COMPARATIVE EFFICACY OF QUININE AND ARTESUNATE IN THE TREATMENT OF SEVERE MALARIA IN CHILDREN: A RANDOMISED CONTROLLED TRIAL IN A TERTIARY HOSPITAL OF NORTH EAST INDIA

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ABSTRACT

BACKGROUND

Around 1.5 million confirmed cases are reported annually by NVBDCP of which 50% are due to Plasmodium falciparum. Artesunate has recently replaced quinine as the first line drug for the management of severe malaria in children in WHO guidelines. There is no definite study comparing efficacy of Quinine and Artesunate in the north east region of India. This study was taken up to compare efficacy of Quinine with Artesunate in treatment of severe malaria in children.

METHODS

All cases up to 12 years of age admitted in the paediatric ward with clinical features of severe malaria as per WHO criteria having asexual forms of P. falciparum in peripheral smear were included in the study. Sixty-eight patients were randomized in Group A (Artemisinin) and Group Q (Quinine). On admission, detailed history and examination findings were recorded and thin and thick smears for MP, QBC assay, CBC, RBS, KFT (Kidney Function tests), serum bilirubin, chest x-ray (CRX), LFT, urine analysis, CSF analysis in cerebral malaria cases were done and repeated as per protocol. In Group A, patients received Artesunate and in Group Q, patients received Quinine and all aspects of supportive treatment as per WHO guidelines. The outcome measures were in-hospital mortality, FCT, PCT, CRT, mean hospital stay, residual neurological deficits and drug toxicity in both the arms.

RESULTS

Mean FCT, mean PCT, mean CRT, mean hospital stay were significantly less in the Artesunate arm. But mortality and residual neurological deficit at 28 days and drug toxicities did not differ significantly between the arms.

CONCLUSIONS

Artesunate is a better choice over quinine for the population of this part of India.

KEYWORDS


BACKGROUND

Malaria is a febrile illness caused Plasmodium parasite and is transmitted from person to person by mosquitos. Five species of Plasmodium are known to cause disease in human: P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi.1,2 Severe malaria is defined by presence of clinical or laboratory evidence of vital organ dysfunction (Table 1). Severe Malaria is most commonly caused by infection with Plasmodium falciparum, although P. Vivax and P. Knowlesi can also cause severe disease.3

Repeated exposure to malaria infection over 5 can produce an acquired immunity in human, which is protective against the most severe forms of the disease.4 Consequently, in high transmission settings as in Africa, young children are most at risk prior to the acquisition of effective immunity, whereas in low transmission settings, or in travellers from non-endemic areas, both children and adults are equally vulnerable to severe disease. There were an estimated 6.27 lakhs malaria deaths worldwide in 2012. Approximately 77% of malaria deaths globally were of children under 5 years of age.5 Malaria is one of the major public health problems of India. Around 1.5 million confirmed cases are reported annually by the National Vector Borne Disease Control Programme (NVBDCP), of which 50% are due to Plasmodium falciparum. Tripura state is located in the North-Eastern India. Transmission is seasonal related to rain fall. Focal outbreaks of malaria are common in this region, which accounts for 8-12% of all the reported malaria cases in India. Plasmodium falciparum is a major malaria parasite in this region, causing 60-80% of
malaria infections. Transmission is caused by Anopheles minimus, Anopheles fluviatilis and Anopheles dirus. There is a possibility for multi-drug resistant falciparum malaria, prevalent in Myanmar and Thailand, entering India through the north-eastern states which warrants monitoring of status of drug resistance in this part of the country. The standard treatment for severe malaria in children has been intravenous (IV) infusion / intramuscular (IM) quinine. However, quinine has a narrow therapeutic index. Indeed, adverse effects from quinine therapy are common even at therapeutic doses. These mild and often reversible symptoms include deafness, dizziness, diarrhoea, vomiting and tinnitus. Hypoglycaemia is a serious adverse effect if quinine infusion rates exceed 5 mg/kg/hr. With quinine over-dosage or too rapid administration, fatal cardiac rhythm disturbance or hypotension can occur. Artesunate, an artemisinin derivative, has recently replaced quinine as the first line drug for the management of severe malaria in children in WHO guidelines. Artesunate can be given as an IV bolus with peak concentration reached within one hour of administration. Artesunate, however, has been associated with neurological damage in animal experiments, However, studies have failed to show any such neurotoxicity in human beings and the drug is felt to be safe in man.

South East Asian Quinine Artesunate Malaria Trial (SEAQAMAT) Group concluded that Artesunate should be the treatment of choice. In a recent Trial conducted in multiple centres in Africa (AQUAMAT-African Quinine Artesunate Malaria Treatment Trial) clearly shown the advantage of artemesine over quinine in African children. In addition, there is limited evidence that the efficacy of quinine in severe malaria may be declining in some parts of South-East Asia. One study in 2011, explored the cost effectiveness of artemesine and quinine in Africa and concluded that artemesine is highly affordable and cost effective alternative to quinine for treating severe malaria in children. Hence in the light of current available information, this randomised trial is under taken to compare the efficacy of quinine and artemesine in the treatment of severe malaria in children of Tripura.

We wanted to compare Quinine with Artesunate in treatment of severe malaria in children in terms of fever clearance time, parasite clearance time, coma resolution time and mortality assessment.

**METHODS**

After obtaining clearance from the ethical committee of the institution, a randomized open-label comparative study of Artesunate and Quinine in the treatment of Severe Falciparum Malaria was carried out in Agartala Government Medical College (AGMC) and G B Pant Hospital, Tripura from January 2013 to June 2014. All cases up to 12 years of age admitted to the Paediatrics ward with clinical features of severe malaria as per WHO criteria (Table 1) having asexual forms of P. falciparum in the peripheral blood smear were included in the study. Patients with QTc interval >0.45 sec in Electrocardiography (ECG), known case of G6PD deficiency, previous treatment with antimalarials for more than 24 hours, patients with contraindication to Artesunate /Quinine and unwilling patients were excluded from the study.

**Clinical Features**

1. Impaired consciousness (including unarousable coma);
2. Severe prostration and patient is unable to sit, stand or walk without assistance;
3. Multiple convulsions; more than two episodes within 24h;
4. Deep breathing and respiratory distress (adolescent breathing);
5. Acute pulmonary oedema and acute respiratory distress syndrome;
6. Circulatory collapse, systolic blood pressure < 80 mm (adults) & < 50 mmHg (children);
7. Acute kidney injury;
8. Clinical jaundice plus evidence of other vital organ dysfunction; and
9. Abnormal bleeding.

**Laboratory and Other Findings**

1. Hypoglycaemia (<2.2 mmol/L or <40 mg/dL);
2. Metabolic acidosis (plasma bicarbonate <15 mmol/L);
3. Severe normocytic anaemia (Hb< 5 g/dL, PCV <15% (children); <7 g/dL, <20% (adults));
4. Haemoglobinuria;
5. Hyperlactataemia (lactate >5 mmol/L);
6. Renal impairment (serum creatinine >265 μmol/L); and
7. Pulmonary oedema (radiological).

**Table 1. Definition of Severe Malaria by World Health Organization**

The sample size was calculated using the formula for comparing two independent group means.

Patients per group = \((\alpha, \beta)^{\frac{Z_{1-\alpha/2}^2}{\delta^2}}\). Here\( \delta = 1\) error, \(\beta = type\ II\ error\) and \(f(\alpha, \beta)\) is the function of \(\alpha, \beta\). With 90% power, 95% confidence interval and 0.05 level of significance value of \(f(\alpha, \beta)\) is 10.5. Considering the acceptable margin(d) of fever clearance time (FCT) as 12 hrs between the two groups and taking SD(\(\sigma\)) of the outcome of interest as 15 hrs from a similar study, 33 patients is to be included in each group the study. After obtaining parents' written, informed consent, patients were randomized in Group A (Artemisinin) and Group Q (Quinine) in blocks of 4 using Microsoft Excel.

All patients invariably received at least 24 hours of intravenous therapy and a complete 7 days course. Oral therapy was substituted as soon as patients were able to tolerate.

On admission, all patients were weighed, a detailed history including residence, travel history; previous treatment, drug history, vaccination etc., were taken. A thorough clinical examination was done and findings were recorded. Axillary temperature were recorded 6 hourly, Glasgow Coma Scale (GCS) score / Blantyre Coma Scale (BCS) score was recorded 8 hourly. Vital parameters were recorded hourly till patient regains consciousness and become haemodynamically stable then vitals were recorded hourly. Systemic and fundus examination were done on daily basis.

All the cases were subjected to the following investigations at the time of admission (Day 0):

1. Simultaneous thin and thick blood slides for species identification and parasite count.
2. Quantitative Buffy Coat (QBC) assay.
3. Complete blood count.
4. Random blood sugar before and after parental anti-malarial doses.
5. Blood urea and creatinine level.
6. Serum bilirubin (total and direct).
7. CSF analysis—pressure, cells, sugar, proteins, culture sensitivity in cerebral malaria cases.
9. Liver function tests.
10. Serum (Na+) and (K+).
11. Urine analysis for sugar, albumin, RBCs, WBC, and for haemoglobinuria.

Blood for malaria parasites both by blood slides and QBC assay, serum bilirubin (total and direct) and Hb% were checked daily up to 7 days and rest of the investigations were repeated on day 3 and 7. Treatment was started immediately. All aspects of supportive treatment, based on WHO guidelines were unaffected by the trial. If assigned, artesunate 2.4 mg/kg bodyweight was given on admission, then at 12h, 24 h, and thereafter once daily until oral medication could be taken reliably. Every 60 mg vial contained anhydrous artesunic acid, which we dissolved in 1 ml of 5% sodium bicarbonate and then mixed with 5 ml of 5% dextrose before injecting as a bolus into an indwelling intravenous cannula. When the patient recovered sufficiently to take tablets, we administered oral Artesunate arm (Artemisinin-based combination therapy—artemether-lumefantrine) for 3 days.

If assigned, quinine dihydrochloride was given in a 20 mg/kg loading dose infused over 4 h followed by 10 mg/kg infused over 2-4 h three times a day until starting oral therapy. When the patient had recovered sufficiently to take tablets, we administered oral quinine 10 mg/kg every 8 h to provide a total quinine course of 7 days. We combined both regimens, with inj. Clindamycin 10 mg/kg/dose IV 8 hourly followed by 30 mg/kg/day 8 hourly for 7 days once the patient could take oral medication. Primovaquine 0.75 mg/kg on day 2 were given as per latest National drug policy of India. Our primary outcome measures were in-hospital mortality, Fever Clearance Time (FCT), Parasite Clearance Time (PCT), Coma Resolution Time (CRT) and secondary outcome measures were mean duration of hospital stay, residual neurological deficits and drug toxicity in both the arms. FCT was defined as the time from administration of the first dose of the antimalarial drug to the time when the patient’s axillary temperature first dropped below 98.4°F and remained so for 48 hrs. CRT was defined as the time in hours from the administration of the first dose of the antimalarial drug to the time when the patient regained full consciousness with a GCS score of 15/ BCS score of 5 and remained so for at least 24 hours. PCT was defined as the time in hours from the administration of the first dose of the antimalarial drug to the time when the first negative blood slide is obtained and remained so for next 72 hours. All the patients were monitored for full duration of hospital stay. Adverse reactions of both drugs are also recorded. After recovery they were discharged with advice to review on day 14 and day 28. Relevant haematological and biochemical tests were repeated on follow up visits. Neurological sequelae were recorded at the time of discharge and at follow up visits.

Data were recorded, compiled, and analysed with computer using the SPSS version 15.0. Statistical tests such as χ2 test and students t-test were used as per applicability. p-Value<0.05 was considered as statistically significant.

RESULTS
In the present study 34 patients were enrolled in the Artesunate arm and another 34 patients were enrolled in the Quinine arm by block randomization. Demographic characteristics of both the groups were not significantly different (p > 0.05) in terms of age, gender, habitat and ethnicity (Table 2). Clinical and laboratory characteristics of the cases in both the arms like mean temperature, GCS/BCS score, severe anaemia, haemoglobinuria, respiratory distress, renal failure, jaundice, convulsion, hypoglycaemia, parasite burden etc., also did not differ significantly (p value > 0.05) (Table 3). No patients were lost to follow up in the study.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Parameter</th>
<th>Artesunate (n=34)</th>
<th>Quinine (n=34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mean Temperature (°F)</td>
<td>101±1.83</td>
<td>101±1.56</td>
<td>1.00</td>
</tr>
<tr>
<td>2.</td>
<td>Glasgow Coma Scale Score &lt; 8</td>
<td>5(14.7%)</td>
<td>3(8.8%)</td>
<td>0.45</td>
</tr>
<tr>
<td>3.</td>
<td>Blantyre coma scale Score &lt; 3</td>
<td>3(8.8%)</td>
<td>4(11.7%)</td>
<td>0.69</td>
</tr>
<tr>
<td>4.</td>
<td>Severe anaemia (Hb% &lt; 5 gm/dl)</td>
<td>20(58.8%)</td>
<td>13(38.2%)</td>
<td>0.09</td>
</tr>
<tr>
<td>5.</td>
<td>Macroscopic haemoglobinuria</td>
<td>3(8.8%)</td>
<td>5(14.7%)</td>
<td>0.96</td>
</tr>
<tr>
<td>6.</td>
<td>Respiratory distress</td>
<td>4(11.7%)</td>
<td>2(5.8%)</td>
<td>0.38</td>
</tr>
<tr>
<td>7.</td>
<td>Renal failure</td>
<td>2(5.9%)</td>
<td>0(0.0%)</td>
<td>0.15</td>
</tr>
<tr>
<td>8.</td>
<td>Jaundice (&gt;3 mg/dl)</td>
<td>6(17.6%)</td>
<td>5(14.7%)</td>
<td>0.63</td>
</tr>
<tr>
<td>9.</td>
<td>Generalised convulsion</td>
<td>3(8.8%)</td>
<td>6(17.6%)</td>
<td>0.57</td>
</tr>
<tr>
<td>10.</td>
<td>Blood Sugar (&lt;40 mg/dl)</td>
<td>5(14.7%)</td>
<td>8(23.5%)</td>
<td>0.35</td>
</tr>
<tr>
<td>11.</td>
<td>Parasite Burden (&gt;100000/μL)</td>
<td>11(32.4%)</td>
<td>10(29.4%)</td>
<td>0.14</td>
</tr>
<tr>
<td>12.</td>
<td>Spleenomegaly</td>
<td>20(58.8%)</td>
<td>17(50.0%)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Table 3. Clinical and Laboratory Characteristics of Study Groups at Presentation

In the present study mean Fever Clearance Time (FCT) was significantly low (p = 0.0122) in the Artesunate arm (44.86±15.09) in comparison to Quinine arm (53.2±11.33). Mean Parasite Clearance Time (FCT) also was significantly low (p<0.0001) in the Artesunate arm (41.22±8.56) in comparison to Quinine arm (56.20±10.35). The mean Coma Resolution Time (CRT) was longer significantly (p = 0.0446) in the Quinine group compared to Artesunate group (42.44±13.57 vs. 34.82±16.93).
Mortality and residual neurological deficit at 28 days did not differ significantly between the Artesunate arm and Quinine arm (p >0.5). However, mean hospital stay in days was significantly less (p=0.0285) in Artesunate arm (8.88±1.20) in comparison to Quinine arm (9.73±1.86) (Table 4).

Drug toxicities like hypotension, infusion site local necrosis, hypoglycaemia, psychosis, tinnitus and nausea & vomiting were higher in the quinine arm by proportion, but the difference was not statistically significant (p value ≥0.05) (Table 5).

DISCUSSION

In the present study a total of 68 patients with severe malaria were enrolled and were allocated in two groups by block randomization. Both the groups were comparable in terms of demographic, clinical and laboratory characteristics. In the present study mean FCT, PCT and CRT were significantly low in the Artesunate arm (44.86±15.09, 41.22±8.56 and 42.44±13.57 respectively) in comparison to Quinine arm (53.2±11.33, 56.20±10.35 and 42.44±13.57 respectively). In a study conducted by Mohanty et al20 in a tertiary hospital of Orissa between 2000 to 2002 involving 80 children with severe malaria found that CRT, FCT and PCT were significantly less in the Artesunate group (50.4±31.49 hrs; 43.55±20.12 hrs, and 41.67±16.78 hrs respectively) as compared to the quinine group (70.15±17.56 hrs, 62.23±16.99 hrs, and 52.24±12.69 hrs respectively). Maka DE et al21 in their randomized trial in 2012 in children with severe malaria in Cameroon found that FCT and PCT were shorter. Among artesunate-treated patients, but there was no difference in CRT. In contrast to our observation, Eltahir HG et al22 in an open randomized comparison of intravenous artemesine and quinine in children with severe malaria in central Sudan (2009) reported no significant difference in fever clearance time (16.2±8.9 vs. 18.2±10.5 hours, p=0.4), parasite clearance time (19.7±7.1 vs. 20.8±9.2 hours, p=0.4) and coma resolution time (8.1 vs. 9.1 hours, p=0.4) in the artemesine and quinine groups respectively. These differences of observations are likely to be a result of differences in sample size.

In the present study mortality did not differ significantly (p = 0.6369) between the quinine arm (8.8%) and the artemesine arm (5.8%). A similar observation was reported by Singh A, Goyal M, Sharma D23 (2015) in their study entitled “Complicated Malaria - A Randomized Control Study Comparing the Efficacy of Quinine and Artesunate in Its Management in Western Rajasthan, India.” Another similar observation was reported by Newton PN et al24 (2003) Randomized comparison of artemesine and quinine in the treatment of severe falciparum malaria. In contrast to our findings data from South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) involving 1461 children a significant difference (p=0.0002) in mortality in artemesine recipients (15%) compared with quinine recipients (22%) was observed. In the AQUAMAT study, involving 5425 African children it was found that 8.5% patients assigned to artemesine treatment died compared with 10.9% assigned to quinine treatment and the difference was significant (p=0.0022).

We did not find any significant difference between the artemesine arm and quinine arm in terms of residual neurological deficit and drug toxicity, but mean hospital stay was significantly less in the artemesine arm. The AQUAMAT study also found no significant difference between the groups with respect to residual neurological deficit, drug toxicity, and mean hospital stay. Marcus Eder et al25 in a retrospective evaluation from a UK centre found no significant difference between the artemesine arm and quinine arm in relation to drug toxicity, but mean hospital stay and hypoglycaemic episodes were significantly low in the artemesine arm. These differences might have emerged due difference in sample size and study design.

CONCLUSIONS

In the present open label randomized comparison between quinine and artemesine in severe malaria cases in this north-eastern state of India, we observed that artemesine is superior to quinine in terms of Fever Clearance Time (FCT), Parasite Clearance Time (PCT), Coma Resolution Time (CRT) and Mean Hospital Stay. In terms of mortality, residual neurological deficit and drug toxicity, artemesine proved not to be inferior to quinine in this study. Ataxia and Hemiparesis were most frequent residual neurological deficits observed at 28 day follow up. Hence, artemesine is a better choice over quinine for the population of this part of India.

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