Rectal versus Intravenous Quinine for the Treatment of Childhood Cerebral Malaria in Kampala, Uganda: A Randomized, Double-Blind Clinical Trial

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**Background.** Although artemesinin derivatives are promising for the treatment of severe Plasmodium falciparum malaria, intravenous quinine remains the most affordable treatment. However, administration of intravenous quinine is often not feasible in rural areas in Africa because of the lack of simple equipment or trained staff. We compared the efficacy and safety of intrarectal quinine with those of intravenous quinine in the treatment of childhood cerebral malaria.

**Methods.** In a randomized, double-blind clinical trial at Mulago Hospital (Kampala, Uganda), Uganda’s national referral hospital, we studied 110 children aged 6 months to 5 years who had cerebral malaria. Patients were randomized to receive either intrarectal or intravenous quinine. Main outcome measures included parasite clearance time, fever clearance time, coma recovery time, time to sit unsupported, time to begin oral intake, time until oral quinine was tolerated, and death.

**Results.** Overall, there was no difference in the clinical and parasitological outcomes between the 2 groups (data are mean ± standard deviation, intrarectal quinine group vs. intravenous quinine group): coma recovery time, 19.4 ± 18.1 h versus 17.0 ± 12.1 h; fever clearance time, 26.7 ± 16.1 h versus 29.9 ± 18.1 h; and parasite clearance time, 43.2 ± 14.2 h versus 41.9 ± 15.2 h. Mortality was similar in both groups; 4 of 56 patients in the intrarectal quinine group died, and 5 of 54 patients in the intravenous quinine group died (odds ratio, 1.3; 95% confidence interval, 0.3–5.2). Intrarectal quinine was well tolerated, and no major immediate adverse events occurred.

**Conclusions.** Intrarectal quinine is efficacious and could be used as an alternative in the treatment of childhood cerebral malaria, especially in situations in which intravenous therapy is not feasible.

Cerebral malaria is the most lethal complication of Plasmodium falciparum malaria [1], with a case-fatality rate of 5%–40% [1, 2]. Recently, the Southeast Asia Quinine Artesunate Malaria Trial revealed a better clinical outcome with intravenous artesunate than with intravenous quinine in adults, but this superiority was not demonstrated in African children [3]. In most African countries, intravenous quinine remains the recommended first-line treatment for cerebral malaria.

However, the administration of intravenous quinine is often not feasible because of the lack of simple equipment or trained staff. When referral is not feasible and oral treatment is not possible, the intramuscular route is usually used. However, widespread use of intramuscular quinine has been associated with complications, including paralysis and infections at injection sites [4–6]. The intrarectal route is of interest in children, because it is painless and simple. Studies of the efficacy of intrarectal quinine in the treatment of cerebral malaria are limited. A few studies in Francophone Africa have reported good clinical efficacy and tolerance of intrarectal quinine [7–11]. Although these studies were randomized trials, they were not blinded and did not use the World Health Organization definition of cerebral malaria as selection criteria. We performed, to our knowledge, the first double-blind, randomized trial to compare the efficacy and safety of intrarectal quinine with those of intravenous quinine in the treatment of childhood cerebral malaria in a different epidemiological context.

**METHODS**

**Participants.** We enrolled 110 patients who were seen at the acute care unit at Mulago Hospital (Kampala, Uganda), Uganda’s national referral hospital, from September 2003 through January 2004. Eligible patients were children aged 6 months to 5 years who satisfied the World Health Organization case definition of cerebral malaria (unarousable coma lasting >30 min after a seizure, with peripheral asexual P. falciparum parasitemia and absence of other causes of coma) [1] and whose
caretakers had given written informed consent. We excluded patients with a Blantyre coma score (BCS) [12] ≥3, diarrhea (>4 loose stools per 24 h), and any recent anal pathologic findings, as well as those who had received quinine in the previous 48 h (ascertained from the medical documents that the caretakers presented to the acute care unit). The study was approved by the Makerere University Faculty of Medicine Research and Ethics Committee and the Uganda National Council of Science and Technology.

**Randomization and blinding.** In this randomized, double-blind clinical trial, treatment assignments were generated using a computer algorithm that randomly allocated patients in approximately equal numbers to receive either intravenous or intrarectal quinine. Assignments were sealed in opaque numbered envelopes, which were picked by the caretakers, who then handed these to the treatment nurses. Patients, investigators, and study nurses were blinded to group assignments; however, independent treatment nurses who were not involved in other aspects of patient care or assessment were aware of the assignments. Preparation of drugs and placebo was done in a separate room by the treatment nurses, who then brought the already prepared drugs and placebo to the patient’s bedside for administration. The treatment nurses documented quinine administration on a treatment chart that was securely kept in the drug preparation room. This chart documented the dose of quinine, route of administration, and time of administration. This ensured that each patient received the prescribed treatment. Rectal quinine and rectal placebo were administered with similar cannula syringes and were similar in appearance. Intravenous quinine was administered in 5% dextrose, and the intrarectal group also received a 5% dextrose drip without quinine as the intravenous placebo. At the time of switching infusions, each patient had rectal administration of drug or placebo and intravenous infusion of drug or placebo, depending on the treatment arm; this ensured adequate blinding.

**Treatment of patients.** The formulation used in both treatment arms was Quinimax (Sanofi–Synthelabo Groupe), which contains 96% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine. This was previously demonstrated to have a pharmacokinetic profile that is similar to that of quinine dihydrochloride [8]. For the intrarectal quinine group, the treatment nurse diluted a 500-mg vial of quinine with 13.5 mL of distilled water to obtain a concentration of 30 mg/mL. For rectal administration, we used a plastic cannula syringe graduated in kilograms to facilitate accurate dose measurements using the child’s body weight. The dosage used was 20 mg/kg of quinine base stat (corresponding to the patient’s full body weight measurement on the cannula syringe), followed by 15 mg/kg of quinine base (corresponding to three-quarters of the patient’s body weight measurement on the cannula syringe), given every 8 h until the patient regained consciousness and was able to receive oral treatment. Each administration was followed by firm compression of the buttocks for 5 min to avoid early expulsion; if the drug was expelled within 30 min, one-half of the dose was readministered. This dosage was revealed by previous pharmacokinetic studies to be the optimal regimen leading to predictable, safe, and effective blood quinine concentrations [9]. These patients also received a 5% dextrose drip (20 mL/kg) without study drug every 8 h as a placebo. Intravenous quinine (8 mg/kg of quinine base) was given as a slow infusion in 5% dextrose (20 mL/kg) over 4 h, given every 8 h until the patient regained consciousness and was able to receive oral treatment, according to the Uganda Ministry of Health treatment guidelines, which does not recommend the use of a loading dose of intravenous quinine in the treatment of patients with severe malaria [13]. These patients also received a rectal placebo (distilled water) every 8 h using a plastic cannula syringe.

For each patient, the active drug and the placebo were administered over the same period. When the patients were able to receive oral treatment, a course of oral quinine sulphate (10 mg/kg of quinine salt) was given to both groups to complete a treatment duration of 7 days.

Study nurses (involved in the day-to-day care of the patients, including observation of vital signs and supportive care) were blinded to the treatment that the patients were receiving. On the other hand, the treatment nurses were only responsible for administration of the study drugs and placebo to the patients and were not involved in any other aspect of patient care or monitoring.

Supportive measures were instituted for control of seizures, hypoglycemia, severe anemia, and fever. Feeding was via nasogastric tubes; oxygen was given to patients with respiratory...
Table 1. Baseline clinical and laboratory characteristics before treatment of patients with cerebral malaria in both treatment arms.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rectal quinine arm (n = 56)</th>
<th>Intravenous quinine arm (n = 54)</th>
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<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
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</tr>
<tr>
<td>Weight, kg</td>
<td>11.5 ± 4.1</td>
<td>11.9 ± 3.9</td>
</tr>
<tr>
<td>Age, months</td>
<td>31.3 ± 29.1</td>
<td>38.0 ± 59.8</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of convulsions</td>
<td>3.2 ± 2.3</td>
<td>5.0 ± 13.9</td>
</tr>
<tr>
<td>Duration of coma, h</td>
<td>7.6 ± 5.5</td>
<td>7.2 ± 4.4</td>
</tr>
<tr>
<td>Temperature, ºC</td>
<td>38.1 ± 0.9</td>
<td>38.2 ± 0.8</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level, g/dL</td>
<td>7.3 ± 2.2</td>
<td>6.9 ± 2.3</td>
</tr>
<tr>
<td>Blood glucose level, mg/dL</td>
<td>118 ± 100</td>
<td>101 ± 99</td>
</tr>
<tr>
<td>WBC count, cells/µL</td>
<td>7907 ± 4320</td>
<td>11,529 ± 19,105</td>
</tr>
<tr>
<td>Total bilirubin level, mg/dL</td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>Creatinine level, mg/dL</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>Platelet count, platelets/mm³</td>
<td>102,381 ± 75,139</td>
<td>95,721 ± 74,538</td>
</tr>
<tr>
<td>Parasite density, parasites/µL</td>
<td>147,511 ± 162,984</td>
<td>177,209 ± 215,197</td>
</tr>
</tbody>
</table>

**NOTE.** The difference in baseline clinical and laboratory characteristics between the 2 treatment arms was not statistically significant.

distress, and antibiotics were given to those with features of pneumonia.

Patients were followed up daily for 7 days. Level of consciousness was assessed using the BCS every 3 h, until full consciousness was regained. Axillary temperature was recorded every 2 h until resolution of fever, then twice daily until day 7.

**Laboratory tests.** Investigations included complete blood cell count, CSF analysis, renal and liver function tests on days 0 and 7, and blood glucose tests every 6 h until the patient regained consciousness. Asexual malaria parasite density was determined using Giemsa-stained thick films and counting per 200 WBCs. Results were expressed as parasites per microliter, assuming a total WBC count of 8000 cells/µL. Serial parasite densities were determined before treatment; at 4, 8, 16, 24, 36, 48, 60, and 72 h of treatment; and at 7 days of treatment. Microscopic examination specialists, blinded to treatment assignment, recorded a negative smear result when they found no asexual forms on examination of 100 high-power fields. For quality control, all slides were read by a second microscopic examination specialist, and a third reviewer settled any discrepant readings.

**Main outcome measures.** The primary outcome measure was parasite clearance time—the time required to obtain negative blood film results on 3 successive examinations from the beginning of antimalarial treatment. We used the 6 following secondary outcomes: coma recovery time was the time from initiation of antimalarial treatment to the time when the patient had a BCS of 5 or became alert; fever clearance time was the time from initiation of antimalarial treatment to the time when the temperature decreased to <37.5 ºC and remained at <37.5 ºC for 24 h; time to begin oral intake and time to sit unsupported were the times from the beginning of antimalarial treatment to the time when the patient was able to receive oral treatment or sit unaided, respectively; and time until oral quinine was tolerated was the time from initiation of treatment with intra-rectal or intravenous quinine to the time when treatment was changed to oral quinine. We recorded adverse events associated with treatment, such as hypotension, jaundice, skin rash, mucoid stools, soft stools, liquid stools, diarrhea, vomiting, blood in stools, and hypoglycemia.

**Sample size estimation and statistical analysis.** We calculated a sample size of 54 patients in each group, for 90% power and 95% CIs. We assumed that the children receiving intravenous quinine would have a mean parasite clearance (±SD) of 55.0 ± 24.3 h (27.5% effect size), according to a study by Aceng et al. [14] in the same hospital, and that those receiving intrarectal quinine would have a mean parasite clearance time (±SD) of 39.9 ± 24.3 h; using these clearance times, we were able to identify a difference that was approximately twice that observed by Barennes et al. [15] (6.8 h) between intrarectal quinine and intravenous quinine in Niger. Efficacy was powered as being superior for intrarectal quinine, because the local standard of care does not recommend a loading dose of intravenous quinine [13].
Table 2. Clinical and parasitological outcomes of treatment for patients with cerebral malaria in the rectal and intravenous quinine treatment arms.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rectal quinine arm (n = 56)</th>
<th>Intravenous quinine arm (n = 54)</th>
<th>Difference</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasite clearance time</td>
<td>43.1 (39.3–46.9)</td>
<td>41.9 (37.7–46.5)</td>
<td>1.22 (–4.5 to 6.9)</td>
<td>.64</td>
</tr>
<tr>
<td>Fever clearance time</td>
<td>26.6 (22.2–30.9)</td>
<td>29.9 (25.0–34.9)</td>
<td>–3.42 (–10.3 to 3.4)</td>
<td>.28</td>
</tr>
<tr>
<td>Coma recovery time</td>
<td>19.4 (14.5–24.2)</td>
<td>16.9 (12.8–21.1)</td>
<td>2.43 (–4.2 to 9.1)</td>
<td>.42</td>
</tr>
<tr>
<td>Time to begin oral intake</td>
<td>27.5 (21.9–33.2)</td>
<td>24.1 (18.7–29.6)</td>
<td>3.41 (–4.8 to 11.6)</td>
<td>.38</td>
</tr>
<tr>
<td>Time to sit unsupported</td>
<td>43.9 (36.6–51.3)</td>
<td>49.3 (27.6–71.1)</td>
<td>–5.41 (–28.8 to 17.9)</td>
<td>.63</td>
</tr>
<tr>
<td>Time until oral quinine tolerated</td>
<td>37.74 (31.9–43.5)</td>
<td>39.8 (33.7–45.9)</td>
<td>–2.04 (–10.7 to 6.7)</td>
<td>.69</td>
</tr>
</tbody>
</table>

* The log-rank test revealed no significant difference in the clinical and parasitological outcomes of treatment with either intravenous quinine or rectal quinine.

Data were double-entered and analyzed using SPSS, version 12.0 (SPSS). Analysis was performed by intention to treat. We compared mean differences between the 2 groups using the Student’s t test for normally distributed continuous data and χ² for categorical outcomes. In supplemental analysis of time-related data, Kaplan-Meier plots and log-rank tests were used.

RESULTS

We screened 193 children for eligibility, 110 of whom were enrolled, treated, and completed 7 days of follow-up; 56 patients received intrarectal quinine, and 54 received intravenous quinine (figure 1). Eighty-three children were excluded for reasons shown in figure 1. Baseline demographic, clinical, and laboratory characteristics were comparable in both groups (table 1).

All of the patients had a BCS ≤2 [12]; 93 patients (84.5%) had a BCS of 2, and 17 patients (15.5%) had a BCS of 1. There was no difference in the coma scores between the 2 groups (P = .25).

Overall, there was no statistically significant difference in the main outcome measures between the 2 treatment groups, as shown in table 2. Kaplan-Meier survival analysis also revealed similar trends of parasite clearance time and coma recovery time in the 2 treatment groups, with the log-rank tests revealing no statistically significant difference (figures 2 and 3).

Parasite clearance was achieved by 72 h in all of the patients evaluated. Patients who survived were afebrile by 80 h and had regained consciousness by 90 h. Neurological sequelae were seen in 4 (3.96%) of the patients who survived; 1 patient was in the intrarectal quinine group, and 3 patients were in the intravenous quinine group. There was no difference in mortality between the 2 treatment arms; 4 patients (7%) died in the intrarectal quinine group, and 5 patients (9%) died in the intravenous quinine arm (P = .69). Postmortem examinations were performed for 5 of the 9 patients. The cause of death was cerebral malaria in 2 patients and cerebral edema in 2 patients; 1 patient died of aspiration pneumonia.

Adverse events. Intrarectal quinine was well tolerated by the patients. No rectal bleeding or mucoid stools were observed during this study. The quinine solution given intrarectally was never expelled. The common adverse effects associated with quinine therapy, such as hypoglycemia, hypotension, skin rash, and jaundice, were not observed in the study patients during the course of treatment. Vomiting occurred for 10 patients, 7 (13.0%) of whom were in the intravenous quinine treatment arm and 3 (5.0%) of whom were in the intrarectal quinine treatment arm. There was no difference between the 2 groups...

with regard to the occurrence of diarrhea and presence of soft or liquid stools (table 3). No abnormalities were detected in the renal and liver function tests on day 7.

**DISCUSSION**

We assessed the efficacy and safety of intrarectal quinine versus intravenous quinine in Ugandan children with cerebral malaria. Overall, there was no statistically significant difference in the outcome of treatment between intravenous quinine treatment and intrarectal quinine treatment. Intrarectal quinine was well tolerated, and no major adverse events were observed.

These findings are particularly important, because there are limited data on the efficacy of intrarectal quinine for treatment of life-threatening forms of malaria. This study addresses a need for more trials, as recommended by Eisenhut et al. [16].

**Coma recovery time.** The coma recovery time in the intravenous quinine arm was comparable to that in the intrarectal quinine arm. The coma recovery time in the intravenous quinine arm in our study was similar to that for the patients who received intravenous quinine in the study by Aceng et al. [13]. Intriguingly, we found a significant difference between the coma recovery times in our intrarectal quinine arm (mean ± SD, 19.4 ± 18.1 h) and those in the rectal artemether arm (mean ± SD, 30.1 ± 24.1 h) in the latter study performed in the same setting (\( P = .01 \)). The longer coma recovery time in this group may be explained by the fact that artemether may be neurotoxic, as observed in animal studies [17]. Similar findings were reported by Hensbroek et al. [18] in Gambian children with cerebral malaria.

**Fever clearance time.** The fever clearance times in the 2 treatment arms were comparable. The values obtained in our study were shorter than those found in similar studies using intrarectal quinine [7, 15, 19]. The explanation for this may be the systematic use of paracetamol and tepid sponging for temperature control in our study. Our study also had shorter fever clearance times, compared with some studies using rectal artemether [14, 20]. The explanation for this may be the more erratic absorption of artemether suppositories [21].

**Parasite clearance time.** The parasite clearance time in the intravenous quinine arm was shorter than that in the intrarectal quinine arm, but this difference was not statistically significant. The parasite clearance times in our study were shorter than those observed in other studies by Barennes et al. [11, 15]. This difference may have occurred as a result of the differing continuation therapy used in the 2 trials. We used quinine tablets, and the latter studies used chloroquine tablets; the better therapeutic response in our study may have been attributable to this. The longer parasite clearance times in the study in Niger [15] may also have occurred because of the longer intervals in assessing serial parasite densities. Our study also revealed an evidently shorter trend in time to parasite clearance than did an earlier study in Uganda by Aceng et al. [14] that used rectal artemether (43.1 h vs. 54.2 h; \( P = .043 \)). This is an interesting finding, because clinical trials performed thus far have indicated

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rectal quinine arm ( (n = 56) )</th>
<th>Intravenous quinine arm ( (n = 54) )</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Percentage of patients (95% CI)</td>
</tr>
<tr>
<td>Vomiting (&gt;4 loose stools per day)</td>
<td>3</td>
<td>5 (0–11)</td>
</tr>
<tr>
<td>Diarrhea (&gt;4 loose stools per day)</td>
<td>2</td>
<td>4 (0–8)</td>
</tr>
<tr>
<td>Soft stools</td>
<td>5</td>
<td>9 (1–16)</td>
</tr>
<tr>
<td>Liquid stools (&lt;3 loose stools per day)</td>
<td>7</td>
<td>13 (4–21)</td>
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</tbody>
</table>
that artemisinin derivatives are associated with faster parasite clearance rates, compared with quinine. The reason that our study deviates from this trend is not clear but may be related to the formulation of quinine that was used (Quinimax), with the other minor alkaloids having a synergistic action, leading to a better therapeutic outcome [22].

**Time until oral quinine was tolerated.** The time until oral quinine was tolerated was similar in both treatment arms. This was a measure of the duration of intervention with either intrarectal quinine or intravenous quinine and is therefore an important clinical finding that has implications for the cost of treatment of cerebral malaria.

**Neurological sequelae and mortality.** The pattern of neurological sequelae that was seen in our study was similar to that described in other studies [23, 24]. The reason for the lower incidence of neurological sequelae in our study is not clear; however, our findings do support the commonly accepted view that the majority of patients with cerebral malaria make a full neurological recovery, despite profound and sometimes prolonged coma [25].

The overall mortality (8.2%) in our study was lower than that in the Niger study (17%) [15]. However, the mortality rate in the intrarectal groups did not differ between our study and the Niger study (4 of 56 patients vs. 4 of 39 patients; \( P = .7 \)). Pooling the Niger and Ugandan data reveals an interesting, although nonsignificant, trend to higher mortality in the intravenous quinine group, compared with the intrarectal quinine group (13.3% [14 of 91 patients] vs. 7.8% [8 of 95 patients]; \( P = .1 \)). This might suggest a need for more studies.

The overall mortality in our study was, however, comparable to that seen in other studies in Uganda and elsewhere in Africa [1, 2, 24]. The reasons for this low mortality may have been related to various aspects of patient care, such as prompt response by the study team, adequate seizure control, availability of blood for transfusion, and adequate nursing care.

**Adverse events.** No major adverse events were detected in our study. Intrarectal quinine was well tolerated, as was observed in the study in Niger [15, 25], in which only 2 mL of distilled water were used for dilution. Another study in Burkina Faso reported infrequent rectal bleeding, diarrhea, and frequent tenesmus and passage of mucoid stools [21], although the dilution of Quinimax was similar to that used in our study. These findings seem to be related to the frequent administration of enemas to infants in this region [21]. In addition, our study consisted of a younger population who may not have been able to complain of certain symptoms, such as tenesmus.

Hypoglycemia was not observed during the course of treatment in our study, most likely because this was sought at enrollment and was managed effectively. In addition, all patients were fed regularly via nasogastric tube and were given intravenous 5% dextrose. Unlike in other studies, the drug administered rectally was never expelled in our study. This could be attributed to the use of the cannula syringe. This was particularly important, because early expulsion during the first hour after rectal administration has been revealed to decrease the blood quinine concentration by 50%, although immediate administration of one-half of the dose is shown to restore an effective blood concentration-to-time profile [9].

One major limitation of our study is that the sample size calculation was based on a rather large effect size and, thus, had insufficient power to demonstrate equivalence between the 2 treatment groups. Because our study was not powered to demonstrate equivalence, we recommend that equivalence studies be conducted to confirm these preliminary data. However, our study does confirm the efficacy of intrarectal quinine in the management of severe malaria.

**Conclusions.** These results indicate that clinical and parasitological outcomes in the intrarectal quinine and intravenous quinine groups were comparable. We conclude that intrarectal quinine is efficacious and could be used as an alternative in the treatment of childhood cerebral malaria, especially in situations in which intravenous therapy is not feasible.

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