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A COMPARATIVE STUDY OF QUININE V/S ARTESUNATE IN SEVERE MALARIA PATIENTS IN NORTHWESTERN RAJASTHAN, INDIA

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ABSTRACT

Plasmodium falciparum (PF) and *Plasmodium vivax* (PV) are responsible for most of the global burden of malaria. With changing spectrum of clinical presentation in malaria, newer treatment regimens are evolving. So we plan to study comparative efficacy of quinine V/S artesunate in treatment of malaria.

The study was conducted among 100 adult patients of severe malaria (Pf, Pv, Pf+Pv). The diagnosis of malaria was confirmed by demonstrating asexual form of parasites in peripheral blood smear and positive rapid antigen test. Amongst study group, 65 were treated with artesunate (2.4 mg/kg over 10 minutes followed by 2.4 mg/kg every 24 hours) and 35 with Quinine (20mg/kg loading dose for 4 hrs in 500 ml D 10% and then 10mg/kg every 8 hrs). In both groups results were compared at PCT, FCT, CRT, side effects observed and hospitalization duration seen. Mean parasite clearance with artesunate 1.62 day while mean PCT with quinine 3.46 day, mean FCT with artesunate 2.17 day while quinine 3.5 day, CRT with artesunate 1.33 day while quinine 2.67 day, hypoglycemia, QTc prolongation, nausea, vomiting, tinnitus, vertigo was frequently seen side effects of quinine while no such side effect was seen with artesunate. We also found that to give artesunate as compare to quinine was easy. Out of 35 patients who were treated with quinine only one mortality occurred while no mortality with artesunate out of 65 patients. Artesunate is preferred drug over quinine to treat severe malaria patients.

Key Words: *Artesunate, Quinine, Severe malaria, Parasite Clearance Time (PCT), Fever Clearance Time (FCT), Coma Resolution Time (CRT)*

INTRODUCTION

Malaria is a protozoal disease transmitted by bite of infected *Anopheles* mosquitos. It is most important of parasitic diseases in humans with transmission in 103 countries (Harrison's Principles of Internal Medicine, 2008). Four species of genus *Plasmodium* cause nearly all malaria infection in humans. These are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Human infection begins when a female *Anopheles* mosquito inoculates *Plasmodium* sporozoites from its salivary glands during a blood meal. This sporozoite is rapidly carried via blood stream to liver where they invade hepatic parenchyma cells and begin a period of asexual reproduction. By this amplification process (which is known as intrahepatic or preerythrocytic schizogony), eventually may produce 10000 to 30000 daughter merozoites. The swollen liver cells eventually burst, discharging motile merozoites into the bloodstream. These then invade the red blood cells and multiply 6 to 12 fold every 48 to 72 hours. When the parasites reach density of 50 / litre of blood, the symptomatic stage of the infection begins (Harrison's Principles of Internal Medicine, 2008).

In *P. vivax* and *P. ovale* infection, a proportion of intrahepatic form do not divide immediately but remain dormant for a period of 3 weeks to one year longer before reproduction begins. These dormant forms or hypnozoites are the cause of relapse that is characteristic of infection with these two parasites (Harrison's Principles of Internal Medicine, 2008).

This disease in human beings is caused by direct effect of RBC invasion and destruction by the asexual parasite and the hosts reaction. After a series of asexual cycles, parasites develop into morphological distinct sexual forms (genotypes) that can transmit malaria. After being ingested in blood meal of a biting female *Anopheline* mosquito, the female and male gametocytes form zygotes, oocyst and sporozoites in last which accumulate in salivary glands of mosquito awaiting inoculation into another human at the next feeding (Harrison's Principles of Internal Medicine, 2008).

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Clinical features

Fever associated with chills and rigors , headache , nausea , vomiting , delirium , hemolytic anemia and jaundice .

Clinically, may present with hepatosplenomegaly, acute renal failure, gastrointestinal symptoms, dehydration, shock, cerebral malaria and black water fever [Harrison's Principles of Internal Medicine (2008)].

Severe malaria

Severe malaria can develop in *P. falciparum* and *P. vivax* infection over a span of time as short as 12 – 24 hours and may lead to death. It may manifest as any one of the following or in cluster:

- Repeated generalized convulsion
- Renal failure (Serum creatinine >3 mg/dl)
- Severe anemia (Hb <5 g/d)
- Pulmonary edema / Acute respiratory distress syndrome (ARDS)
- Hypoglycemia (Plasma glucose <60 mg/dl)
- Metabolic acidosis
- Circulatory collapse / Shock (SBP <90 mmHg)
- Abnormal bleeding and DIC
- Haemoglobinuria
- Hyperthermia
- Hyperparasitemia (>5% parasitized RBC in low endemic and >10% in hyperendemic areas)
- Jaundice (Serum bilirubin >3 mg/dl)

MATERIALS AND METHODS

The study was conducted among 100 adult patients of severe malaria (Pf, Pv, Pf+Pv) in a tertiary care hospital in northwestern Rajasthan , PBM Hospital , Bikaner . The diagnosis of malaria was confirmed by demonstrating asexual form of parasites in peripheral blood smear and positive rapid antigen test.

Inclusion Criteria

- Adult patients (age ≥ 14 years) having asexual form of Plasmodium parasites in peripheral smear and positive rapid antigen test, given consent for study and satisfying the WHO criteria for severe malaria.
- Patient not suffering from chronic illness like diabetes , chronic renal failure and chronic liver disease

Exclusion Criteria

- Known case of glucose-6-phosphate dehydrogenase deficiency, congenital OT prolongation syndrome.
- Patient with history of cardiac disease

Patients qualified for study were randomized to receive either quinine or artesunate arm. In both arm clindamycin was added besides above mentioned drugs [Harrison's Principles of Internal Medicine (2008)]. The end points were parasite clearance time (PCT), fever clearance time (FCT), coma resolution time (CRT) and mortality. The adverse effect of these two drugs were also studied. Oral therapy was substituted as soon as patient could tolerate them. Patient in quinine arm were given a loading dose of 20 mg/kg of quinine salt in 5% dextrose I.V. over 4 hours. Followed by 10 mg/kg of quinine 8 hourly infusion . The maximum dose 2400 mg/d in first 24 hours. No dose adjustment was made during first 48 hours even in with renal and hepatic failure. After 48 hours, dose was reduced by 50% in patients had renal failure (Tripathi, 2001).

In artesunate arm , 2.4 mg/kg I.V. artesunate on first day 12 hourly followed by 2.4 mg I.V. artesunate for 7 days [Harrison's Principles of Internal Medicine (2008)]. All patients were admitted in general ward and seasonal disease ward. Clinical and laboratory workup was done on day of admission and daily, vital signs were recorded 6 hourly and systemic examinations were done daily. A complete blood count , ESR , urine examination , X ray chest , serum Na , K and ca , serum bilirubin and serum creatinine were

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obtained. Serial ECG and blood sugar estimation were done before, during and after the loading dose of antimalarial drugs and repeated daily. The hemoglobin, packed cell volume, platelet count, parasite density, body temperature, serum bilirubin, blood urea and serum creatinine were also monitored daily. Cerebrospinal fluid examination was done in all patients with the diagnosis of cerebral malaria to rule out meningitis. A contrast CT scan was done in all patients with delayed response to antimalarials or with seizures and signs of raised intracranial tension. The diagnosis and assessment of treatment response was done by serial blood smear examination and parasite asexual form count. A total leukocyte count of 8000 / cumm was assumed for the patient and parasite count was multiplied by a factor of 40 to yield the parasite density / microliter [Harrison's Principles of Internal Medicine (2008)].

In serial ECG QTc interval was calculated. Parametric data was compared using the student's t test, non parametric data were analyzed using the Pearson's chi square test. The confidence interval taken 95%. All the statistical work was done using the SPSS (Ver 11.0) for windows software.

RESULTS

Table 1 – Mean Parasite Clearance Time (PCT) of Quinine & Artesunate arm

	Quinine	Artesunate
Mean	3.46	1.62
SD	0.78	0.65

The parasite clearance time is 1.84 days shorter with artesunate than quinine which is statistically significantly ($p < 0.01$).

Table 2 – Mean Fever Clearance Time (FCT) of Quinine & Artesunate arm

	Quinine	Artesunate
Mean	3.57	2.17
SD	0.74	0.82

The fever clearance time with artesunate is 1.4 days less as compared to quinine. This was found statistically significant ($p < 0.03$).

Table 3 – Mean Coma Resolution Time (CRT) of Quinine and Artesunate arm

	Quinine	Artesunate
Mean	2.67	1.33
SD	1.03	0.65

The coma resolution time with artesunate is 1.34 days less compared to quinine. This was found statistically significant ($p < 0.03$).

Table 4 – Effect of quinine and artesunate on Parasite Density

	Quinine	Artesunate
Day 1	33%	80%
Day 2	85%	92%
Complete parasite clearance	5 day	3 day

QTc prolongation was found with quinine and no evidence of QTc prolongation was found with artesunate. ($p < 0.05$)

Total no. of visits only to administer quinine for 5 days was 30

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$(3 \times 2) \times 5 \text{ days} = 30$

Artesunate required only

$(2 \times 1 \text{ day}) + (1 \times 4 \text{ days}) = 6$

Five times more patient visit needed by nursing staff to administer quinine.

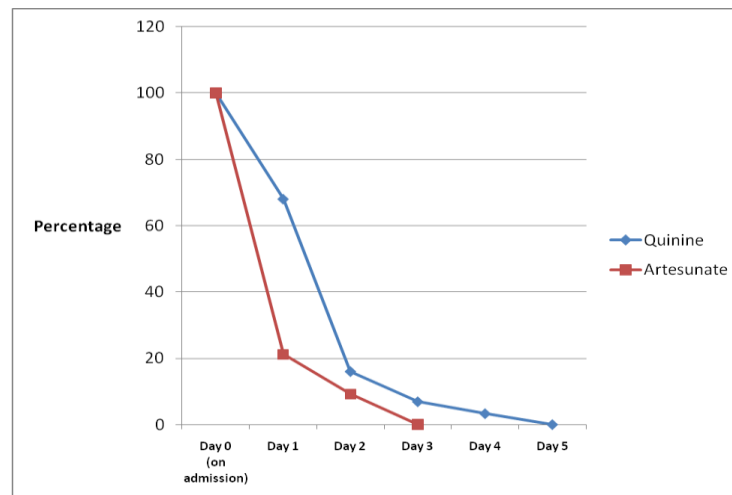


Figure 1 . Line graph showing parasite clearance v/s days of drug administration

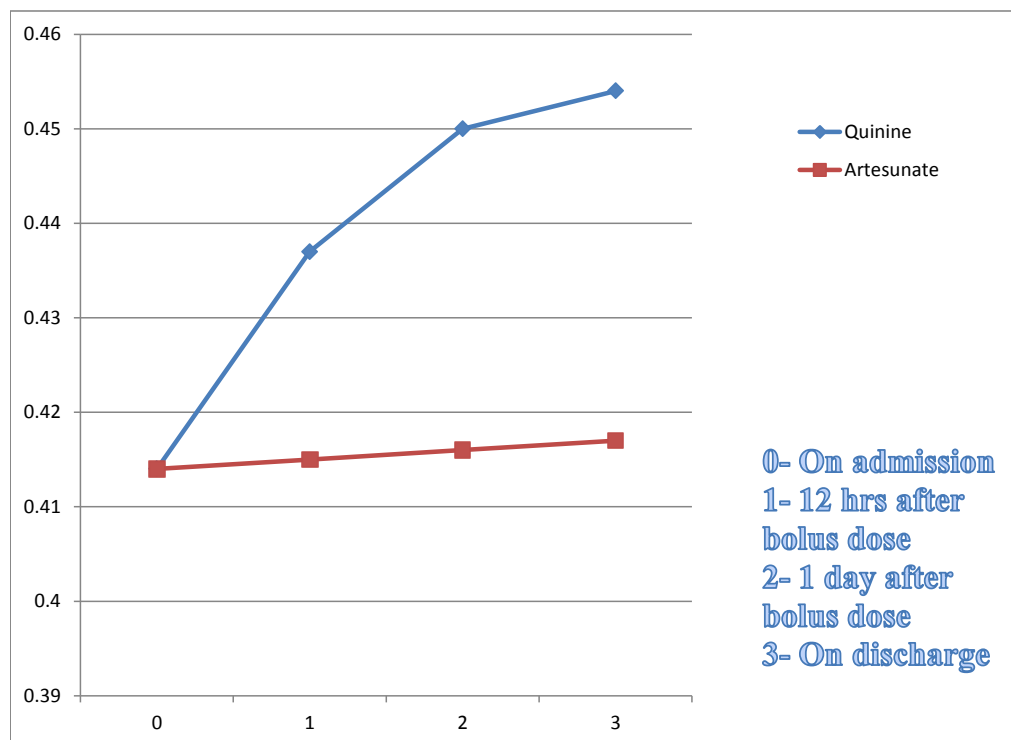


Figure 2. Line graph showing QTc interval v/s duration after drug initiation

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DISCUSSION

In our study all the severe malaria patients were randomized between quinine and artesunate arm. Out of 100 patients 73 were male and 27 were female. Out of 100, 19 had cerebral malaria , 8 had severe anemia , 67 had thrombocytopenia , 30 had hyperbilirubinemia , 8 were in shock and 11 had deranged renal functions.

In our study, parasite clearance time (PCT) with artesunate (1.6 ± 0.65) days as compared to quinine (3.41 ± 0.78) days. On the basis of our study artesunate is significantly faster acting than quinine in clearing of parasites .

Fever clearance time (FCT) in artesunate group was 2.17 ± 0.82 day while in quinine it was 3.57 ± 0.74 day. On the basis of our study artesunate is faster than quinine in achieving afebrile state

Coma resolution time (CRT) with artesunate was 1.3 ± 0.65 days while it was 2.67 ± 0.03 day. Again in view of CRT , artesunate is better than quinine .

In our study no mortality occurred in patients treated with artesunate out of 65 while one mortality occurred in out of 35 who were treated with quinine.

We also found that mean QTc increased after the bolus dose of quinine and had more value as compared to baseline. On discharge , QTc was found elevated at the end of last dose (0.454 compared to base 0.414). While in artesunate treated group not even a single patient out of 65 showed QTc prolongation, which can be explained only on the basis of drug etiology..

Conclusion

On the basis of our study we found decreased PCT, FCT, CRT , mortality and decreased side effects with artesunate as compared to quinine. Artesunate is given in bolus form so less visit is required. With artesunate we found no need of monitoring for blood sugar and QTc by ECG . On comparing both drugs in severe malaria, artesunate is superior to quinine .

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