Artemether for Severe Malaria: A Meta-Analysis of Randomized Clinical Trials

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The treatment of choice for severe malaria is quinine. However, a gradual progression of resistance to quinine has become a concern in parts of the world. Artemisinin-related compounds are a relatively new class of drugs. This meta-analysis assesses the evidence regarding the clinical effectiveness of artemether for severe malaria. Computerized literature searches identified all randomized clinical trials of artemether in comparison with quinine. Standardized data extraction was independently performed by both authors. Results of nine trials, entered in the meta-analysis, demonstrate the absence of a significant difference between artemether and quinine in terms of mortality rate (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.50–1.14). Statistical pooling of data from trials in Southeast Asia showed a trend toward enhanced reduction of mortality (OR, 0.38; 95% CI, 0.14–1.02). These data demonstrate the equality of artemether and quinine for severe malaria and indicate a trend toward greater effectiveness of artemether in regions where there is recognized quinine resistance.

Malaria is one of the major infectious diseases in the world today. The World Health Organization estimates that 40% of the world’s population is threatened by malaria [1, 2]. The contribution of malaria to the global burden of disease is substantial and represents a major public health concern [3, 4]. The most virulent of the four Plasmodium species causing malaria in humans, Plasmodium falciparum, is potentially life-threatening [5] and responsible for 1.5–3.0 million deaths per year worldwide from severe malaria [6]. Quinine is the drug of choice for severe malaria [7]. However, a gradual progression of resistance to quinine has been recognized, especially in Southeast Asia [6, 8]. Artemisinin-related compounds are a relatively new class of drugs for the treatment of severe malaria.

Artemisinin, a sesquiterpene endoperoxide, is the active principle of the Chinese herb qinghao (Artemisia annua) [9]. In traditional Chinese medicine, extracts of qinghao have been used to treat all forms of febrile illnesses. The leaves of cultivated A. annua are used today as raw material for this drug class [10]. One artemisinin-related compound is the methyl ether derivative artemether [11]. Effectiveness of artemether in the treatment of severe malaria has been suggested by a number of uncontrolled and controlled but nonrandomized studies [12–16]. Uncontrolled studies cannot differentiate between nonspecific effects such as the natural course of disease and specific therapeutic effects [17], while nonrandomization may lead to substantial overestimation of the effect and thus introduce bias [18]. Therefore, randomized controlled trials (RCTs) are needed to estimate the true clinical effectiveness of artemether for severe malaria. This meta-analysis is aimed at assessing the evidence from RCTs regarding the clinical effectiveness of artemether for severe malaria.

Methods

Computerized literature searches were performed to identify all RCTs of artemether for severe malaria. MEDLINE, Embase, Biosis, CISCOM, and the Cochrane Library databases were searched (all from their respective inceptions to January 1998). The search terms used were artemether, artemisinin, qinghaosu, and Artemisia annua. In addition, manufacturers of pharmaceuticals containing artemether were asked to contribute published and unpublished material. Furthermore, our own files were searched for relevant publications. The bibliographies of the studies and reviews thus retrieved were scanned for further studies. There were no restrictions regarding the language of publication.

RCTs were included if they involved patients with severe malaria treated with artemether and controls treated with quinine for comparison. Studies not involving artemether monotherapy were excluded. Data extraction was performed in a standardized, predefined fashion. Trial outcomes and methodological quality were independently assessed by both authors, using a standard scoring system to measure the likelihood of bias inherent in the studies [19] (with items on random allocation, double-blinding, and description of dropouts and withdrawals). Discrepancies in the evaluation of individual trials were resolved by discussion.

Statistical pooling of trial results was performed with use of standard meta-analysis software (RevMan 3.01; Update Soft-
Table 1. Data from randomized clinical trials of artemether vs. quinine for severe malaria.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study site</th>
<th>Quality score (maximum, 5)</th>
<th>Study design</th>
<th>Manifestation of disease; sample size, as no. of artemether/quineine recipients (mean ages in years)</th>
<th>Treatment group (artemether, or A) and control group (quinine, or Q) dosages</th>
<th>Mortality rate: no. (%) of deaths per no. of patients (artemether group vs. quinine group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[23]</td>
<td>Ho Chi Minh City, Vietnam</td>
<td>5</td>
<td>Double-blind; 2 parallel arms</td>
<td>A: 4-mg/kg loading dose, then 2 mg/kg q8h im until patient could drink Q: 20-mg/kg loading dose, then 10 mg/kg q8h im until patient could drink</td>
<td>A: 4-mg/kg loading dose, then 2 mg/kg q8h im until patient could drink Q: 20-mg/kg loading dose, then 10 mg/kg q8h im until patient could drink</td>
<td>36/284 (12.7) vs. 47/276 (17.0)</td>
</tr>
<tr>
<td>[24]</td>
<td>Chantaburi, Thailand</td>
<td>3</td>
<td>Open; 2 parallel arms</td>
<td>A: 160-mg loading dose, then 80 mg/d for 6 d, im Q: 20-mg/kg loading dose, then 10 mg/kg q8h for 7 d, iv</td>
<td>A: 160-mg loading dose, then 80 mg/d for 6 d, im Q: 20-mg/kg loading dose, then 10 mg/kg q8h for 7 d, iv</td>
<td>6/47 (12.8) vs. 18/49 (36.7)</td>
</tr>
<tr>
<td>[25]</td>
<td>Kilifi, Kenya</td>
<td>3</td>
<td>Open; 2 parallel arms</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) im until parasitemia cleared Q: 20-mg/kg loading dose, then 10 mg/kg q8h iv until parasitemia cleared</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) im until parasitemia cleared Q: 20-mg/kg loading dose, then 10 mg/kg q8h iv until parasitemia cleared</td>
<td>18/89 (20.2) vs. 8/71 (11.3)</td>
</tr>
<tr>
<td>[26]</td>
<td>Banjul area, The Gambia</td>
<td>3</td>
<td>Open; 2 parallel arms</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) for 3 d, im Q: 20-mg/kg loading dose, then 10 mg/kg q12h im for 4 d</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) for 3 d, im Q: 20-mg/kg loading dose, then 10 mg/kg q12h im for 4 d</td>
<td>59/288 (20.5) vs. 62/288 (21.5)</td>
</tr>
<tr>
<td>[27]</td>
<td>Ibadan, Nigeria</td>
<td>2</td>
<td>Open; 2 parallel arms</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) for 4 d, im Q: 20-mg/kg loading dose, then 10 mg/kg q8h for 7 d, iv</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) for 4 d, im Q: 20-mg/kg loading dose, then 10 mg/kg q8h for 7 d, iv</td>
<td>3/25 (12.0) vs. 6/29 (20.7)</td>
</tr>
<tr>
<td>[28]</td>
<td>Abidjan, Ivory Coast; Bamako, Mali; Brazzaville, Congo; Libreville, Gabon; Yaoundé, Cameroon</td>
<td>2</td>
<td>Open, multicenter; 2 parallel arms</td>
<td>A: for patients &lt;50 kg, 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) for 4 d, im; for patients ≥50 kg, 160-mg loading dose, then 80 mg/d for 4 d</td>
<td>A: for patients &lt;50 kg, 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) for 4 d, im; for patients ≥50 kg, 160-mg loading dose, then 80 mg/d for 4 d</td>
<td>8/133 (6.0) vs. 8/135 (5.9)</td>
</tr>
<tr>
<td>[29]</td>
<td>Chantaburi, Thailand</td>
<td>1</td>
<td>Open; 2 parallel arms</td>
<td>A: 160-mg loading dose, then 80 mg/d for 6 d, im Q: 20-mg/kg loading dose, then 10 mg/kg q8h for 7 d, iv</td>
<td>A: 160-mg loading dose, then 80 mg/d for 6 d, im Q: 20-mg/kg loading dose, then 10 mg/kg q8h for 7 d, iv</td>
<td>1/14 (7.1) vs. 5/12 (41.7)</td>
</tr>
<tr>
<td>[30]</td>
<td>Kilifi, Kenya</td>
<td>1</td>
<td>Open; 2 parallel arms</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) im until parasitemia cleared Q: 20-mg/kg loading dose, then 10 mg/kg q8h iv until parasitemia cleared</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) im until parasitemia cleared Q: 20-mg/kg loading dose, then 10 mg/kg q8h iv until parasitemia cleared</td>
<td>0/7 (0) vs. 1/7 (14.3)</td>
</tr>
<tr>
<td>[31]</td>
<td>Blantyre, Malawi</td>
<td>1</td>
<td>Open; 2 parallel arms</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) im until parasitemia cleared Q: 20-mg/kg loading dose, then 10 mg/kg q8h iv until parasitemia cleared</td>
<td>A: 3.2-mg/kg loading dose, then 1.6 mg/(kg·d) im until parasitemia cleared Q: 20-mg/kg loading dose, then 10 mg/kg q8h iv until parasitemia cleared</td>
<td>3/28 (10.7) vs. 4/37 (10.8)</td>
</tr>
</tbody>
</table>

Mortality was defined as the primary endpoint and assessed with site-specific and combined datasets. Mortality rates in the artemether and quinine arms were used as a basis for calculating odds ratios and were weighted according to sample size. Odds ratios and 95% confidence intervals were calculated with use of a random effects model. Chi-squared tests were used for differences in mortality rate between the artemether and quinine groups.
Three trials were conducted in Southeast Asia [23, 24, 29]. Although one trial [24] showed a significantly lower mortality rate among patients treated with artemether, the overall result of these trials reveals no significant difference between artemether and quinine treatment (OR, 0.38; 95% CI, 0.14–1.02). The survival rate was 87.5% for patients treated with artemether and 79.2% for patients treated with quinine.

Adverse effects encountered in the analyzed studies are summarized in Table 2. In general, artemether was well tolerated. Patients treated with artemether experienced less frequent and generally milder adverse effects than did patients treated with quinine.

### Discussion

To our knowledge this is the first meta-analysis assessing the clinical effectiveness of artemether against standard therapy for severe malaria with respect to geographic differences of study site. The increasing resistance of *P. falciparum* to quinine may render its use a risk factor in parts of the world [32].

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Adverse effect of drug (frequency, as percentage of cases)</th>
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<tbody>
<tr>
<td>[23]</td>
<td>Hypoglycemia (11%); corrected QT interval prolonged by &gt;25% (7%); longer recovery time from coma</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia (25%); corrected QT interval prolonged by &gt;25% (9%); abscess at site of im injection (3%)</td>
</tr>
<tr>
<td>[24]</td>
<td>None</td>
</tr>
<tr>
<td>[25]</td>
<td>QT-interval prolongation of &gt;25% (23%)</td>
</tr>
<tr>
<td>[26]</td>
<td>Local reactions at site of im injection (0.7%); longer recovery time from coma; convulsions after onset of treatment (39%)</td>
</tr>
<tr>
<td>[27]</td>
<td>None</td>
</tr>
<tr>
<td>[28]</td>
<td>Abdominal and injection-site pain (NR); overall frequency of adverse effects was 25%</td>
</tr>
<tr>
<td>[29]</td>
<td>None</td>
</tr>
<tr>
<td>[30]</td>
<td>NR</td>
</tr>
<tr>
<td>[31]</td>
<td>NR</td>
</tr>
</tbody>
</table>

NOTE. NR = not reported.
Overall, the meta-analysis demonstrates no significant difference in mortality rate between recipients of artemether vs. quinine for severe malaria. All trials conducted in sub-Saharan African countries suggest the absence of a significant difference between artemether and quinine and corroborate the results of an earlier meta-analysis of African children with cerebral malaria [33]. In contrast, pooled data of studies conducted in Southeast Asia show a trend toward a more effective reduction of mortality with use of artemether rather than quinine. In such trials the mortality rate was 40% lower among patients treated with artemether than among those treated with quinine. This finding must be viewed in relation to the increased resistance of P. falciparum to quinine in Asian countries.

Although there is recognized criticism about the pooling of trial data in meta-analyses [34, 35], particularly in that the findings of large RCTs do not always agree with their results [35], the findings in the present meta-analysis are supported by the largest trials in each (African and Asian) setting [23, 26].

While treatment with artemether as effective as standard therapy, the drug may have considerable advantages over quinine with respect to the developing problem of drug resistance. The chemical structure and mode of action of the artemisinin derivatives distinguish them from other currently available antimalarial agents [36, 37] and render them less liable to cross-resistance [38]. Artemisinin derivatives reach 100 to 300 times higher concentrations in P. falciparum—infected erythrocytes than in uninfected erythrocytes [38, 39]. They are hydrophobic and partition into biological membranes, particularly into digestive vacuole membranes and mitochondria, with subsequent damage to such membranes [10]. This, in turn, leads to vacuole rupture and parasite autodigestion [40]. The involved mechanisms are understood in part, and more research is needed to uncover the precise mode of action [41].

Artemether has a favorable safety profile, as demonstrated in pharmacological studies [42]. There is no evidence of significant systemic adverse effects in humans [9]. This is supported by all of the above studies [23–31] and the fact that one of seven studies that focused on adverse effects did not reveal any in patients treated with artemether (table 2). Adverse effects reported with artemether were hypoglycemia, abdominal and local injection site pain, and QT-interval prolongation of >25%. The latter was not associated with arrhythmia or clinical symptoms [23, 25]. Two studies [23, 26] showed an increased recovery time from coma among patients treated with artemether, while this was noted in a study [31] of patients treated with quinine. In comparison to those of quinine, the observed adverse effects of artemether were generally less frequent and milder. However, more information is needed, particularly on the safety of long-term clinical use [43].

In conclusion, artemether is as effective as quinine for severe malaria. Furthermore, it is relatively safe and has advantages with respect to the developing quinine resistance. These characteristics render artemether an attractive option for the management of severe malaria.

References
23. Tran V, Pittler and Ernst CID 1999;28 (March)