Efficacy of arteether in chloroquine resistant falciparum malaria in eastern India

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Received March 24, 2003

Background & objectives: Morbidity and mortality due to falciparum malaria are increasing in many tropical areas. The situation is further complicated by drug resistant malaria. The present study was undertaken to evaluate the efficacy of arteether on acute chloroquine resistant Plasmodium falciparum malaria in eastern coalfield area of Asansol.

Methods: A total of 30 patients with chloroquine resistant falciparum malaria smear and histidine-rich protein II (HRPII) antigen positive were given arteether intramuscularly in a single daily dose of 150 mg (3mg/kg body weight in case of children) for three consecutive days. They were followed up to 28 days of arteether therapy. Each patient was assessed in terms of fever clearance time, parasite clearance time and parasite reappearance rate.

Results: The cure rate was found to be 100% with fever clearance time between 1-3 days (mean ± SD 48.2 ± 10.6h) and mean parasite clearance time of 1.2 ± 0.3 days. Parasite reappearance rate was found to be 0%. No adverse effect due to arteether therapy was observed following the treatment.

Interpretation & conclusion: The results indicated that arteether was effective in patients with acute chloroquine resistant, complicated as well as uncomplicated, falciparum malaria and might be considered as a suitable alternative to quinine.

Key words Arteether - chloroquine resistant - efficacy - falciparum malaria

Morbidity and mortality due to Plasmodium falciparum malaria are increasing in many tropical areas. The incidence of malaria worldwide is estimated to be 300 to 500 million clinical cases each year resulting in 1.1-2.7 million deaths. Of these, about 1 million are children < 5 yr of age in Africa, south of the Sahara. There has been a resurgence, further complicated by drug resistant malaria, especially due to P. falciparum infection frequently accompanied by involvement of renal, hepatic and cerebral complications.

The only therapy of chloroquine resistant P. falciparum infections presenting with complications is administration of quinine. However, high incidence of side effects with quinine and advent of resistance to all known antimalarial drugs in current use has precipitated an urgent need for new anti malarial drugs. Qinghaosu (artemisinin), a novel antimalarial drug was isolated from the plant Artemisia annua L. It is a sesquiterpene lactone peroxide, structurally unrelated to other known antimalarial drugs. Three formulations viz., an oil based preparation for intramuscular injection (artemether and arteether), an unstable water soluble succinate salt (artesunate) and qinghaosu (artemisinin) have been used and are being investigated in different parts of the world.
Arteether, artemether and artesunate are equally effective as far as rapidity of action and parasite clearance are concerned, injectable arteether is easy to administer as once daily dose and is convenient.

Clinical trials with qinghaosu derivatives in patients with *P. falciparum* malaria undertaken in Myanmar, Thailand, Vietnam, China, Tanzania and Nigeria showed that fever clearance and parasite clearance time were remarkably rapid but most of these clinical trials reported a very high recrudescence rate. Several studies have been carried out in India on the efficacy of arteether (α,β) in patients with uncomplicated and complicated *P. falciparum* malaria. The cure rate ranged from 93 to 100 per cent with a rapid but variable parasite clearance and fever clearance time. Recrudescence rate ranged from 0-20 per cent. Studies on chloroquine resistant *P. falciparum* malaria have not been done especially in eastern part of India. Clinical experience with this drug in patients with chloroquine resistant and complicated malaria is very sparcely reported. The present study was therefore undertaken to evaluate the efficacy of arteether (α,β) in patients with acute chloroquine resistant *P. falciparum* infection in eastern India.

**Material & Methods**

This prospective study was carried out from February 2002 to January 2003 in the Central Hospital, Kalla, Asansol after obtaining approval from the hospital ethics committee. Planned as a pilot study, the sample size was decided on the basis of availability of patients and feasibility of investigations. Patients of various age groups (adults, children) presented with fever admitted in the medicine and paediatrics wards, slides positive for *P. falciparum* and diagnosed as a case of chloroquine resistant malaria, were included in the study. The patients were further confirmed by immunochromatographic test. Patients who presented with fever and were positive for *P. falciparum* but could not complete the three doses of arteether therapy and were not confirmed cases of chloroquine resistant malaria were excluded. A total of 46 patients were positive for *P. falciparum* infection during the study period. Among these, six were not chloroquine resistant and five were seriously ill, treated with quinine and tetracycline and they were excluded from the study. Of the 35 patients included, two died after one dose of arteether therapy and three patients had taken discharge on their own risk before completion of arteether therapy. These five patients were also excluded. Written informed consent was taken from patients or their relatives before initiation of therapy.

**Malaria diagnosis with thin and thick smear films:** Thin and thick smear blood films were stained with Giemsa (E. Merck, Mumbai, India) diluted 1:10 with phosphate buffered saline (pH 7.2). Stained slides were examined under a compound light microscope [Olympus, (India) Pvt. Ltd., New Delhi] using 1,000x oil immersion magnification. A maximum of 300 thick film fields were read before a slide was labelled negative. Parasitaemia levels were calculated with results from thick smear films as per recognized way of estimating the parasite count per µl in thick films. Thus parasites counted until 200 leucocytes were seen. The parasite count was multiplied by 40 to give parasite per µl of blood, as standard value 8000/µl for the white blood cell/µl was used.

**Histidine-rich protein II (HRP II) antigen detection of *P. falciparum*:** HRP II antigen was detected by the commercial kit ‘Para check’ (Orchid Biomedical Systems, Goa, India) using the principal of immunochromatographic test.

**Chloroquine resistant *P. falciparum* malaria:** This was decided as per criteria of the World Health Organization. Smear positive patient or relatives (in case of unconscious patients) were enquired about intake of chloroquine prior to hospitalization in the preceding 28 days period. Chloroquine was administered orally as per recommended doses (chloroquine 10 mg base/kg body wt (600 mg maximum dose) as a single dose followed by 5 mg/kg (300 mg maximum) at 6, 24 and 48 h) to the conscious and less sick patients (8 of 30 patients) who had no such history and thick blood film was examined on day 4. The type of resistance RII (following treatment, there was a reduction but no clearance of parasitaemia) or RIII (following treatment there was no reduction of parasitaemia) was determined comparing the pre- and post- treatment parasite count. Unconscious and seriously ill patients having no such history were excluded from this trial. A detailed history including clinical response after chloroquine therapy, day of chloroquine therapy before hospitalization, laboratory report if any etc., was taken from the patients or relatives.
The response of arteether therapy was measured in terms of fever clearance time, parasite clearance time and parasite reappearance rate.

**Statistical analysis:** Results of individual parameters were expressed as mean ± SD. Two way ANOVA (Friedman test -Non parametric) test was used to evaluate the significant differences of the pre- and post-treatment parasite count. Biochemical and haematological parameters were evaluated by Wilcoxon’s signed Rank test and paired ‘t’ test wherever appropriate. P value <0.05 was considered significant.

**Results & Discussion**

A total of 30 patients (19 males, 11 females) microscopically and antigenically positive for P. falciparum infection and confirmed cases of chloroquine resistant malaria who completed the three doses of arteether therapy were included in the study. The age ranged between 3 to 60 yr (mean 31.6±12.97 yr). Twenty patients presented with cerebral symptoms, 3 having fever associated with diarrhoea and remaining 7 had no cerebral symptoms or diarrhoea except chills and rigor.

Clinical examination showed that spleen was enlarged in 20 patients before initiating arteether therapy. The median Glasgow coma score was 9 (range 3-12); 8 patients had a score <8. On biochemical examination, serum bilirubin level was found higher (>3mg/dl) in 7 patients and higher serum urea (>50mg/dl) and serum creatinine (>1.5mg/dl) in 5 patients. Hb per cent was low (<5gm%) in 4 patients. The biochemical abnormalities came to normalcy during the course of treatment and subsequent follow up. Temperature varied between 37.8° to 40° C (mean ± SD 39.45±0.74° C). Of the 30 patients, 12 became afebrile within 24 h of initiating arteether therapy and by 48 h another 14 patients became afebrile (i.e., after two injections) and by 72 h (after three injections of arteether) all 30 patients regained normal body temperature. The mean recovery time from coma was 29.7 ± 16.37 h (range 6-72 h) The parasite count was done before and 24, 48 and 72 h of initiating arteether therapy, then on days 7, 14 and 28 of follow up. The initial count ranged between 24,000-4,50,000/µl (mean ± SD 85133.33 ± 85756.16/µl). There was a rapid
parasite clearance with arteether therapy (Table I). No parasite was detected after 72 h of arteether therapy and during subsequent follow up period. The mean parasite clearance time was 1.2±0.3 days. The parasite reappearance was not seen in any patients during the 4-wk follow up period, which gave cure rate of 100 per cent. The splenomegaly which was found in 20 patients before initiating therapy regressed by day 28 post-therapy. No further biochemical and haematological abnormality was detected in any patient after one week of hospitalization (Table II).

In the present study a high cure rate (100%) was observed with mean parasite clearance time of 1.2±0.3 days fever controlled within 3 days of arteether therapy. In a study from Rourkela, Mohanty et al\textsuperscript{12} showed a cure rate of 96 per cent in patients of complicated falciparum malaria. In a multicentric study Asthana et al\textsuperscript{4} showed an overall cure rate of 97 per cent in patients with uncomplicated \textit{P. falciparum} malaria. However, in the subsequent multicentric study by the same group\textsuperscript{3} in patients with complicated falciparum malaria a cure rate of 93 per cent was observed. A higher cure rate in the present study might be due to exclusion of patients not completing the three doses of arteether therapy and small number of study subjects. In a study from Dibrugarh\textsuperscript{11} showed a cure rate of 100 per cent in 30 patients with uncomplicated \textit{P. falciparum} malaria but the recrudescence rate was 6.7 per cent. Mohanty et al\textsuperscript{12} observed a very high recrudescence rate (20%) in patients with complicated falciparum malaria. In this present study, the recrudescence rate was not observed inspite of inclusion of both complicated and uncomplicated chloroquine resistant falciparum cases. Asthana et al\textsuperscript{4} also observed 100 per cent cure rate and no recrudescence in patients with uncomplicated \textit{P. falciparum} malaria. The overall recrudescence rate was very low (0.3%) in their subsequent multicentric study in patients with complicated falciparum malaria\textsuperscript{3}. The parasite clearance time and fever clearance time in the present study were consistent with the earlier studies\textsuperscript{4,10}. A rapid recovery from coma was observed in the cerebral malaria patients in the present study. The mean coma recovery time was low compared to that reported in quinine treated patients\textsuperscript{21}. This might be due to longer half-life as well as better accumulation of arteether in brain tissue\textsuperscript{14}.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-therapy (day 0)</th>
<th>Post-therapy (day 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>8.22±1.89</td>
<td>9.20±1.78**</td>
</tr>
<tr>
<td>(4.0-12.0)</td>
<td>(5.2-12.5)</td>
<td></td>
</tr>
<tr>
<td>TLC (mm\textsuperscript{3})</td>
<td>7178.3±1366.1</td>
<td>7833.33±1077.7**</td>
</tr>
<tr>
<td>(3,500-9,350)</td>
<td>(4,500-10,000)</td>
<td></td>
</tr>
<tr>
<td>Random blood sugar (mg/dl)</td>
<td>122.0±30.86</td>
<td>87.7±6.83**</td>
</tr>
<tr>
<td>(50-430)</td>
<td>(70-210)</td>
<td></td>
</tr>
<tr>
<td>Serum urea (mg/dl)</td>
<td>42.2±27.16</td>
<td>35.8±6.4**</td>
</tr>
<tr>
<td>(24-164)</td>
<td>(18-36)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.22±1.11</td>
<td>0.72±0.10*</td>
</tr>
<tr>
<td>(0.6-4.2)</td>
<td>(0.6-1.3)</td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>2.46±2.69</td>
<td>0.78±2.11**</td>
</tr>
<tr>
<td>(0.6-10.4)</td>
<td>(0.6-2.4)</td>
<td></td>
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Values expressed as mean±SD with the range in parentheses (n=30)
TLC, total leucocyte count
\(P<0.05, **<0.001\) compared to pre-therapy

Table I. Pre- and post-arteether therapy parasite count/µl in patients with acute chloroquine resistant \textit{P. falciparum} malaria

<table>
<thead>
<tr>
<th>Parasite count/µl</th>
<th>Pre-therapy</th>
<th>Time post-therapy (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Range:</td>
<td>24000-450,000</td>
<td>400-3600\textsuperscript{*}</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>85133.33±85756.16</td>
<td>926.66±668.98</td>
</tr>
</tbody>
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N=30
\(*P<0.05\) compared to pre-therapy
\(**P<0.05\) compared to 24 h post-therapy
Another important observation in the present study was that the patients with haemolytic jaundice, acute renal impairment and severe anaemia recovered completely after arteether therapy and other supportive measures, as required. No adverse effect due to arteether therapy was observed in the study as has been noted by the earlier workers.\textsuperscript{1,4,10-12}

In conclusion, arteether was found to be effective in patients with acute chloroquine resistant \textit{P. falciparum} malaria. It was equally effective in patients with complicated as well as uncomplicated \textit{P. falciparum} malaria. Arteether may be considered as a suitable alternative to quinine because of its efficacy, safety and ease of administration, particularly for patients in peripheral hospitals with chloroquine resistant falciparum malaria. As this study was done with a limited number of patients, further studies with a larger sample size need to be done in other parts of India.

Acknowledgment

Authors thank Dr Rajbir Singh, Scientist, Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, for statistical analysis of the data.

References


17. Dias D. The relentless fight against malaria-1. \textit{Medicine Update} 2001; \textit{10}: 1-5.


