Original Article

Efficacy of loading versus standard doses of quinine in cerebral malaria

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ABSTRACT

Objective
To compare the efficacy of loading dose of quinine with the standard doses of quinine in cerebral malaria.

Patients and Methods
This study was conducted in Hayat Abad Medical Complex, Postgraduate Medical Institute, Peshawar from January 2009 to December 2009. Fifty consecutive cases of cerebral malaria fulfilling the WHO’s diagnostic criteria for cerebral malaria were placed at random into two groups with 25 patients in each group. Group A patients received loading doses (20mg/kg body weight over 4 hours) of quinine followed by the standard dosages (10mg/kg body weight) and group B patients was administered standard doses of quinine. Clinical features as well as temperature and laboratory diagnosis for detection of Falciparum by microscopy was noted every twelve hours. Side effects were noted and blood sugar at baseline as well as at 12 hour interval was taken from all patients. A baseline ECG with daily monitoring for possible QT prolongation was done in all patients.

Results
In Group A, 22 (88%) patients recovered completely while three patients died (12%) and in Group B, 21(84%) patients recovered while four patients (16%) died. Four patients in group A developed hypoglycemia (16%) at 12 hours but none of the patient developed hypoglycemia in group B. Tinnitus and transient deafness were more common in patients recovering from coma in
group A (20%). None of the patient had any evidence of QT prolongation or arrhythmia. Mean disappearance time of Plasmodium from the blood of Group A was 12 hours and in group B it was 36 hours. Mean time for regaining full consciousness with orientation in time space and person and no neurological deficit was 24 hours in group A and 36 hours in group B.

**Conclusion**
Loading dose of quinine seems to be well tolerated and may clear parasitaemia faster than standard doses of quinine. (Rawal Med J 2011;36:86-88).

**Keywords**
Cerebral malaria, quinine, plasmodium.

**INTRODUCTION**
Malaria kills millions every year and 85% of deaths are in children under 5 years of age.\(^1\) It every year infects 300-500 million.\(^2\) Cerebral malaria is the most devastating complication which, if untreated, has a mortality approaching 100%.\(^3\) Early recognition and treatment is the cornerstones of management, drug resistance has further complicated the issue.\(^3,4\) According to WHO, the diagnosis of cerebral malaria requires the presence of Plasmodium falciparum parasitaemia and the patient to be unarousable with a Glasgow Coma Scale score of 9 or less, and other causes (e.g. hypoglycemia, bacterial meningitis and viral encephalitis) ruled out.\(^5,6\)

Intravenous quinine is currently the most widely used agent for treatment of severe falciparum malaria. Both quinine and quinidine may cause cinchonism (bitter taste, dysphoria, tremor, tinnitus, reversible high-tone hearing loss, headache, nausea, vomiting, and abdominal pain) or pruritus, which should not lead to dose reduction.\(^7\) Both drugs have narrow therapeutic windows with severe toxicities including cardiac arrhythmias, hypotension, blindness, deafness, and hyper-insulinemic hypoglycemia.\(^7\) WHO recommends use of quinine in a loading dose as 20 mg/kg in a four hour rapid infusion followed by half the dose i.e. 10 mg/kg every eight hours till parasitaemia disappears from the blood.\(^6,7\) Objective of the study was to compare the loading dose with the conventional doses of quinine in cerebral malaria.

**PATIENTS AND METHODS**
This study was conducted in Hayat Abad Medical Complex, Postgraduate Medical Institute, Peshawar from January 2009 to December 2009. Patients with Falciparum Malaria and only Falciparum positive cases who were deeply comatose and fulfilling the criteria of WHO for
cerebral malaria (unarousable coma, asexual Falciparum parasitaemia and no other demonstrable cause of coma) were included in the study. All patients had GCS of less than nine. Fifty cases were enrolled at random during the one year time.

Pretreatment evaluation included a detailed physical examination, hematological and biochemistry analysis, chest radiography and a lumbar puncture with CSF examination. Patients were assigned to two groups with 25 in each group. Group A patients received loading dose (20mg/kg body weight over 4 hours) of quinine followed by the standard dosages (10mg/kg body weight) and group B patients was administered only standard doses of quinine. The treatment was continued for a total of seven days in the hospital. Clinical features, temperature and laboratory detection of Falciparum was noted every twelve hours. Side effects of quinine were also noted and baseline plus12 hourly blood sugar was taken from all patients. A baseline ECG with daily monitoring for possible QT prolongation and arrhythmia was done in all patients. GCS was checked daily.

RESULTS

The demographic and baseline characteristics are shown in Table I. Out of 50 patients, 7 (14%) died while the remaining 43(86%) completed the study. In Group A, 22(88%) patients recovered completely while three patients (12%) died and in Group B, 21(84%) patients recovered while four (16%) died. Four (16%) patients in group A developed hypoglycemia at 12 hours, none in group B had this. Tinnitus and transient deafness were more common in patients recovering from coma in group A which occurred in 5 (20%) patients.

Table 1. Demographic characteristics of study population (n=50).

<table>
<thead>
<tr>
<th>Patients</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Male/Female</td>
<td>12/13</td>
<td>13/12</td>
<td>25/25</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Range:</td>
<td>20-50</td>
<td>20-50</td>
<td>20-50</td>
</tr>
<tr>
<td>Mean:</td>
<td>27 Years</td>
<td>27 Years</td>
<td>27 Years</td>
</tr>
<tr>
<td>Female Range:</td>
<td>18-35</td>
<td>18-35</td>
<td>18-35</td>
</tr>
<tr>
<td>Mean:</td>
<td>24 Years</td>
<td>24 Years</td>
<td>24 Years</td>
</tr>
</tbody>
</table>
Mean disappearance time of Plasmodium from the blood of Group A was 12 hours while in group B, it was 36 hours (Table 2).

Table 2. Clinical and hematological response to quinine.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25(50%)</td>
<td>25(50%)</td>
<td>50(100%)</td>
<td></td>
</tr>
<tr>
<td>Number of patients recovered</td>
<td>22(88%)</td>
<td>21(84%)</td>
<td>43(86%)</td>
<td>0.683</td>
</tr>
<tr>
<td>Mean disappearance time of Plasmodium from the blood</td>
<td>12 Hrs</td>
<td>36 Hrs</td>
<td>24 Hrs</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean time for regaining full consciousness</td>
<td>24 Hrs</td>
<td>36 Hrs</td>
<td>30 Hrs</td>
<td>0.000</td>
</tr>
<tr>
<td>Deaths</td>
<td>3(12%)</td>
<td>4(16%)</td>
<td>7(14%)</td>
<td>0.683</td>
</tr>
<tr>
<td>Side Effects</td>
<td>9(36)*</td>
<td>0(0%)</td>
<td>9(36%)*</td>
<td>0.000</td>
</tr>
</tbody>
</table>

* The side effect noted was hypoglycemia, tinnitus and deafness.

The patients who died never gained consciousness and their coma worsened with time. These deaths occurred during the first 48 hours of treatment. One of them died within twelve hours. None of the patient had QT prolongation or arrhythmia during the treatment. The GCS improved during the course of treatment in all patients who survived and gradually they were fully alert. In the group A, they were fully alert within 24 hours, while in group B they were fully alert after 36 hours.

**DISCUSSION**

Cerebral Malaria is a dangerous complication of Falciparum malaria. WHO is constantly devising guidelines for treatment of this highly deadly disease and the latest guidelines were issued in 2010. Quinine is the standard drug used for the treatment of cerebral malaria. It is given in the standard dose of 10mg/kg body weight usually for a period of five to seven days. WHO, however, recommends a double loading dose of 20 mg/kg body weight as the first dose over a period of four hours which is considered to be efficacious in reducing parasitaemia very
quickly, reduce mortality and hasten early recovery. In our study, we found loading dose to be efficacious in reducing parasitaemia and disappearance of Plasmodium falciparum from the circulation much earlier than the standard dose. This also led to early defervescence, early gain of consciousness and a better outcome. The reduction in mortality was also seen but this is not significant probably due to the small study size.

The side effects like hypoglycaemia, tinnitus and deafness were, however, more common in the loading dosage group. This is understandable and these side effects were easily manageable. The deafness was transient and disappeared after the drug was stopped. These trivial side effects are acceptable keeping in mind the high mortality of cerebral malaria. Our study is comparable to other studies. A study in children found no significant difference in mortality between two quinine regimens, however, parasite and fever clearance times were reduced in the former. In one RCT involving 33 patients, transient partial hearing loss was significantly increased in the group receiving a high initial dose (59%) compared with standard dose (19%). In another RCT, there was no significant difference between the two groups in neurological sequelae.

CONCLUSION

We found that loading dose regimen of Quinine was more effective in cerebral malaria than standard dose and loading doses were well tolerated. Use of a loading dose of quinine in cerebral malaria is recommended to reduce mortality and with acceptable side effects.

REFERENCES


