Comparative study on clinical efficacy between Artesunate and Quinine in the treatment of Cerebral Malaria

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Abstract:
Malaria remains a serious health problem in tropical regions causing 0.86 million death in 2009. Quinine is still effective against Plasmodium falciparum (P.f) but in recent years rising trends of resistance is emerging in sense of response time, and fever clearance time. The objective of the study was to compare the clinical efficacy of Artesunate with Quinine in the treatment of cerebral malaria. The study was conducted on 50 confirmed patients of cerebral malaria in the Department of Medicine in Katihar Medical College, Katihar, Bihar. Diagnosis was confirmed clinically on the basis of World Health Organization (WHO) criteria, positive blood films and by Parahit total rapid dipstick for malaria. Patients were randomized to receive either Artesunate or Quinine. Our study shows that 68% of patients treated with Artesunate improved within 8-24 hrs against 16% from Quinine. There were no serious side effects noted in patients who are treated with Artesunate while 44% of the patients who are treated with Quinine developed side effects. Our study suggests that Artesunate is a good alternative to Quinine in the treatment for cerebral malaria and can be used as first line treatment.

Key words: Artesunate, Quinine, Cerebral Malaria, Plasmodium falciparum
Introduction

Malaria is a protozoal disease caused by infection of erythrocytes with any of four of the parasite of the genus *Plasmodium* – *falciparum*, *vivax*, *malariae* and *ovale*. It is transmitted by the bite of female *anopheles* mosquito. Malaria remains a serious health problem in tropical regions causing 0.86 million death in 2009, with annual death rate of upto 93% of affected severe malaria. As per the National Vector Borne Disease Control Programme (N.V.B.D.C.P) data in 2007, 14,76,562 malaria cases (of which 7,25,502 were caused by *Plasmodium falciparum*) and 1,173 deaths were reported from India.

In the classic malarial paroxysm, fever spikes, chills and rigors occur at regular interval. Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specially associated with *falciparum* malaria and may herald the development of encephalopathy (cerebral malaria), leading to coma.

Quinine is still effective against *Plasmodium falciparum* (P.f) but in recent years rising trends of resistance is emerging in sense of response time, and fever clearance time. Quinine can be given intramuscularly but its potential disadvantage is local toxicity. It can cause severe hypoglycaemia. The recommended first line therapy for cerebral malaria is intravenous Quinine but the case fatality rate is 10-30% despite treatment. Because of its potential toxicity it is ideally administered by carefully controlled intravenous infusion, a procedure that is impractical in rural areas.

Qinghaosu (Artemisinin) derivatives are synthetics of Chinese plant *Artemisia annua* which has been used in for centuries. Since 1979 several derivatives of Artemisinin (artesunate, arteether, dihydroartemisinin, artilinic acid and artemotil) have been synthesized and studied in China. Artemisinin compounds have gained importance from the fact it is highly effective, rapid in parasite clearance as compared to Quinine, and significantly less toxic. It is better than Quinine in rapid coma resolution and fever clearance there by reducing mortalities.

South East Asian Quinine Artesunate Malaria Trial (S.E.A.Q.A.M.A.T) Group concluded that Artesunate should be the treatment of choice. The drug is more effective than Quinine, easy to administer and is safe. It is a potential candidate for use in rural areas of India that comprises of about 70 % of India and where health care facilities are not adequate. Hence in the light of current available information, an urgent need was felt to conduct a careful controlled prospective and comparative study regarding the efficacy of Artesunate and Quinine in the management of cerebral malaria.

Materials and Methods

After obtaining clearance from the ethical committee of the institution, the study was carried out in the Department of Medicine, Katihar Medical College and Hospital, Katihar. The study was conducted from 2006 to 2009. A total no of 50 patients, irrespective of age and sex who were
suffering from fever with rigor, headache and altered consciousness were included in the study. The cases were confirmed on the basis of positive blood films and supported by Parahit Total Dipstick Rapid Malaria Test. The diagnosis of cerebral malaria caused by P.f was made by W.H.O criteria (2000)\textsuperscript{11}.

1. Unarousable coma not attributable to any other cause in a patient with falciparum malaria. The coma should persist for at least one hour after generalized convulsions to make the difference from transient postictal coma. Coma was assessed using the Blantyre Coma Scale\textsuperscript{12} in children and Glasgow Coma Scale\textsuperscript{13} in adults

2. Clinically by intermittent fever with chills, headache, drowsiness, convulsion and palpable spleen.

Finger was punctured with a sterile lancet which is provided in the kit. The blood was aspirated into the heparinized glass capillary and transferred immediately into the test strip on the absorbent pad. Test strip was placed into the reaction tube containing 200 picolitre of reaction buffer provided with the kit. After 15 minutes the dipstick was taken out from the sample tube and then the result was interpreted. Results should not be read beyond thirty minutes as this can give false positive results.

The patients were randomized to receive either Quinine or Artesunate with the following schedule. Artesunate is given as 2.4 mg/kg body weight stat by intravenous (i.v) route, then 2.4 mg/kg bodyweight i.v. after 12 hours (hrs) then repeated at 24 hrs in same dose, followed by 2.4 mg/kg body weight once a day for 7 days. Quinine dihydrochloride is given as a loading dose of 20 mg/kg body weight in 500 ml 5% dextrose i.v over 4 hours infusion, then followed by 10 mg/kg body weight every 8 hourly for 7 days\textsuperscript{4}. Oral quinine is started as soon as the patient is able to take orally. The patients were assessed for – fever clearance time and coma resolution time and all side effects occurring during and after giving drugs. Median values of fever clearance time (F.C.T) and coma clearance time (C.C.T) were calculated for the two drugs using the formula.

\[
\text{Median} = \frac{N}{2} - \frac{C.f}{f} \times I \\
\text{Median Class} = \frac{N}{2}\text{th item, L1 = lower limit, N= no of observations, C.f = cumulative frequency of the above class interval, f = frequency of median class, I = class interval.}
\]

**Results**

Our study shows that 68% of patients treated with Artesunate improved within 8 – 24 hrs against 16% from Quinine. The median coma clearance time (C.C.T) in patients treated with Artesunate was 20 hrs and in Quinine treated patients it was 34 hrs. (Table 1)
Table 1 – The coma clearance time (in Hrs) in patients treated with Quinine (n = 25) and Artesunate (n = 25)

<table>
<thead>
<tr>
<th>Time (in Hrs)</th>
<th>Quinine</th>
<th>Artesunate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>%</td>
</tr>
<tr>
<td>8-24</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>&gt;24-48</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>&gt;48-72</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

Median Coma clearance Time (Q) - 34H
Median Coma clearance Time (A) - 20H

Majority of cases improved within 48 to 72 hrs, in both the test groups, but the percentage of Artesunate was slightly higher (60%) in comparison to the Quinine (48%). Death recorded in Artesunate was 12% in contrast to 28% in Quinine. The median clearance time in Artesunate treated patients was 58 hrs and in Quinine treated patients it was 60 hrs. (Table 2)

Table 2 – Fever clearance time (in Hrs) in patients treated with Quinine (n = 25) and Artesunate (n = 25)

<table>
<thead>
<tr>
<th>Time (in Hrs)</th>
<th>Quinine</th>
<th>Artesunate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>%</td>
</tr>
<tr>
<td>24-48</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>&gt;48-72</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>&gt;72-96</td>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>

There was no serious side effects noted in Artesunate patients but 44% of patients had developed side effects with Quinine among which the commonest was nausea and vomiting in 16% followed by hypoglycaemia in 80% of cases (Table 3)
Table 3 – Drug toxicity found in patients of cerebral malaria undergoing treatment with Quinine and Artesunate.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cases on Quinine</th>
<th>Cases on Artesunate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>%</td>
</tr>
<tr>
<td>Intolerance</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Local pain Reaction, Necrosis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Cardiac Toxicity</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Neurotoxicity (phychosis)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Overall mortality was 20%. Only 3 patients died in group receiving Artesunate compared with Quinine in which 7 patients died during treatment (Table 4).

Table 4 – No of deaths occurring due to cerebral malaria in groups treated with Artesunate (n=25) and Quinine (n=25)

<table>
<thead>
<tr>
<th></th>
<th>NO OF DEATHS</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artesunate</td>
<td>3</td>
<td>12 %</td>
</tr>
<tr>
<td>Quinine</td>
<td>7</td>
<td>28 %</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>20 %</td>
</tr>
</tbody>
</table>

No side effects occurred with Artesunate, but Quinine showed various side effects as hemiplegia and ataxia both seen in 8% of the cases. (Table 5)

Table 5 – Residual neurological deficient in cases of cerebral malaria treated with Quinine and Artesunate (4 weeks after recovery)

<table>
<thead>
<tr>
<th>Neurological Deficit</th>
<th>Quinine</th>
<th>Artesunate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>%</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Any Other</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>
Discussion

No disease is static. Its clinical profile keeps changing with time. Newer diagnostic techniques and resistance to conventional drugs throw up fresh challenges requiring major reappraisals at frequent intervals. This comment also hold true for malaria. This has played a major role in human history and has caused more harm to more people than any other infectious disease.

In our study we found that fever and unconsciousness was present in 100% cases and apart from central nervous system (CNS), abdomen was the most common system involved in complicated malaria. Splenomegaly was present in 92% of the patients. Whereas Mohanty et al found splenomegaly in 80% cases. Cerebrospinal fluid examination was done in all cases of cerebral malaria and it was normal in all the cases. Many other authors have also reported normal CSF in all the cases.

Glasgow coma scale was < 7 in 50% cases, 7-10 in 32% cases and > 10 in 18% of cases.

Primary end point of study was to see duration of fever clearance, duration of coma resolution in hours and mortality in both study groups. The median coma clearance time in Artesunate treated patient was 20 hrs and in Quinine treated patient it was 34 hrs. Only 16% patients gained consciousness in first 8-24 hrs while 68% of the patients treated with Artesunate gained consciousness in first 8-24hrs.

Taylor WR et al observed in their study that patient treated with quinine consistently developed side effects and incidence of hypoglycaemia and cardiac toxicity were higher. They also found that artemisinin derivatives have no dose related adverse side effects and only very rarely produce allergic reactions.

Dandrop A et al in their study (which was largest ever clinical trial) found artemisinin derivatives (artesunate) to be safe and very well tolerated. Baird JK in 2005 had found higher side effects with quinine.

Rolling T et al found that adverse effect in patients treated with Artesunate were limited to delayed haemolysis and temporary deterioration in renal function that too only in 60% of the patients while those treated with Quinine it was 71%. Most common adverse effect with Quinine was hearing tinnitus (37%), hypoglycaemia (32%) and cardiotoxicity (14%).

Jones KL et al observed that treatment with Artesunate significantly reduced the risk of death (RR 0.62, 95% CI 0.51-0.75), reduce parasite clearance time (MD 8.14 hrs) and hypoglycaemia.

Conclusion

Our study suggest that Artesunate is a good alternative to Quinine in cerebral malaria as the fever clearance time was not significantly shorter but the percentage of patients becoming afebrile was greater in Artesunate group and coma clearance time was shorter with Artesunate than with Quinine. And also Artesunate is simple to administer, safe, continuous monitoring is not required, minimal or no side effect. So it is well suited for rural areas and in the setting of poor infrastructure. By contrast Quininie is locally toxic after intramuscular use, cannot be used as...
bolus i.v. required three times daily infusion and is associated with potentially serious side effects like hypoglycaemia necessitating continuous monitoring.

As per W.H.O Artesunate can be used as a good Alternative therapy for cerebral malaria and in cases which are resistant to Quinine. The present study favours that Artesunate should be used as a first line treatment over Quinine for cerebral malaria.

References


