Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206 (Online)**
Sch. Acad. J. Pharm., 2016; 5(2): 27-33 **ISSN 2347-9531 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Original Research Article

A Study of Prognostic Indicators in Patients of Severe Falciparum Malaria on Treatment with Artesunate And Quinine

Dr. Shivendra Verma[1], Dr. Richa Giri[2], Dr. Rajendra Verma[3], Dr. Vaibhav Srivastav[4], Dr. Saumya Gupta[5]
[1,3]Assistant Professor, [2]Professor & Head, [4]Lecterur, [5]Senior Resident, Department of Medicine, GSVM Medical College, Kanpur, Uttar Pradesh, India

***Corresponding author**
Dr. Shivendra Verma
Email: dr.shivendra@gmail.com

Abstract: Severe falciparum malaria is a common and fatal malarial illness. The recommended regimen for severe falciparum malaria includes either artesunate or quinine based treatment. 100 patients of severe falciparum malaria were divided into two groups and randomly assigned to either ARTESUNATE or QUININE based regimen. A detailed clinical and biochemical evaluation of both groups was compared. Most common clinical signs were pallor, icterus, hepatosplenomegaly, altered sensorium and decreased urine output. 30% of patients had GCS <11, 87% had serum lactate >5mmol/L, S. Bilirubin was raised in 50% but abnormal AST/ALT was found in all patients and equally distributed in both groups. Of the two regimens hypoglycemia during treatment was more common in QUININE group than ARTESUNATE group (30% vs 12%), there was also increased mortality in quinine group (13 vs 7) but was not statistically significant. However, mean hemoglobin rise, normalization of GCS, LFT, time to death and coma recovery time were no different in two groups. Among the quinine treated patients there was an increased incidence of hearing disturbances (24%), QT interval prolongation (6%), ARF (4%) and visual disturbance was present in one patient.
Keywords: GCS, AST/ALT, LFT, GBP, KFT, ABG, PT, APTT, CRT.

INTRODUCTION:

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes. Features indicating poor prognosis in severe falciparum malaria are marked agitation, hyperventilation (respiratory distress), hypothermia (36.5ºC), bleeding, deep coma, repeated convulsions, anuria and shock. Laboratory findings indicating severity are hypoglycemia (<2.2mmol/l), hyperlactatemia (>5mmol/l), acidosis, elevated serum creatinine, total bilirubin, liver enzymes, muscle enzymes, urate, leucocytosis, severe anaemia, coagulopathy and parasitemia>2%[1,5].

The mortality risk of severe falciparum malaria is very high compared to those with uncomplicated malaria (pts who can take medications orally and with no major organ dysfunction). The recommended regimen for treatment of severe falciparum malaria is either artemisinin based or quinine/quinidine[2]. Although artemisinin compounds remain the drug of choice, quinine is still used in our region[3]. Among the two drugs artesunate is safe in liver failure, hepatic failure and pregnancy and doesn't require dose alteration in these states. Quinine on the other hand, requires dose modification in acute renal failure and severe organ dysfunction. Moreover, there is risk of hypoglycemia and slight risk of arrhythmias in patients with underlying heart disease. Despite this preliminary knowledge in favor of artesunate the present study was designed to see the difference in efficacy, outcomes and side effects of the two most commonly used regimens in severe falciparum malaria in actual clinical scenario[4,5].

STUDY METHODS

The study was carried out in the post graduate institute of medicine, G.S.V.M. Medical College. The material of the study included cases of SEVERE FALCIPARUM malaria selected from medicine indoor wards.

TYPE OF STUDY: Randomised Control Trial

INCLUSION CRITERIA FOR SEVERE FALCIPARUM MALARIA

	Manifestations
Major	
Unarousable coma/cerebral malaria	Failure to localize or respond appropriately to noxious stimuli; coma persisting for >30 min after generalized convulsion
Academia/acidosis	Arterial pH <7.25 or plasma bicarbonate level of <15 mmol/L; venous lactate level of >5 mmol/L; manifests as laboured deep breathing, often termed "respiratory distress"
Severe normochromic, normocytic anaemia	Hematocrit of <15% or hemoglobin level of <50 g/L (<5 g/dL) with parasitemia level of >100,000/L
Renal failure	Urine output (24 h) of <400 mL in adults or <12 mL/kg in children; no improvement with rehydration; serum creatinine level of >265 mol/L (>3.0 mg/dL)
Pulmonary edema/adult respiratory distress syndrome	Noncardiogenic pulmonary edema, often aggravated by over hydration
Hypoglycemia	Plasma glucose level of <2.2 mmol/L (<40 mg/dL)
Hypotension/shock	Systolic blood pressure of <50 mmHg in children 1–5 years or <80 mmHg in adults; core/skin temperature difference of >10°C; capillary refill >2 s
Bleeding/disseminated intravascular coagulation	Significant bleeding and hemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of disseminated intravascular coagulation
Convulsions	More than two generalized seizures in 24 h; signs of continued seizure activity sometimes subtle (e.g., tonic-clonic eye movements without limb or face movement)
Hemoglobinuria[a]	Macroscopic black, brown, or red urine; not associated with effects of oxidant drugs and red blood cell enzyme defects (such as G6PD deficiency)
Other	
Impaired consciousness/arousable	Unable to sit or stand without support
Extreme weakness	Prostration; inability to sit unaided[b]
Hyperparasitemia	Parasitemia level of >5% in no immune patients (>20% in any patient)
Jaundice	Serum bilirubin level of >50 mmol/L (>3.0 mg/dL) if combined with other evidence of vital-organ dysfunction

EXCLUSION CRITERIA:

1: MALARIA CAUSED BY SPECIES OTHER THAN P.FALCIPARUM

2: PATIENT FREE FROM CONDITION SUCH AS:

a. Patient should not be diabetic
b. Known case of haemolytic anaemia
c. Respiratory illness and cardiovascular disorders.
d. Antiarrythmics
e. CKD patients
f. Seizure disorders
g. Other infectious diseases – septic and viral meningitis excluded by CSF studies.
h. Acute or chronic liver diseases.
i. Pregnancy.

METHODS:

HISTORY: Fever usually associated with chills and rigors. Headache, myalgia and abdominal discomfort, generalized seizures, jaundice.

2. EXAMINATION:

3. INVESTIGATIONS

1. THICK AND THIN BLOOD SMEAR.
2. rapid diagnostic test
3. HB WITH GBP
4. URINE ROUTINE AND MICROSCOPY
5. ECG
6. LFT
7. PT, APTT, BT, CT
8. KFT
9. ABG
10. S. lactate

TREATMENT

The patients who were diagnosed as cases of severe falciparum malaria were divided into two groups: GROUP A receiving ARTESUNATE and group B receiving QUININE. The patients while on treatment were monitored on day of admission, 48 hrs, 72 hrs and 7th day both clinically and biochemically

OBSERVATIONS

Table1: Clinical Features of Patients

Clinical signs	Patient distribution	%
Pallor	90	90
Icterus	50	50
Hepatomegaly	25	25
Splenomegaly	60	60
Altered sensorium	49	49
Decreased urine output	10	10

Table2: Distribution of Patients of Severe Falciparum Malaria on treatment with Artesunate and Quinine according to Prognostic Indicators

Criteria	Total	Artesunate receiving group (A)	Quinine receiving group (B)
Glasgow coma scale <11	30	14 (28%)	16 (32%)
Serum lactate levels >5mmol/l	87	43	44
Plasma glucose levels <2.2mmol/l (40 mg/dl)	10	8	2
Hb< 5gm%	22	10	12
Liver function test			
Serum bilirubin levels >50µmol/l	50	26	24
SGPT/SGOT	100/98	50/49	50/49
PT	65	30	35
Se ALP	90	42	48
Se protein (total/albumin)	70	36	34

Table 3: Laboratory Details on Admission for the Patients of Severe Falciparum Malaria on Artesunate or Quinine

Variable	All (n=100)	Artesunate (50)	Quinine (40)	P
Median glassgow coma scale score (range)	15 (3-15)	15 (3-15)	13 (3-15)	0.30
Serum lactate level, medial mmol/l (range)	4.3 (0.3-27.3)	4.8 (1.0-20.1)	3.8 (0.3 27.3)	0.65
Plasma glucose levels, mean mmol/l	8.5 (7.7-9.3)	8.2 (7.2-9.3)	8.4 (7.4-9.5)	0.07
Hb median (range)	7.0 (2-11.8)	7.6 (2-11.8)	6.8 (2.4-11)	0.37
Liver function test				
Total serum bilirubin levels, median µmol/l (range)	51 (9-646)	54 (8-646)	54 (11-453)	0.98
SGPT/SGOT	115/75 (71-158) /(52-98)	153/116 (55-251)/ (4-228)	149/77 (46-351)/ (4-300)	0.02/0.34
Se ALP	310 (100- 800)	320 (100-556)	300 (120-800)	0.54
Se Protein T/A	6.3/2.2 (5-8)/ (1.5-3.5)	6.3/2.3 (5-8)/ (1.5-3.5)	6.5/2.2 (5-8)/ (1.5-3.5)	0.46/0.57
PT	18 (10-23)	17 (10-23)	16 (11-20)	0.68

Normal plasma glucose levels 3.5-5.5 mmol/l
Normal serum lactate levels <2mmol/l
Normal Hb levels >11 gm%
Normal serum bilirubin levels 3-17µmol/l, Normal serum Alkaline Phosphatase level 20-140 IU/l,Normal range of PT 10-14 seconds , serum proteins/ albumin- 7-9/3.5-5.5, PT/OT- <40

Table 4: Outcome Measures For Treatment Of the Patients enrolled In The Study

Variables	All	Artesunate (A)	Quinine (B)	P value
Hypoglycemic episodes, no. of patients	21	6 (12%)	15 (30%)	0.027
Time to plasma lactate levels <2 mmol/l, median h (range)	12 (1-120)	18 (2-72)	12 (1-120)	0.63
Coma recovery time , median h (range)	17 (1-188)	17 (1-125)	18 (1-188)	0.87
No. of patients who died	20	7	13	0.13
Time to death, median h (range)	42 (3-408)	48 (29-408)	21 (3-144)	0.24
Time for normalization of LFT h (range)	72 (24-160)	72 (24-120)	72 (24-160)	0.77
Hb level	7.0 (2-11.8)	7.6 (2-11.8)	6.8 (2.4-11)	0.37

Table 5: Reported Adverse Events in the two groups of Patients

Primary treatment	Quinine (n=50) (B)	Artesunate (n=50) (A)	P value
Hypoglycemia	15 (30%)	6 (12%)	0.027
Hearing disturbances	12 (24%)	0	0.0004
Visual disturbances	1 (2%)	0	0.33
Hepatotoxicity	1 (2%)	0	0.33
Prolongation of QTc-interval	3 (6%)	0	0.09
Acute renal failure	2 (4%)	0	0.17
Other	2 (4%)	3 (6%)	0.58

Other adverse reactions include idiosyncratic reactions, skin rashes.

Patients in group B receiving Quinine experienced more number of adverse effects as compared to patients of Artesunate receiving group A. out of these, occurrence of hypoglycemia and hearing disturbances were statistically significant.

Table-6: Hypoglycemic Episodes in Patients of Severe Falciparum Malaria on Treatment with Artesunate or Quinine

	ACT Group (A)	Quinine Group (B)
Hypoglycemic episodes	6	15
Mean±SD.	0.12±0.33	0.30±0.46

Out of the 21 patients who experienced hypoglycemic episodes 6 were in Artesunate receiving group A and mean ± SD. for this group was 0.12±0.33 and 15 patients were in the Quinine receiving group B and mean±SD. for this group was 0.30±0.46; the **P value** for this was **0.027** which was statistically significant**.**

Table 7: Mortality In Patients Of Severe Falciparum Malaria On Treatment With Artesunate Or Quinine

Results	Artesunate Group (A)	Quinine Group (B)
Expired	7	13
Improved	43	37
Mean±SD.	0.14±0.35	0.26±0.44

In the present study 21 patients expired. 7 patients were in group A and mean±SD. was 0.14±0.35 and 13 patients were in group B and mean±SD. was 0.26±0.44; the **P value** for this was **0.13** which was statistically not significant.

Table 8: Time (In Hrs.) For Normalization of Serum Lactate Levels

Time (hours)	Artesunate Group (A)	Quinine Group (B)
<7 hrs	6	9
7-21 hrs	31	20
21-35 hrs	1	4
35-49 hrs	1	1
49-63 hrs	1	0
63-77 hrs	3	11
77-91 hrs	0	0
>91 hrs	0	2
Expired	7	13
Mean±SD.	17.08±17.49	15.12±23.25

Time for normalization of serum lactate levels was slightly lower for the Quinine receiving group B and mean±SD. was 17.08±17.49 whereas for Artesunate receiving group Amean±SD. was 15.12±23.25; the **P value** for this was **0.63** which was statistically not significant.

Table-9: Coma Recovery Time (In Hrs.) In Patients of Severe Falciparum Malaria

Time (hours)	Artesunate Group (A)	Quinine Group (B)
<25 hrs	13	13
25-50 hrs	3	6
50-100 hrs	2	0
100-150 hrs	2	1
150-200 hrs	0	1
Expired	7	13
Mean±SD.	13.72±28.53	14.66±33.24

Coma Recovery Time (CRT) was slightly lower for the Artesunate receiving group A and mean±SD for this group was 13.72±28.53 whereas mean±SD for the Quinine receiving group B was 14.66±33.24; the **P value** for this was **0.87** which was statistically not significant.

Table 10: Time to Death (In Hrs.) In Patients

Time (hours)	Artesunate Group (A)	Quinine Group (B)
<25 hrs	1	7
25-50 hrs	5	3
50-100 hrs	0	2
100-150 hrs	0	1
>150	1	0
Mean±SD.	90.86±140.26	41.77±40.15

The time to death for group A was longer as compared to group B. The mean±SD for group A was 90.86±140.26 whereas mean±SD for group B was 41.77±40.15; the **P value** for this was **0.24** which was statistically not significant.

Table 10: Time for Normalization of LFT

Time (hours)	Artesunate Group	Quinine Group
<25 hrs	2	2
25-50 hrs	19	14
50-100 hrs	19	17
100-150 hrs	3	4
Expired	7	13
Mean±SD.	53.68±29.42	51.68±40.43

There was no significant difference in the time for normalization of LFT in both groups A and B. The

mean±SD. for group A was 53.72±29.42 whereas mean±SD. for group B was 51.68±40.43; the **P value** for this was **0.77** which was statistically not significant.

DISCUSSION

Clinical and laboratory parameters of patients on admission did not differ significantly between the quinine and artesunate groups for all patients and for the subset of patients with severe malaria. The median admission GCS score was lower in the quinine group; 32% of the patients in that group had cerebral malaria, compared with 28% in the artesunate group.

The overall mortality was 20%,7 patients in the ARTESUNATE receiving group A expired (14%), and 12 patients in the quinine receiving group B expired (24%)The mean±SD was 0.14±0.35 for group A and mean±SD was 0.26±0.44 for group B ; the P value for this was 0.13 which was statistically not significant. The causes of death were usually multifactorial. The SEQUAMAT trial comparing intravenous Artesunate with parenteral Quinine demonstrated a 35% lower mortality with Artesunate, confirming that more rapid initial parasite clearance may translate to reduced mortality in severe adult malaria. The overall median time between the initiation of antimalarial treatment and death was 42 h (range, 3–408 h). This was significantly shorter for quinine-treated group B patients (21 h; range, 3–144 h) than for artesunate-treated group A patients (48 h; range, 29–408 h).The time to death for group A was longer as compared to group B. The mean±SD for group A was 90.86±140.26 whereas mean±SD for group B was 41.77±40.15; the P value for this was 0.24 which was statistically not significant.

The overall median coma recovery time for patients who presented with a GCS score of 15 was 17 h (range, 1–188 h), and this was not significantly different between the 2 treatment groups. Coma recovery times in those who presented with a GCS score of 11 were not significantly different. The mean for CRT (Coma Recovery Time) in the patients taking ARTESNATE in group A was 13.72 and those taking Quinine in group B was 14.66 (p=0.8797); this difference was statistically not significant. But a study reported that CRT was significantly lower with Quinine treatment (median= 12 hours) as compared to Artesunate group (median=32 hours) (p=.04); and this was statistically significant[10]. This delay in the CRT was probably attributed to the neurotoxicity of the Artemesnin compounds. However, the study was conducted in a small group of patients (n=35).

There were significant differences between the artesunate and quinine treated patients in the frequency of hypoglycemia (6 of 50 in group A vs. 15 of 50 patients in group B), the mean±SD for group A was 0.12±0.33 and for group B was 0.30±0.46; P value was 0.027 which was statistically significant. An earlier study reported that in Falciparum malaria quinine-induced insulin secretion may precipitate hypoglycemia but other factors including the large glucose requirements of the malaria parasites may also contribute[6].

There were no significant changes found in the Hemoglobin levels in both the study groups A and B during the treatment period of 7 days. Contrary to this, one study reported late onset of anemia due to delayed hemolysis which was a complication only in hyperparasitaemic patients treated with Artesunate but not in patients treated with Quinine. The aetiology of delayed hemolysis remains unknown, the fact that only hyperparasaetimic patients develop hemolysis may point to the contribution of a mechanism called ‘pitting’[7].

Time for normalization of serum lactate levels was slightly lower for the Quinine receiving group B and mean±SD was 17.08±17.49 whereas for Artesunate receiving group Amean±SD was 15.12±23.25; the P value for this was 0.63 which was statistically not significant. The presence of hyperlactatemia, metabolic acidosis (SBD, >3.3), and acidemia (pH <7.35) are strongly associated with a fatal outcome[8]. The SBD was the single best clinical or laboratory predictor of fatal outcome. The overall median lactate/pyruvate ratio was raised at 30.6 (range, 20.6-62.3; normal range, <15), suggesting hypoxia and anaerobic glycolysis, and was significantly higher in fatal case. The two main independent contributors to metabolic acidosis were plasma creatinine, as a measure of renal dysfunction, and venous plasma lactate, together accounting for 63% of the variance in SBD.

There was no significant difference in the time for normalization of LFT in both groups A and B. The mean±SD. for group A was 53.72±29.42 whereas mean±SD. for group B was 51.68±40.43; the P value for this was 0.77 which was statistically not significant. As is clear from earlier study jaundice is common in severe malaria and may be multifactoria. Hepatocellular jaundice in malaria should be more appropriately labelled as malarial hepatopathy rather than malarial hepatitis. Although the significance of malarial hepatopathy in causing morbidity in its own right may be in question, there is no doubt about its association with severe dysfunction of other organs, overall morbidity and mortality. Clinical relevance of malarial hepatopathy also lies in the fact that the more severe presentation with cerebral malaria can be misdiagnosed as fulminant hepatic failure[9].

The incidence of adverse events was more in group B patients receiving Quinine. Hypoglycemia was reported in 15 out of 50 patients in group B whereas only 6 patients developed hypoglycemia that was on Artesunate in group A. The P value for this was 0.027 and this was statistically significant. In group B, 12 patients reported hearing disturbances whereas no such

events occurred in group A. The P value for this was 0.0004, which was statistically significant. one patient in group B developed visual disturbance and one patient developed hepatotoxicity, no such events occurred in group A, the P value for this was 0.33, which was statistically not significant. Prolongation of QTc-interval was noted in 3 patients of group B and P value for this was 0.09. 2 patients in group B developed acute renal failure during the course of treatment whereas no such events occurred in group A and P value for this was 0.17. Idiosyncratic reactions and rashes occurred in 2 patients in group B and 3 patients in group A and P value for this was 0.58 which was statistically not significant.

CONCLUSION

The present study suggests that artesunate is an effective and non inferior alternative to quinine in the treatment of severe malaria. The mortality was less and time to death was longer in patients of group A who received Artesunate as compared to group B. Among group A patients, incidence of post treatment hypoglycemia was significantly lower. The Coma Recovery Time (CRT) was also less for group A patients but the difference was not statistically significant. Time to normalization of plasma lactate levels was not significantly lower for the Quinine receiving group B patients as compared to group A patients.

No significant difference was found between the two groups regarding the liver function tests or haemoglobin levels. Moreover, the incidence of adverse events was more in group B patients receiving Quinine, and the occurrence of hypoglycemia and hearing disturbances was found to be statistically significant. Thus, Artesunate performed fairly well in almost all the clinical and biochemical parameters and patient outcomes, confirming the results of previous studies and hence establish the very fact that Artesuate based regimen is treatment of choice in patients of severe falciparum malaria.

Although this study revealed significant inference as above but limitation of this study was small number of cases and further studies are required to confirm the above findings.

REFERENCES:

1. Trampuz A, Jereb M, Muzlovic I, Prabhu RM; Clinical review: Severe malaria. Critical Care-London, 2003; 7(4):315-323.
2. Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, D'Alessandro U; Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malaria journal, 2011; 10(1):1.
3. Li Q, Weina P; Artesunate: The best drug in the treatment of severe and complicated malaria. Pharmaceuticals, 2010;3(7):2322-2332.
4. Alecrim MG, Lacerda MV, Mourao MP, Alecrim WD, Padilha A, Cardoso BS, Boulos M; Successful treatment of Plasmodium falciparum malaria with a six-dose regimen of artemether-lumefantrine versus quinine-doxycycline in the Western Amazon region of Brazil. The American journal of tropical medicine and hygiene, 2006; 74(1):20-25.
5. Murphy GS, Oldfield E C; Falciparum malaria. Infectious disease clinics of North America, 1996;10(4):747-775.
6. White NJ, Warrell DA, Chanthavanich P, Looareesuwan S, Warrell MJ, Krishna S et al.; Severe Hypoglycemia and Hyperinsulinemia in Falciparum Malaria. N Engl J Med 1983; 309:61-66.
7. Rolling T, Wichmann D, Schmiedel S, Burchard GD, Kluge S, Cramer JP; Artesunate versus quinine in the treatment of severe imported malaria: comparat ive analysis ofadverse events focussing on delayed haemolysis. Malar J. 2013; 12:241.
8. Nicholas PJ, Nguyen H, Nguyen TH, Chau TTH, Phu LP, Can CL, et al.; The pathophysiologic and prognostic significance of acidosis in severe adult malaria. 2000; 28(6): 1833-1840.
9. Anil AC, Pankaj P; Jaundice in malaria. Journal of Gastroenterology and Hepatology, 2005; 220(9): 1322–1332.
10. Nigil Haroon, Kalpesh Amichandwala, Mahesah G Solu; Comparative Efficacy of Quinine and Artesunate in the Treatment of Severe Malaria: A Randomized Controlled Trial. 2005; 7(1).