<sup>19</sup>. A study in Africa,

reported a similar finding: 32.14% of patients treated with intravenous quinine for severe malaria showed plasma glucose concentrations below 2.8 mmol/l with increase in the insulin: glucose ratio<sup>20</sup>. Therefore, patients with cerebral malaria should be monitored frequently for hypoglycaemia especially during quinine treatment and treated rapidly with intravenous glucose if hypoglycaemia is detected.

**Table 1: Clinical and laboratory findings in patients with cerebral malaria on admission.**

Findings	Quinine(17)	Artemether(24)
Coma	17	24
Temperature	39.8± 0.40 C°	39.9± 0.57 C°
Hemoglobin	8.6± 1.6g/dl	8.4± 2.2g/dl
Jaundice	0	1
TWBCs	5453±1597 cells	5213±70 cells
Vomiting	11	12
Diarrhea	5	3
Headache	9	13
Convulsions	15	22
Hallucination	6	6
Past history of epilepsy	1	1
Past history of febrile convulsions	3	4
Past history of malaria	13	18
Past history of cerebral malaria	2	2

Besides hypoglycemia, the level of ALT was significantly increased in the group treated with quinine. When we compared the level of ALT on day 0 and day in the Artemether treated group the level was lower, but the difference was not significantly different. Few cases of quinine hepatotoxicity have been reported, occurring as an acute illness characterized by fever, nausea, malaise associated with moderately high levels of aminotransferase, and manifested by a clinical syndrome mimicking a viral illness and a mixed hepatocellular-cholestatic

liver injury pattern<sup>21-23</sup>. Moreover, in comparison of artemether and quinine in the treatment of severe falciparum malaria in south-east Thailand and Manipur, artemether gave a better survival rate, less neurological sequelae after recovery of consciousness and side effects than quinine<sup>24, 25</sup>.

In conclusion, artemether is as effective as quinine for CM. Furthermore, it is relatively safe and has advantages with respect to the developing hypoglycemia, quinine-induced hepatotoxicity, quinine adverse effects, and quinine resistance. These characteristics render artemether an attractive option for the management of cerebral malaria. More trials with a larger number of participants are needed for comprehensive reassessment of this little-recognized manifestation of quinine use.

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**Table 2: Glucose, creatinine, urea, total protein, albumin, globulin, ALT, AST and ALP serum levels in Quinine treated patients on Day 0 and Day 2.**

Group	Glucose	creatinine	urea	total protein	albumin	globulin	ALT	AST	ALP
Quinine D0	81.57±26.45	0.79±0.38	31.87±24.28	7.02±0.79	4.44±0.75	2.58±0.95	40.71±26.32	22.50±9.35	46.39±34.64
Quinine D2	54.87±28.67	0.98±0.58	33.81±34.15	7.28±0.74	4.50±0.81	2.78±0.77	52.12±29.80	24.50±9.80	38.85±31.53
P value	0.01	NS	NS	NS	NS	NS	NS	NS	NS

**Table 3: Glucose, creatinine, urea, total protein, albumin, globulin, ALT, AST and ALP serum levels in Artemether treated patients on Day 0 and Day 2.**

Group	Glucose	creatinine	urea	total protein	albumin	globulin	ALT	AST	ALP
Artemether D0	82.37±31.84	1.16±0.97	35.38±27.56	7.88±1.41	4.51±0.76	3.40±1.18	40.79±31.75	21.81±12.52	36.14±19.10
Artemether D2	83.06±37.42	1.07±0.55	28.08±17.28	7.70±1.06	4.68±1.03	3.02±1.11	33.08±25.40	28.08±14.95	43.25±28.22
P value	NS	NS	NS	NS	NS	NS	NS	NS	NS

**Table 4: Glucose, creatinine, urea, total protein, albumin, globulin, ALT, AST and ALP serum levels in Quinine and Artemether treated patients on Day 2.**

Group	Glucose	creatinine	urea	total protein	albumin	globulin	ALT	AST	ALP
Quinine D2	54.87±28.67	0.98±0.58	33.81±34.15	7.28±0.74	4.50±0.81	2.78±0.77	52.12±29.80	24.50±9.80	38.85±31.53
Artemether D2	83.06±37.42	1.07±0.55	28.08±17.28	7.70±1.06	4.68±1.03	3.02±1.11	33.08±25.40	28.08±14.95	43.25±28.22
P value	0.01	NS	NS	NS	NS	NS	0.03	NS	NS

NS: not significant.



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