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## Original Article

### **Efficacy and safety of quinine loading dose in patients with severe Falciparum malaria at a tertiary care hospital in Pakistan**

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#### **Abstract**

**Objective:** To compare the clinical outcomes of a loading dose regimen of quinine with a uniform dose regimen in patients with severe falciparum malaria.

**Methods:** A retrospective chart review of 315 patients admitted with severe falciparum malaria and treated with quinine at a tertiary care teaching hospital of Karachi, Pakistan during 1999-2006 was conducted. Group A with 103 patients (32.7%) was given an initial loading dose of quinine while group B with 212 patients (67.3%) did not receive the loading dose. The two groups were compared in terms of reduction of parasite load, resolution of fever, recovery of consciousness and incidence of adverse effects. Outcome parameters were measured on the third day of therapy.

**Results:** More individuals in group A (62.1%) were afebrile as compared to group B (54.7%) at day 3 of therapy. Patients in group B showed greater reduction in parasitaemia (47.2% at baseline to 4.7% on day 3) as compared to group A (56.3 % at baseline to 9.7% on day 3). Following therapy, fewer patients in group B had altered consciousness (7.1% at baseline to 4.7% on day 3) as compared to patients in group A (7.8% at baseline to 5.8% on day 3). However, these associations were not statistically significant. The incidence of thrombocytopenia was higher in Group A (5.8%) as compared to Group B (0.9%).

**Conclusion:** Although quinine loading dose may be more effective than uniform dose in rapid fever clearance; it also appears to be associated with higher toxicity. Uniform dose of quinine may be prescribed in severe falciparum malaria in view of its better safety profile.

**Keywords:** Severe falciparum malaria; Quinine; Loading Dose; Pakistan (JPMA 61:27; 2011).

#### **Introduction**

Falciparum malaria is a severe and a potentially life-threatening parasitic disease with increasing prevalence in most endemic regions of the world. This translates into devastating health and socio-economic consequences; especially in areas where there is increasing drug resistance in

the causative organism or where the cases are inappropriately managed.<sup>1,2</sup> The disease affects more than 500 million people and causes 2-3 million deaths each year worldwide.<sup>2-4</sup> Malaria is also a major health problem in Pakistan, with an estimated number of annual episodes of about 1.6 million. Of these, about 33% are reported as falciparum malaria cases. Most of

the disease episodes have been recorded in the post-monsoon period (August-November); the stagnant water pools providing optimal breeding conditions for the mosquitoes.<sup>5</sup>

Falciparum malaria is associated with significant morbidity and mortality.<sup>2,6</sup> In particular, severe falciparum malaria may be complicated by Acute Renal Failure (ARF), Disseminated Intravascular Coagulation (DIC), Cerebral Malaria, Hypoglycaemia, Metabolic Acidosis, Pneumonia, Acute Respiratory Distress Syndrome (ARDS) and Anaemia.<sup>4,7</sup>

Early and effective treatment of severe falciparum malaria may shorten its duration and prevent development of complications with a reduction in associated mortality. However, there is little consensus with regards to the most optimum modus operandi for the therapeutic management of this condition. Quinine is still being used as a first-line drug in falciparum malaria since resistance to Chloroquine has been widely reported from many parts of the world including Pakistan.<sup>2,4,6,8</sup> The World Health Organization (WHO) recommends in its handbook for management of severe malaria, that the course of treatment with Quinine may follow a high initial Loading Dose (qLD) regimen of 20mg/kg of body weight followed by Maintenance Dose (qMD) of 10mg/kg repeated 8 hourly to complete a 7 day course of treatment.<sup>4</sup>

However, according to a Cochrane Review of 2004,<sup>9</sup> the use of an initial loading dose of quinine remains debatable. Randomized controlled trials (RCTs) assessing this subject are few and far between; only 4 trials (n=144) fulfilled the inclusion criteria of this Cochrane Review. It was concluded that while qLD was associated with fewer deaths, this association was not statistically significant. qLD caused a reduction in fever clearance time and parasite clearance time but there was no statistically significant impact on the recovery of consciousness, neurological sequelae, as convulsions.

Thus on one hand, there are studies that have illustrated the use of a high initial IV Quinine Loading Dose as being beneficial;<sup>2,10-12</sup> on the other hand, there are studies that negate the advantages of the Loading Dose Regime over standard treatment of maintenance dose for severe/complicated malaria.<sup>6,13,14</sup>

Thus, it is important to collect more data on the subject in order to delineate the direction of the therapeutic trend with regards to use of loading dose of quinine. Current data are insufficient to directly demonstrate the benefits or drawbacks of this form of treatment. Therefore, the current study was undertaken to assess the efficacy and safety of Quinine Loading Dose in the treatment of severe falciparum malaria in a malaria endemic geographical region of the world in order to evaluate its effect on various parameters such as (1) reduction of parasite load, (2) resolution of fever, (3) recovery of

consciousness and (4) adverse effects. The results of this study may, therefore, help improve current prescribing practices in the treatment of severe falciparum malaria.

## Methods

This retrospective review of patient charts was conducted in the Department of Medicine, Aga Khan University Hospital (AKUH) Karachi, Pakistan. A computerized data base search for anonymous patient information was conducted under the guidelines of Ethical Review Committee (ERC) of the Aga Khan University Hospital. No patient was individually identified and the data was obtained in an anonymous fashion without ever alluding to the identity of the patient. The data of hospitalized adult patients was extracted meeting the following inclusion criteria: a) age 15 or above, b) admitted with the diagnosis of 'Severe Falciparum Malaria' c) admitted during an 8 year period from January 1, 1999 to December 31, 2006 d) treated with intravenous (IV) or oral Quinine. All hospitalized patients were considered to have severe malaria based on the categorization as per WHO classification for severe falciparum malaria.<sup>4</sup> We excluded those patients who were negative for Malarial Parasite (MP) on admission or who were diagnosed on the basis of Immuno-chromatographic (ICT) test. Quantitative assessment of parasitemia through MP test was categorized as 'heavy' when there were more than 1000 parasites/100 high power microscopic field, 'moderate' when there were 11-1000 parasites/100 high power microscopic fields and "scanty" when there were 1-10 parasites/100 high power microscopic fields. Two comparison groups were made based on the administration of quinine regime. The loading dose (qLD) regime consisted of 20mg/kg of body weight given IV followed by maintenance dose of 10 mg/kg body weight given either IV or oral repeated 8 hourly for 5-7 days. The "no loading" dose regime comprised of quinine maintenance dose (qMD) only. The primary comparison between the two groups in terms of different parameters was done on the 3rd day after therapy was administered. Data was entered and analyzed using Windows Statistical Package for Social Sciences (SPSS) version 14.<sup>15</sup> Data were described calculating means and standard deviations for continuous variables and frequencies for categorical variables. Univariate analysis was conducted defining dependent variables on the basis of first dose of quinine therapy and it was categorized in two groups, i.e., quinine loading dose (qLD) group and no loading dose group (qMD). Student's t-test was used to compare means among qLD and qMD groups. Chi-square test or Fisher's exact test, as appropriate, were used to compare categorical independent variables among the two groups. A p-value of < 0.05 was considered statistically significant; unless otherwise specified.

## Results

A total of 315 patients were included in this study. The mean age was  $38.5 \pm 16.8$  years with 239 (75.9%) males and 76 (24.1%) females. Most patients (87.9%) were admitted through emergency room (ER) while the remaining were admitted through consulting clinics. The majority (69.8%) of the patients were admitted during a four month post-monsoon period from August to November. The initial Loading dose of quinine (qLD) was given to Group A with 103 (32.7%) patients. Group B with 212 (67.3%) patients did not receive

qLD. All patients received maintenance dose, either IV (33%) or oral (67%).

Thrombocytopenia, cerebral malaria, anaemia, pneumonia, Acute Respiratory Distress Syndrome (ARDS), metabolic acidosis, hypoglycaemia, volume depletion and jaundice were complications equally distributed ( $p > 0.05$ ) in the two groups at the time of presentation. Acute renal failure ( $p = 0.008$ ) and disseminated intravascular coagulation (DIC) ( $p = 0.008$ ) were complications more common in patients in Group A. A comparison of other clinical parameters between

**Table-1: Socio demographic characteristics and other baseline features by quinine group in patients with severe falciparum malaria admitted at AKUH from 1999-2006.**

Characteristic	Group A (n = 103) %	Group B (n = 212) %	p-value
<b>Gender</b>			
Male	69.9	78.8	0.084
Female	30.1	21.2	
Mean Age in years §	$38.2 \pm 16.7$	$38.7 \pm 17.0$	0.793
Mean Duration of fever in days @	$7.3 \pm 6.6$	$7.4 \pm 6.6$	0.846
<b>Malaria complications present at baseline</b>			
Thrombocytopenia	27.2	25	0.677
Acute renal failure	17.5	7.5	0.008
Cerebral malaria	10.7	9	0.626
Anaemia	9.7	9	0.83
Disseminated intravascular coagulation	9.7	2.4	0.008 #
Pneumonia	7.8	2.8	0.076 #
Acute respiratory distress syndrome	6.8	2.4	0.064 #
Metabolic acidosis	3.9	1.9	0.446 #
Hypoglycaemia	1.9	1.9	0.999 #
Volume depletion	37.9	31.6	0.27
Jaundice	34	31.1	0.611
Presence of altered consciousness at baseline (as measured by GCS $\leq$ 14)	7.8	7.1	0.825
Mean temperature documented at baseline (degree Celsius)	$38 \pm 1.2$	$37.9 \pm 1.17$	0.104
<b>Malarial parasite load at baseline</b>			
Heavy	13.6	8.5	
Moderate	42.7	38.7	0.039
Scanty	43.6	52.8	

§ Information missing in 3 patients; @ Information missing in 11 patients; # Fisher exact test p-value.

**Table-2 Comparison of outcomes between groups based on type of quinine therapy received.**

Outcome measure	Group A (n = 103) %	Group B (n = 212) %	p-value
<b>Parasite load at day 3</b>			
Heavy	2.9	0	
Moderate	6.8	4.7	0.08
Scanty	36.9	36.8	
Negative MP	53.4	58.5	
Presence of altered consciousness at day 3 (as measured by GCS $\geq$ 14)	5.8	4.7	0.674
Fever resolution at day 3 (temperature $<$ 38 degree Celsius for last 24 hours)	62.1	54.7	0.59
<b>Adverse effects of quinine therapy</b>			
Vomiting	5.8	3.3	0.366 #
Cinchonism / tinnitus	5.8	4.2	0.577 #
Arrhythmias	1.9	1	0.250 #
Hypoglycemia	1.9	0.5	0.999 #
Thrombocytopenia	5.8	0.9	0.017 #
Pulmonary oedema	1	0	0.327 #

# Fisher exact test p-value.

the two groups including altered level of consciousness (GCS 14 or less), documented mean temperature and quantitative MP on microscopy is shown in Table-1.

Table-2 shows a comparison of the outcomes between the two groups. These were measured on the third day of the administration of therapy. It was seen that by third day of therapy, the difference in quantitative parasitaemia between the two groups was insignificant ( $p=0.08$ ). In terms of recovery of consciousness at day 3, the two groups were again comparable ( $p=0.674$ ). There was no statistically significant difference between the two groups in terms of fever resolution at day 3 ( $p=0.59$ ). However, more individuals in Group A were afebrile as compared to Group B (62.1 % vs. 54.7%).

Group A and Group B were also comparable with regards to the majority of the in-hospital quinine-specific major side effects including cinchonism/tinnitus (headache, dizziness, hearing loss, and ringing in the ears) nausea/vomiting, hypoglycaemia, pulmonary oedema and cardiac arrhythmia (prolongation of QT interval). The groups, however, showed a statistically significant difference with regards to the incidence of thrombocytopenia (platelet count  $\leq 150,000$  cells per microliter); more patients who had received qLD showed this adverse effect ( $p=0.017$ ).

## Discussion

This study assessed the effectiveness and beneficial aspects of incorporating the rationale of a high initial IV quinine loading dose in the treatment of adult patients with moderate to severe and/or complicated falciparum malaria. Demographic details in this study showed that majority of patients were males possibly as a result of more exposure to the vectors of malaria although no evidence was found to substantiate this internationally.

According to literature, quinine has evolved to be the first-line drug for severe / complicated falciparum malaria.<sup>2,4,6,9,16,17</sup> As per standard recommendations of WHO,<sup>4</sup> the globally advised rationale comprises of high initial loading dose of quinine followed by a maintenance dose.

Our analysis showed that only one third of the patients received qLD, which in addition to the attending physician's choice may be attributed to either lack of ascertainment of prior drug administration, or use of quinine and its derivatives in past 12 hours.<sup>4,6</sup> Results of our study show success in early achievement of fever clearance in patients who received qLD, but parasite clearance (negative MP) was not significant.

Assessment of scientific literature and discussions over the efficacy and advantages of quinine loading dose regime revealed that qLD may contribute a beneficial effect in terms of Fever Clearance Time (FCT) as well as Parasite Clearance Time (PCT).<sup>2,9,10,14,18-20</sup>

Patients given qLD showed an improvement in the level of consciousness, accounting for early recovery of mental stability. Fargier et al<sup>19</sup> commented on significant reduction of coma recovery time in patients on qLD therapy. However, the Cochrane Review<sup>9</sup> advocates insufficient evidence to determine association of qLD with shorter recovery of consciousness, with many other citations suggesting no beneficial effects on the coma recovery.<sup>6,10,13,18</sup>

Other authors have suggested IV quinine dosage regimen may be associated with multiple adverse effects, which lead to poor compliance and side effects including, cinchonism, cardiac arrhythmias, hypotension, vomiting and abdominal pain, thrombocytopenia, anaemia, partial hearing loss/tinnitus and hypoglycaemia.<sup>2,4,6,17,18,21-23</sup> Many authors have cited that qLD was affiliated more with the development of these side-effects rather than the no qLD regimen.<sup>9,13,14,16,18,20,24,25</sup> We observed no difference in terms of adverse effects except thrombocytopenia which was higher in Group A as compared to Group B.

A few limitations of this study include its retrospective design and patient sample from a single hospital. Also, while studying malaria cases for a period of eight years, we encountered deficient data in the compiled records, leading to elimination of such cases. Attention in these areas is advised for future research to collate significant results. Paucity of data from South Asian countries should be addressed with well designed prospective clinical trials which we are planning to conduct with the baseline information from the current study.

## Conclusion

This study showed that quinine loading dose may be more effective than uniform dose in rapid fever clearance but it is also associated with higher toxicity. Maintenance dose of quinine maybe prescribed in severe falciparum malaria because of its better safety profile. Further well-designed, prospective studies are needed to directly demonstrate the impact of loading dose on parasitemia reduction and consciousness recovery in severe falciparum malaria.

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