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## Effect of Iron Chelation Therapy on Recovery From Deep Coma in Children With Cerebral Malaria

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## EFFECT OF IRON CHELATION THERAPY ON RECOVERY FROM DEEP COMA IN CHILDREN WITH CEREBRAL MALARIA

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**Abstract Background.** Cerebral malaria is a severe complication of *Plasmodium falciparum* infection in children, with a mortality rate of 15 to 50 percent despite antimalarial therapy.

**Methods.** To determine whether combining iron chelation with quinine therapy speeds the recovery of consciousness, we conducted a randomized, double-blind, placebo-controlled trial of the iron chelator deferoxamine in 83 Zambian children with cerebral malaria. To be enrolled, patients had to be less than six years old, have *P. falciparum* parasitemia, have normal cerebrospinal fluid without evidence of bacterial infection, and be in a coma from which they could not be aroused. Deferoxamine (100 mg per kilogram of body weight per day, infused intravenously for 72 hours) or placebo was added to standard therapy with quinine and sulfadoxine-pyrimethamine. The time to the recovery of full consciousness, time to parasite clearance, and mortality were examined with Cox proportional-hazards regression analysis.

**Results.** The rate of recovery of full consciousness

among the 42 patients given deferoxamine was 1.3 times that among the 41 given placebo (95 percent confidence interval, 0.7 to 2.3); the median time to recovery was 20.2 hours in the deferoxamine group and 43.1 hours in the placebo group ( $P = 0.38$ ). Among 50 patients with deep coma, the rate of recovery of full consciousness was increased 2.2-fold with deferoxamine (95 percent confidence interval, 1.1 to 4.7), decreasing the median recovery time from 68.2 to 24.1 hours ( $P = 0.03$ ). Among 69 patients for whom data on parasite clearance were available, the rate of clearance with deferoxamine was 2.0 times that with placebo (95 percent confidence interval, 1.2 to 3.6). Among all 83 patients, mortality was 17 percent in the deferoxamine group and 22 percent in the placebo group ( $P = 0.52$ ).

**Conclusions.** Iron chelation therapy may hasten the clearance of parasitemia and enhance recovery from deep coma in cerebral malaria. (N Engl J Med 1992; 327:1473-7.)

CEREBRAL malaria, one of the most severe complications of infection with *Plasmodium falciparum*, is especially common among young children. Despite therapy with parenteral antimalarial agents and attentive management of complications, the mortality rate is 15 to 50 percent and gross neurologic sequelae persist in about 10 percent of the children who survive.<sup>1-3</sup> It is estimated that in sub-Saharan Africa alone, over 1 million children die from severe forms of malaria annually.<sup>4,5</sup>

Cerebral malaria is diagnosed when asexual forms of *P. falciparum* are found in the blood of a patient with

signs of an acute, diffuse symmetric encephalopathy not attributable to other causes. It is characterized by the sequestration of parasitized erythrocytes in cerebral venules and capillaries.<sup>6,7</sup> Knobs appear on the membrane of the infected erythrocytes and adhere to the endothelium, causing microvascular obstruction,<sup>8</sup> but the precise mechanisms of these events are not understood.<sup>3</sup> Ring hemorrhages around cerebral veins are frequently found post mortem<sup>6</sup>; elevated concentrations of lactate in cerebrospinal fluid suggest the presence of cerebral hypoxia.<sup>9</sup>

Iron is an essential nutrient for the growth of *P. falciparum*.<sup>10,11</sup> The iron-chelating agent deferoxamine (Desferal) enhances the clearance of *P. falciparum* parasitemia in adults with asymptomatic infection.<sup>12</sup> Iron also serves as a redox agent in the generation of free radicals that mediate ischemic and hemorrhagic tissue injury,<sup>13,14</sup> and iron chelation with deferoxamine inhibits peroxidant damage to central nervous system tissue in animals.<sup>15</sup>

We postulated that in some patients with cerebral malaria, the release of free hemoglobin and iron gen-

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erates oxygen-derived free radicals that cause lipid peroxidant damage to cellular and subcellular membranes of the central nervous system. We proposed that iron chelation therapy with deferoxamine might be beneficial because it might inhibit the growth of *P. falciparum* organisms and protect the central nervous system from ischemic and hemorrhagic toxicity mediated by free radicals. Since there has been substantial experience with the safety of the long-term use of deferoxamine in children with iron overload secondary to thalassemias,<sup>16</sup> we proceeded directly to a clinical trial to determine whether adding iron chelation with deferoxamine to standard quinine therapy for children with cerebral malaria could speed their recovery of full consciousness.

## METHODS

The study was approved by the Ethical and Research Committee of the University of Zambia (Lusaka, Zambia) and by the Committee on Human Investigations of MetroHealth Medical Center, Case Western Reserve University School of Medicine (Cleveland). Informed consent was obtained for all participants. The project was undertaken at Macha Mission Hospital in the Southern Province of Zambia in 1990 and 1991.

### Enrollment

Patients were considered for the study if they were comatose, were less than six years old, had asexual forms of *P. falciparum* in the peripheral blood, had normal cerebrospinal fluid with no evidence of bacterial infection, could not be aroused from a coma that lasted more than 30 minutes after any previous convulsion, and had no other identifiable cause of altered consciousness. Twelve clinical and demographic characteristics were recorded at the time of enrollment: sex, age, degree of coma, glucose concentration, hemoglobin concentration, white-cell count, peripheral-blood parasite concentration, and histories regarding the time of onset of fever and of coma, the occurrence of convulsions, and treatment with traditional herbal medicine or chloroquine. If the blood glucose concentration was less than 40 mg per deciliter (2.2 mmol per liter) before enrollment, the patient was given 50 percent dextrose (1 ml per kilogram of body weight, intravenously) and was included in the study if coma persisted after the hypoglycemia was corrected.

The level of consciousness was determined according to the Glasgow coma scale as modified for children.<sup>1</sup> Scores were assigned for the best motor response to a painful stimulus (a score of 2 for localization, 1 for withdrawal, or 0 for no response), the best vocal response to a painful stimulus (2 for a normal vocal response, 1 for an abnormal moan or cry, or 0 for no vocal response), and eye movement (1 for following the mother's face or a bright light, or 0 for not following). To be enrolled, a patient had to have a total score of less than 5 (the maximal score of 5 indicated a normal level of consciousness) and a score of 0 for eye movement (this score indicated that the child could not be aroused to a level of consciousness that would permit recognition and following of the mother's face).

### Treatment

The patients enrolled were treated in an urgent manner. An intravenous line was established immediately, and physiologic saline (10 to 15 ml per kilogram of body weight) was infused over a 30-minute period to maintain hydration. Then, quinine (10 mg of salt per kilogram in 200 ml of 5 percent dextrose solution) was infused over a 4-hour period, and the infusion was repeated every 8 hours for 72 hours; the drug was then given orally in the same dose for 48 hours more. A course of sulfadoxine-pyrimethamine (respectively, 25 and 1.2 mg per kilogram) was given by nasogastric tube within the first few hours after hydration was complete. If the patient had a history

of convulsions, phenobarbital (10 mg per kilogram) was given by intramuscular injection at the time of presentation; if convulsions recurred, the drug was given again, in a dose of 5 mg per kilogram at intervals of 30 minutes or more, up to a maximal dose of 20 mg per kilogram in 24 hours. Folic acid (1.0 mg) was given daily for five days by mouth or nasogastric tube. Blood transfusions (20 ml of whole blood per kilogram) were administered if anemia was present and accompanied by signs of heart failure; the blood was donated by relatives and screened for the human immunodeficiency virus.

### Standard and Deferoxamine Therapy

The patients were randomly assigned to treatment with deferoxamine mesylate (100 mg per kilogram per day) or placebo (5 percent dextrose solution) given by continuous intravenous infusion for 72 hours. The deferoxamine was donated by Ciba-Geigy (Basel, Switzerland); the placebo was prepared by members of the pharmacy staff of Macha Mission Hospital, who were also responsible for the randomization procedures. The study medication was started at approximately the same time as the quinine treatment.

### Assessment

The primary response variable was the time to the recovery of full consciousness, measured with the revised Glasgow coma scale (see Enrollment, above). The coma score was determined every six hours throughout the treatment period. The blood glucose concentration was determined by monitor every 6 to 12 hours (Accu-ChekR11 Blood Glucose Monitor, Boehringer-Mannheim Diagnostics, Indianapolis). If the concentration was less than 40 mg per deciliter (2.2 mmol per liter), the patient was given 50 percent dextrose (1 ml per kilogram intravenously) and the concentration was rechecked in six hours. The hemoglobin concentration was determined with a photometric method,<sup>17</sup> and the white-cell count with a counting chamber at 24-hour intervals. The plasma creatinine concentration was determined photometrically<sup>18</sup> at time 0 (the start of treatment) and after the infusion of the study drug was completed. The concentration of asexual intraerythrocytic parasites in peripheral blood was estimated at 12-hour intervals.<sup>19</sup> In brief, the number of ring forms per 200 white cells in a thick blood smear treated with Giemsa stain was determined by microscopical examination and then multiplied by the most recent white-cell count. If there were fewer than 10 parasites per 200 white cells, the number of organisms per 500 white cells was determined. The duration of coma was considered to be the time from the start of treatment to the point at which the coma score reached a sustained level of 5, and the time to parasite clearance to be the time in which the peripheral-blood concentration of ring forms decreased to less than 22 per cubic millimeter, the approximate limit of sensitivity of our assay method.

### Statistical Analysis

Eighty-three children were enrolled and studied prospectively in a randomized, double-blind fashion. In the first 30 children enrolled, a paired sequential design was used so that any unexpected complications of deferoxamine therapy could be detected early. Cox proportional-hazards models were used to examine the relation between iron chelation and three measures of outcome: the time to recovery of full consciousness, the clearance of parasitemia, and mortality.<sup>20</sup> As recommended by Molyneux et al.,<sup>1</sup> the time to recovery of full consciousness was evaluated with subsidiary analyses after stratification for the degree of coma at time 0. The log-rank test was used to compare the effects of deferoxamine and placebo; a P value of less than 0.05 was considered to indicate significance. Certain outcome measures were compared by Student's t-test for continuous variables and by the chi-square test or Fisher's exact test for proportions; all tests were two-sided.

## RESULTS

Eighty-three children were enrolled in the study; 42 received deferoxamine, and 41 received placebo. The clinical and demographic characteristics of the two

Table 1. Clinical and Demographic Characteristics of 83 Children with Cerebral Malaria, According to Treatment Group and Degree of Coma.\*

CHARACTERISTIC	ALL PATIENTS		LIGHT COMA		DEEP COMA	
	DEFEROXAMINE (N = 42)	PLACEBO (N = 41)	DEFEROXAMINE (N = 20)	PLACEBO (N = 13)	DEFEROXAMINE (N = 22)	PLACEBO (N = 28)
Age — mo	35±16	32±10	38±16	37±10	33±15	30±10
Female sex — no. (%)	22 (52)	19 (46)	11 (55)	3 (23)	11 (50)	16 (57)
Coma score — no. (%)						
0	2 (5)	0	—	—	2 (9)	0
1	4 (10)	9 (22)	—	—	4 (18)	9 (32)
2	16 (38)	19 (46)	—	—	16 (73)	19 (68)
3	11 (26)	6 (15)	11 (55)	6 (46)	—	—
4	9 (21)	7 (17)	9 (45)	7 (54)	—	—
Onset of fever before presentation — hr	67±69	57±31	54±29	57±25	80±90	57±34
Onset of coma before presentation — hr	13±13	12±12	9±6	9±11	17±17	14±13
History of convulsions — no. (%)	34 (81)	33 (80)	16 (80)	9 (69)	18 (82)	24 (86)
History of treatment with traditional medicine — no. (%)	17 (40)	15 (37)	7 (35)	3 (23)	10 (45)	12 (43)
History of treatment with chloroquine — no. (%)	27 (64)	28 (68)	13 (65)	10 (77)	14 (64)	18 (64)
Hemoglobin — g/dl	7.6±2.0	7.0±1.9	7.9±1.8	7.2±1.9	7.4±2.1	6.9±1.9
White-cell count — ×10 <sup>3</sup> /mm <sup>3</sup>	10.9±5.4	11.7±6.8	9.9±4.4	10.3±3.4	11.8±6.1	12.4±7.8
Blood glucose — mg/dl†	90±38	93±55	80±40	86±38	99±35	96±61
Parasite concentration — ×10 <sup>-3</sup> /mm <sup>3</sup> (range)‡	46.0 (8.1–260.6)	44.5 (4.3–464.5)	51.8 (12.1–221.8)	31.5 (2.6–375.8)	41.4 (5.7–300.6)	52.1 (5.2–526.0)

\*Plus-minus values are means ±SD. There were no significant differences between the treatment groups.

†To convert values for glucose to millimoles per liter, multiply by 0.05551.

‡Values are geometric means, with ranges of standard deviations.

groups at time 0 are summarized in Table 1. There were no significant differences between the groups.

### Recovery from Coma

Recovery of full consciousness during the 72-hour period of therapy with deferoxamine or placebo was analyzed in all 83 patients. After adjustment for the coma score at time 0, the duration of coma before enrollment, and the hemoglobin concentration at time 0, the rate of recovery of full consciousness in the deferoxamine group was 1.3 times that in the placebo group (95 percent confidence interval, 0.7 to 2.3); the estimated median time to recovery was 20.2 hours in the deferoxamine group, as compared with 43.1 hours in the placebo group ( $P = 0.38$ ).

The data on the recovery of full consciousness were examined after the patients were stratified according to their degree of coma at time 0. In the 33 patients with light coma (initial score, 3 or 4), the estimated median time to regain full consciousness among the 20 given deferoxamine was 20.0 hours, as compared with 17.8 hours in the 13 given placebo ( $P = 0.99$ ). Among the 50 patients with deep coma (initial score, 0 to 2), the time to full consciousness was shorter with deferoxamine (Fig. 1). After adjustment for the glucose concentration and the duration of coma before enrollment, the estimated rate of recovery of full consciousness was increased 2.2-fold in the deferoxa-

mine group (95 percent confidence interval, 1.1 to 4.7), resulting in a decrease in the estimated median recovery time, from 68.2 hours with placebo (28 patients) to 24.1 hours with deferoxamine (22 patients) ( $P = 0.03$ ).

Because the primary response variable (chosen before the study began) was the recovery of full consciousness in surviving patients, we repeated the

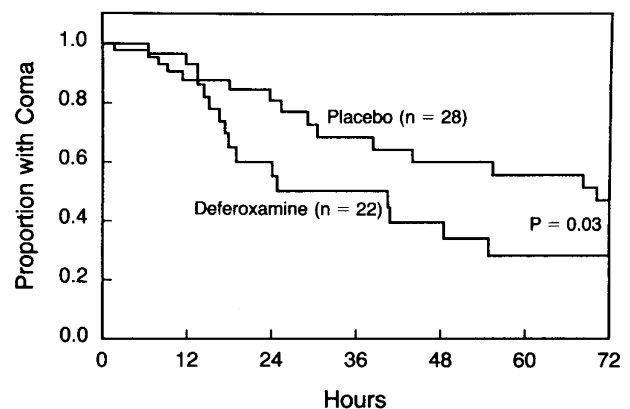


Figure 1. Recovery of Full Consciousness in 50 Children with Deep Coma (Initial Glasgow Coma Scores, 0 to 2), According to Treatment Group.

Time 0 denotes the start of treatment.

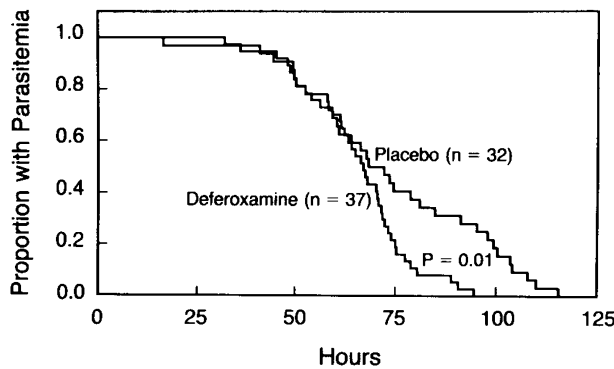


Figure 2. Clearance of Parasitemia in 69 Children.

analysis after excluding the patients who died, and obtained similar results. Among the 38 surviving patients with deep coma, the estimated rate of recovery of full consciousness was increased 3.0-fold with deferoxamine (95 percent confidence interval, 1.3 to 7.1), after adjustment for the glucose concentration and the duration of coma before enrollment. The estimated median recovery time was halved, from 38.4 hours with placebo (21 patients) to 19 hours with deferoxamine (17 patients) ( $P = 0.008$ ).

#### Clearance of Parasitemia

The time to parasite clearance could be measured in 69 patients (Fig. 2). None of the 12 base-line variables evaluated (see the Methods section) significantly affected the time to clearance. The rate of clearance was significantly increased by the addition of deferoxamine therapy ( $P = 0.01$ ). The estimated rate of parasite clearance with deferoxamine was 2.0 times that with placebo (95 percent confidence interval, 1.2 to 3.6).

#### Mortality

The study was not designed to detect a significant reduction in mortality since too few patients were enrolled, but this outcome was a subsidiary variable. Mortality was 17 percent among the 42 patients given deferoxamine and 22 percent among the 41 given placebo. The difference between these groups was not significant even after adjustment for sex and for the glucose concentration and white-cell count at time 0 ( $P = 0.52$ ). The risk of mortality with placebo was 1.4 times that with deferoxamine (95 percent confidence interval, 0.4 to 2.4).

#### Other Outcomes in Survivors

As shown in Table 2, the mean decrease in the hemoglobin concentration in surviving patients was not significantly different between

treatment groups, and the proportions of patients who had convulsions during therapy or required blood transfusions were similar in both groups. At the time of discharge, paresis was observed in two patients, both of whom had received placebo. All the surviving patients had serum creatinine concentrations in the normal range at the time of enrollment, and none had evidence of renal dysfunction according to measurements of creatinine after the administration of deferoxamine or placebo. During the study period, no toxic reaction or side effect could be attributed to deferoxamine therapy, despite the absence of iron overload.

#### DISCUSSION

This prospective, placebo-controlled trial of iron chelation with deferoxamine combined with standard quinine therapy was prompted by concern that cerebral malaria is a major cause of mortality due to infection among children in Africa despite therapy with parenteral antimalarial agents and attentive management of complications. The mortality rate among children treated for cerebral malaria at Macha Mission Hospital during the past five years was approximately 15 percent, similar to the rates in series of patients described by workers at other centers in Africa.<sup>1,2</sup> Given this mortality rate, a study of hundreds of children with cerebral malaria would be needed to link a significant drop in mortality with a new therapeutic intervention. We chose recovery from coma as the primary response variable, since a shortened duration of coma might be expected to presage reduced mortality and morbidity in a larger study.

As shown in Table 1, the two treatment groups were comparable at the time of enrollment. About two thirds of the children with cerebral malaria had received chloroquine, with no curative effect; this may reflect the high prevalence of chloroquine-resistant malaria and possibly also the use of a suboptimal regimen of chloroquine in the community.

Our results indicate that a 72-hour course of iron chelation with deferoxamine hastens the clearance of

Table 2. Outcomes Other Than Recovery from Coma and Clearance of Parasitemia in 67 Surviving Patients, According to Treatment Group and Degree of Coma.\*

OUTCOME	ALL SURVIVORS		LIGHT COMA		DEEP COMA	
	DEFEROXAMINE (N = 35)	PLACEBO (N = 32)	DEFEROXAMINE (N = 18)	PLACEBO (N = 11)	DEFEROXAMINE (N = 17)	PLACEBO (N = 21)
Maximal decline in hemoglobin — g/dl (no. of patients)†	1.8±1.0 (22)	1.8±1.1 (21)	1.8±0.9 (13)	1.5±1.0 (8)	1.6±1.0 (9)	1.9±1.2 (13)
Convulsions during treatment — no. (%)	12 (34)	14 (44)	5 (28)	4 (36)	7 (41)	10 (48)
Transfusion given — no. (%)	13 (37)	11 (34)	5 (28)	3 (27)	8 (47)	8 (38)
Paresis at discharge — no. (%)	0	2‡ (6)	0	0	0	2‡ (10)

\* $P \geq 0.45$  for each comparison of the deferoxamine group with the placebo group. Plus-minus values are means  $\pm$  SD.

†Values shown are for the patients who did not receive transfusions.

‡One patient had quadriplegia, and the other had hemiparesis.

parasitemia and speeds recovery from deep coma in children who are also given standard quinine therapy for cerebral malaria. We have previously shown that deferoxamine enhances the clearance of *P. falciparum* parasitemia in mild malaria,<sup>12</sup> and our present study indicates that iron chelation also has a clinically detectable effect on severe malaria. The incidence of neurologic sequelae of cerebral malaria is significantly higher when the recovery from coma is delayed,<sup>2</sup> and the fact that deferoxamine shortens the duration of coma in deeply comatose children suggests that its use might decrease their neurologic sequelae. Two of the surviving children given placebo (6 percent) had paresis at discharge — a finding similar to that reported in recent studies<sup>1,2</sup>; by contrast, none of the survivors given deferoxamine had this complication.

We do not know the mechanism whereby iron chelation therapy with deferoxamine reduces the time necessary to regain full consciousness in cerebral malaria. Aside from the possibility that deferoxamine has a direct antiparasitodal action, the chelator may have had a protective effect on cerebral tissue. Superoxide and hydrogen peroxide are formed in all aerobic cells, and their concentrations may be increased by ischemic and hemorrhagic injury. In the presence of iron, these species generate free radicals, highly reactive and biologically hazardous substances that can cause lipid peroxidation of cellular and subcellular membranes.<sup>13,14</sup> A final pathway in ischemic and hemorrhagic injury to the brain and other organs may be mediated by these iron-generated, oxygen-derived free radicals.<sup>13,21,22</sup> Ischemia and microhemorrhage affect the brain in cerebral malaria and may be mediated by free radicals. Iron chelation with deferoxamine has been shown to inhibit peroxidant damage to lung tissue, myocardium, and the central nervous system in animals.<sup>15,23,24</sup>

These results suggest that iron chelation therapy with deferoxamine enhances the clearance of parasitemia and hastens the recovery of full consciousness in deeply comatose children with cerebral malaria. A larger clinical trial will be needed to determine whether this therapy can reduce mortality from this common tropical infection and prevent the permanent neurologic sequelae associated with it.

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