

Treating Severe Malaria: Artesunate or Quinine?

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INTRODUCTION

Severe (complicated) malaria caused by *Plasmodium falciparum* kills over a million people every year. The annual death toll can be as high as one in 100 children under the age of five(1). Intravenous infusion of quinine is recommended as an initial therapy for these children. Recent years have witnessed increasing use of artemisinin derivatives (mainly artesunate) in the treatment of severe malaria. This systematic review from the Cochrane Library compared artesunate with quinine for treating severe malaria.

SUMMARY

Six randomized trials enrolling 1938 patients with severe malaria (1664 adults, 274 children) were included in this systematic review. All six trials were conducted in Asia. Of these, only one trial ($n=72$) was exclusively conducted in children. Artesunate was administered intravenously in 5 trials and intramuscularly in one study; against intravenous quinine. Treatment with artesunate significantly reduced the risk of death [relative risk (RR) 0.62, 95% confidence interval (CI) 0.51 to 0.75; 1938 participants, 6 trials], reduced parasite clearance time [weighted mean difference (WMD) 8.14 h, 95% CI 11.55 to 4.73; 292 participants, 3 trials], and hypoglycemia detected by routine monitoring (RR 0.46, 95% CI 0.25 to 0.87; 185 participants, 2 trials). The reduction in mortality was consistent across all trials and excluding trials with inadequate allocation concealment; trials in which all participants had

cerebral malaria, and those with no loading dose of quinine did not alter the significance of the result. There was no difference in the risk of neurological sequelae at discharge, coma recovery time, time to hospital discharge, fever clearance time, or adverse effects other than hypoglycemia, between the groups administered artesunate and quinine. This review recommends intravenous artesunate as the drug of choice for adults with severe malaria, particularly in Asia.

COMMENTARY

Are the results valid?

The review addresses a sensible and specific clinical question. The search of relevant studies was exhaustive and the studies included were sound in methods. However, the nature of intervention made blinding difficult and thus absence of blinding was not taken as a criterion to exclude studies from this review. Four of the included trials were conducted in single centers in Vietnam and the other two were multicentered. The largest of these trials ($n=1,461$) included centers throughout Bangladesh, Myanmar, India, and Indonesia. About three-fourth of the weightage in assessing the outcome of mortality in this review was contributed by this trial. The main strength of this review was that most of the outcomes assessed (mortality, adverse effects, sequelae, recovery time) were functionally important for influencing the policy and recommendations.

Though most of the participants enrolled in this review were adults, there is no reason to believe that children should behave differently. It is possible that children might fare even better with artesunate as children tend to present with a more severe disease and hyperparasitemia. One of the included trials demonstrated the greater benefit of artesunate in patients with hyperparasitemia. Also, the complications and mortality of quinine induced hypoglycemia is expected to be higher in children. However, one must admit that the present review

KEY MESSAGE

- Treatment of severe malaria with parenteral artesunate is associated with a greater reduction in mortality and lesser risk of hypoglycemia in comparison to intravenous quinine, in adults.

lacked significant power for the results to be valid in children.

How precise and clinically significant is the treatment effect?

The review reported a 38% (RR 0.62, 95% CI 0.51 to 0.75) reduction in relative risk of death with artesunate in comparison to quinine. If the range of 95% CI is taken into consideration, this risk reduction varies from 25% to 49%. In terms of absolute risk reduction, the risk of death in patients treated with artesunate was 8.5% less than those treated with quinine (13.7% vs. 22.2%). In other words, we need to treat about 12 patients of severe malaria with artesunate to prevent one death (Number needed to treat 'NNT'=12). This appears reasonably good especially when the adverse effect profile (especially risk of hypoglycemia) of artesunate is also better as evident from results of this systematic review.

Implications for Practice and Policy

Almost all current guidelines (including IAP guidelines) for treating severe malaria recommend intravenous quinine as first line therapy(1,2). An earlier Cochrane Review found a significant reduction in fever clearance time and parasite clearance time with a loading dose of quinine compared with no loading dose(3). Thus, initial loading dose of quinine is also a standard recommendation in all such guidelines. Artemisinin derivatives were recommended to be used when quinine is contraindicated or evidence of inadequate response or resistance to quinine noted(1,2). It was well-known before the publication of this review that artesunate results in faster clearance of parasitemia but absence of a direct evidence on reduction of mortality as compared with quinine precluded its inclusion as a first line drug.

Systematic review of randomized controlled trials is considered the best evidence for changing the policy or practice. With the publication of the result of this review, guidelines are likely to recommend artesunate as first line therapy for severe falciparum malaria especially in adults. The results of some ongoing trials in children would most likely be awaited before giving any recommendations in children. However, indiscriminate use of artesunate (as for empirical therapy without documentation of falciparum parasitemia) should be avoided to prevent development of resistance. In fact, it is recommended to use artesunate in combination with mefloquine or pyrimethamine-sulfadoxine to avoid resistance to this highly effective drug in this age old enemy of humans. Also, the recrudescence rates are lower when artemisinin derivatives are used in combination rather than when these are used alone.

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