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A Comparison of Iron and Folate with Folate Alone in Hematologic Recovery of Children Treated for Acute Malaria

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Abstract. Concern has been raised that iron supplementation for treatment of acute malaria may worsen the severity of malaria. We compared the effect of iron and folate with folate alone on hematologic recovery in children treated for acute malaria. We randomized 82 children 6–60 months of age from Nigeria with smear-positive malaria and anemia (hematocrit < 33%) to receive iron (2 mg/kg/day) plus folate (5 mg/day) or folate alone in addition to antimalarial drugs. The mean ± SD hematocrit at baseline was 28.5% ± 2.9%. At four weeks, the mean hematocrit increased by 2.5% ± 1.6% in the iron plus folate group and by 1.4% ± 1.0% in the folate alone group ($P = 0.001$). Baseline hematocrit, iron supplementation, weight for height, and weekly meat intake were significant predictors of final hematocrit. The effect of iron was not significantly modified by baseline hematocrit, weekly meat intake, nutritional status, mother's education, sex, or age of the child. Iron supplementation improved hematologic recovery in children with malarial anemia.

INTRODUCTION

Malaria is a leading cause of death of children less than five years of age in Africa, and Nigeria has the greatest number of malaria deaths of any country.[1] In areas with intense *Plasmodium falciparum* transmission, severe malarial anemia is the primary symptom of serious malarial disease among children less than two years of age and accounts for more than half of all malarial deaths in African children.[2,3] In malaria-endemic areas, anemia is usually multifactorial in origin, but *P. falciparum* infection is the major factor in the etiology of severe anemia.[3] In areas of stable malaria transmission, anemia appears in the first few months of life, and has the highest prevalence towards the end of the first year.[4] Malaria, nutritional deficiencies, bacteremia, intestinal helminths, infection with human immunodeficiency virus, and hemoglobinopathies produce a complex interplay that leads to anemia in children in Africa.[4–7]

Malarial anemia has been associated with high-density and low-density parasitemia. Malaria infection leads to anemia through several mechanisms, including hemolysis of parasitized and non-parasitized erythrocytes, reduced erythropoiesis, and reduced iron release from macrophages.[8] Although higher density parasitemia is associated with symptoms and acute anemia, asymptomatic low-density parasitemia may also result in anemia, particularly if the parasitemia persists for prolonged periods resulting from inadequate treatment.[6,9]

Iron deficiency is the commonest cause of anemia worldwide.[10] Maternal iron deficiency, low birth weight, prematurity, early introduction of cereal-based weaning foods (from which iron absorption can be as low as 5%), cow's milk (low in iron), and hookworm infection are all risk factors for iron deficiency in children in Africa.[5,10,11]

Iron deficiency anemia in children in Zanzibar was associated with reduced motor activity and delayed language development.[12,13] Supplementation with iron and folic acid reduced the time required for children to learn to walk.[14] Malaria infection has been associated with poorer iron status in children less than 30 months of age.[11] Iron supplementation improved the hematocrit of children in Tanzania less than 12 months of age, and the response did not differ between those protected and unprotected against malaria.[15,16] Among children in Kenya, intermittent iron supplementation had a more pronounced effect on hemoglobin status than sulfadoxine-pyrimethamine.[17] Iron, but not folic acid, combined with effective antimalarial therapy promoted hematologic recovery in children in the Gambia after acute *P. falciparum* malaria.[18]

Several concerns have been raised about iron supplementation in acute malaria and have prevented its adoption in some malaria-endemic countries, including Nigeria. Iron is essential for the growth of malaria parasites and other bacterial pathogens, and iron supplementation could worsen the clinical severity of malarial infection and interfere with recovery.[19] Hemolysis accounts for the acute anemia associated with malaria infection, and the accompanying inflammatory response leads to an acute reduction in serum iron, likely caused by iron sequestration in macrophages induced by increased hepcidin concentrations.[8] This sequestration reduces the iron that is available for bone marrow erythropoiesis. Intestinal iron absorption is reduced for at least two weeks after an episode of acute malaria.[20] Making a diagnosis of iron deficiency in acute malaria can be difficult because of alterations in serum ferritin and iron in acute malarial infection. Furthermore, there is no international consensus on the best way to assess the iron status of populations.[21] In a large trial in Zanzibar, children who received routine supplementation with iron and folic acid were more likely to die or experience adverse events than children who did not receive supplementation.[22]

Despite these concerns, a Cochrane review did not identify any increased risk of clinical malaria or death with iron supplementation in malaria-endemic areas, as long as appropriate malarial surveillance and treatment were available.[23] In a systematic review of 28 randomized controlled trials, iron supplementation had no effect on the overall incidence of infectious illnesses or on the frequency of positive malaria smears in children, except for a possible slight increase in diarrhea.[24]

The aim of this study was to test the hypothesis that iron with folate is more effective than folate alone in the hematologic recovery of children with malarial anemia.

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PATIENTS AND METHODS

We recruited consecutive children 6–60 months of age with a history of fever from the General Outpatient Department of the Jos University Teaching Hospital in Jos, Nigeria. Jos is an urban center in central Nigeria and had a population of approximately one million persons. The General Outpatient Department is a walk-in clinic for patients seeking primary and secondary care. In 2004, a total of 35,966 patients were seen, and 16% had a diagnosis of malaria.[25]

The study design was an experimental, randomized, controlled trial. It was conducted during December 2004–June 2005: five months during the dry season and two months in the rainy season. Children 6–60 months of age were considered eligible for enrollment if they had a recent history of fever, malaria parasitemia with trophozoites in a peripheral blood film, anemia (hematocrit ≤ 33%), and the ability to take medication orally. Children were excluded if they had severe malaria demonstrated by inability to drink or breast feed, prostration, repeated vomiting, shock, dyspnea, or convulsions during the current illness. Children with any associated illness requiring hospitalization were also excluded.

Written informed consent was obtained from a literate parent or guardian of all enrolled children. Those persons who were unable to sign their name used their thumb print on the consent form. Ethical approval for the study was obtained from the research and ethical committee of the Jos University Teaching Hospital.

We obtained information regarding date of birth, if known, or their approximate age in months of each participant. We also obtained information regarding the mother's education, characteristics of the current illness, use of medications, number of febrile illnesses in the preceding three months, use of insecticide-treated bed nets, and the frequency of dietary intake of meat, fish, and eggs.

Each child's weight was measured on a scale that was calibrated daily with a 5-kg standard. Standing height was measured with a wall-mounted stadiometer. Length was measured in those who were unable to stand. Physical examination was performed to determine axillary temperature, clinical pallor, jaundice, respiratory rate, and pulse. The heart was auscultated for gallop rhythm and murmurs. The abdomen was examined for splenomegaly, and the liver span was measured by percussion for hepatomegaly.

Children with a history of recent fever had blood collected from a fingerprick sample. Blood was drawn into a heparinized capillary tube; additional drops were used to prepare thick and thin Giemsa-stained blood films for malaria. The capillary tube was centrifuged for five minutes, and a hematocrit reader was used to determine each child's hematocrit. Malaria parasite density was determined by counting the number of parasites corresponding to 200 leukocytes, assuming 8,000 leukocytes per microliter of blood. A hematologist evaluated the blood film for erythrocyte morphology.

Children with a positive malaria smear and a hematocrit < 33% were enrolled and randomized by using a lottery method in blocks of 20 to receive iron plus folate or folate alone in addition to antimalarial treatment. The active treatment group was given iron (ferric ammonium citrate, 2 mg/kg/day, as syrup) plus folate (5 mg/day as a tablet), and the control group was given only folate (5 mg/day). Both groups were instructed to take their assigned medications for four weeks. All enrolled children were treated with chloroquine (10 mg/kg for the first two days and 5 mg/kg on the third day) and sulfadoxine-pyrimethamine (25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine) as a supervised single dose, which had been demonstrated to be effective for the treatment of malaria in this population.[26] Parents were instructed to return with their children in four weeks or sooner if there was any problem. All parents were counseled on the use of insecticide-treated bed nets and other preventive measures against malaria. At the return visit, the quantity of remaining syrup and pill counts were recorded to assess compliance. We did not assess if medication was shared with others in the household. The child was weighed and a hematocrit was obtained. Children who remained anemic at the end of the study underwent further evaluation and continued treatment with iron and folate as appropriate.

A sample size of 35 children in each group was estimated to provide 95% confidence and 80% power to detect a 2% mean difference in hematocrit, which was regarded as clinically important. To allow attrition, we targeted recruitment to 40 children in each group, for a total of 80 children. Data were entered and analyzed in Epi Info 3.3 (Centers for Disease Control and Prevention, Atlanta, GA). The primary outcome variable was the change in hematocrit at the four-week visit. Student's *t*-test was used to compare mean values of normally distributed continuous variables at baseline between the two groups. In the case of ordinal or continuous variables with a non-normal distribution, the Mann-Whitney test was used to compare the two groups. Proportions were compared by using the chi-square test. The effect of variables on the change in hematocrit was assessed by a multiple linear regression analysis with the final hematocrit as the dependent variable and including the baseline hematocrit as one of the independent variables. P values < 0.05 were considered significant.

RESULTS

A total of 417 children who came for outpatient care with fever were screened for malaria and anemia (Figure 1). Of these children, 176 (42%) had a positive malaria smear. Of those with a positive malaria smear, 82 (47%) had a hematocrit < 33% and were randomized to receive iron plus folate

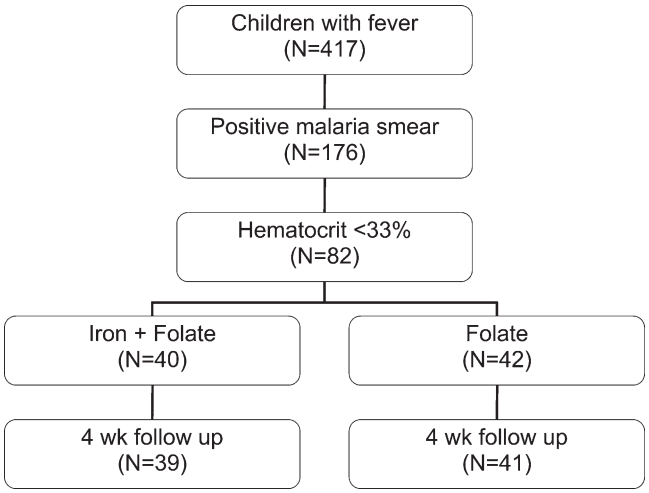

FIGURE 1. Flow chart of the study in Nigeria.

or folate alone. Of the 241 children with a negative malaria smear, 71 (29%) had a hematocrit < 33%.

Characteristics of study participants in the two groups were similar, except for a greater weekly meat intake and a greater parasite density in the folate alone group than in the iron plus folate group (Table 1). Most (55%) of enrolled children were ≤ 24 months of age. Most (60%) mothers had ≤ 6 years of formal education. A total of 33 children (40%) had another febrile illness in the preceding 3 months. Overall, 34% of children were wasted (weight for height z-score < –2) and 28% were stunted (height for age z-score < –2).

Despite the greater parasite density in the folate alone group than in the folate plus iron group, the mean baseline hematocrit in the two groups was similar. Baseline hematocrit was unrelated to weekly meat intake, anthropometric measures, maternal education, parasite density, or duration of fever. A hematologist reviewed 68 of the 82 slides (4 were missing and 10 were considered poor films). Of these slides, 33 (49%) indicated normocytic, normochromic anemia; 25 (37%) had hypochromic, microcytic anemia; 6 (9%) had a mixture of hypochromic, macrocytic, and microcytic cells; and 4 (6%) had normocytic, hypochromic anemia. Sickled cells were seen in two patients.

One child in each treatment group failed to return for follow-up at four weeks. One child in the folate group returned three days after initiating treatment; the child had persistent fever, inability to tolerate oral feeding, and prostration. This child was treated in the hospital and returned at the four-week follow-up visit, and was included in the final analysis. Seven children in the iron plus folate group and four children in the folate group reported vomiting early in the treatment. At the four-week follow up, four children in the iron plus folate group had three or four folate tablets left, and three children in the folate group had two folate tablets left. None of the children in the iron plus folate group had any iron syrup left at follow-up.

The mean ± SD post-intervention hematocrit was 30.9 ± 2.7% in the iron plus folate group and 30.0 ± 2.5% in the folate group. The mean ± SD increment in the hematocrit was 2.5 ± 1.6% in the iron plus folate group and 1.4 ± 1.0% in the folate group (Figure 2) ($P = 0.001$). After 4 weeks, 32 (82%) in the iron plus folate group and 40 (98%) in the folate group were still anemic ($P = 0.03$). Multiple linear regression was performed with backward elimination to identify factors that were independently predictive of the final hematocrit while controlling for the baseline hematocrit. The model that explained the greatest variance in the post-intervention hematocrit included the baseline hematocrit, iron supplementation, wasting, and weekly meat intake as significant predictors of final hematocrit, and accounted for 84% of the variance in final hematocrit (Table 2). When other variables were controlled, iron supplementation was significantly associated with a greater post-intervention hematocrit ($P < 0.001$). The age, sex, erythrocyte morphology, and mother's educational level were not significantly predictive of the post-intervention hematocrit. Wasting was associated with a greater hematocrit at four weeks. When this variable was removed from the analysis, iron supplementation remained significantly associated with final hematocrit. There were no interactions between variables that indicated the benefit of iron supplementation was limited to those with low baseline hematocrit, worse nutritional status, or low meat intake.

TABLE 1

Characteristics of study participants in the two treatment groups, Nigeria*

Characteristic	Iron plus folate (n = 40)	Folate (n = 42)	*P*
Age (months)	26.78 ± 17.8	32.5 ± 17.4	0.14
Sex (F/M)	20/20	15/27	0.19
Maternal education (years)	4.9 ± 4.2	6.1 ± 4.4	0.23
Meat intake (servings/week)	1.1 ± 1.3	2.0 ± 1.7	0.01
Fish intake (servings/week)	5.1 ± 2.0	5.4 ± 2.1	0.46
Egg intake (servings/week)	0.05 ± 0.23	0.15 ± 0.48	0.41
Bed net use (no.)	2	0	0.23
Duration of fever (days)	3.3 ± 2.2	2.4 ± 1.5	0.09
Febrile illnesses in preceding 3 months (no.)	0.79 ± 1.0	0.71 ± 1.2	0.32
Temperature (°C)	37.6 ± 0.7	37.6 ± 0.6	0.72
Respiratory rate	22 ± 5	22 ± 4	0.41
Pulse rate	110 ± 11	108 ± 16	0.53
Palpable spleen	1 (2.5)	3 (7.2)	0.62
Weight (kg)	11.1 ± 3.6	12.5 ± 3.7	0.08
Height (cm)	84.7 ± 17.0	88.2 ± 15.7	0.33
Height for age (z-score)	–0.43 ± 1.0	–0.85 ± 0.90	0.38
Weight for age (z-score)	–0.72 ± 1.1	–0.79 ± 0.95	0.75
Weight for height (z-score)	–0.44 ± 1.2	–0.46 ± 1.1	0.95
Hematocrit (%)	28.4 ± 3.2	28.5 ± 2.7	0.85
Parasite density (per mm^3)	2,480 ± 1,570	4,140 ± 2,630	0.002

*Values are mean ± SD or no. (%) unless otherwise indicated.

DISCUSSION

Supplementation with iron in acute malarial anemia produced a significant increase in hematocrit at four weeks than no iron supplementation. The observed increase in hematocrit of 2.5% at four weeks in the iron-supplemented group was similar to that found in other studies of iron supplementation in children with malaria.[18,20] In a study in the Gambia, this benefit persisted for at least several months after treatment with iron.[18]

The antimalarial agents used in our study may have affected the response to iron supplementation. We used a combination of sulfadoxine-pyrimethamine and chloroquine for treatment of acute malaria, which at the time of our study had an adequate clinical response rate of 87% in our setting.[26] The anti-inflammatory effect of chloroquine may promote the remobilization of iron sequestered in macrophages and result in more rapid recovery from malarial anemia.[8]

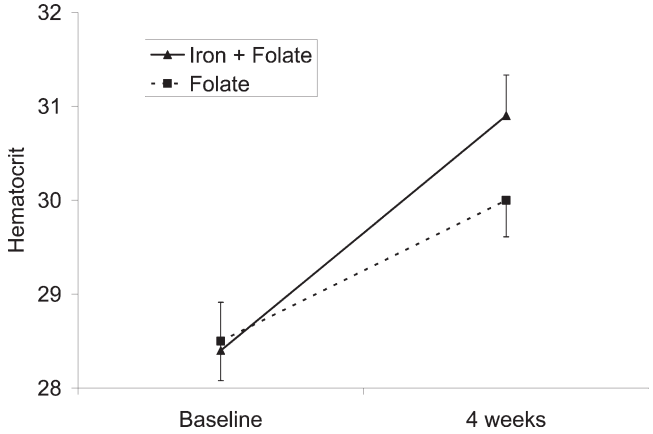

FIGURE 2. Change in hematocrits in the two treatment groups, Nigeria.

TABLE 2

Multiple linear regression analysis of factors predictive of final hematocrit, Nigeria*

Variable	Coefficient	*P*
Baseline hematocrit	0.77	< 0.001
Iron supplement	0.94	< 0.001
Wasting	1.1	< 0.001
Meat servings per week	0.17	0.04

* $R^2 = 0.84$, no significant interactions.

Doherty and others reported reduced iron absorption in children with acute malarial anemia than in children who have iron deficiency alone.[20] In that study, which also used sulfadoxine-pyrimethamine and chloroquine for treatment, wasting was associated with reduced iron absorption. We found that children with wasting had a greater hematocrit at four weeks than children without wasting, when adjusted for baseline hematocrit, iron supplementation, and meat intake.

A randomized comparison of two anemia treatment regimens in Tanzania with either a standard 14 days of ferrous sulfate and an antimalarial drug or an extended regimen of three months of ferrous sulfate and three antimalarial treatments showed that the mean hematocrit was significantly higher in the extended treatment arm (32.1% versus 30.8%).[16] A multiple linear regression model that included pre-intervention hematocrit, iron, weekly meat intake explained 80% of the variation in the post-intervention hematocrit. This model showed that iron had a statistically significant effect on the outcome hematocrit when we controlled for baseline hematocrit, mother's educational status, and the amount of meat eaten per week.

We confirmed that iron deficiency anemia is an important co-morbid factor of malaria and responds to iron supplementation. It is advantageous to provide iron supplementation in anemic children at the time of diagnosis of malaria because once they have had a clinical response to antimalarial agents, they may not return for follow-up and additional diagnostic testing and treatment. Although the magnitude of benefit from iron after four weeks of supplementation was relatively small, a small increase in hematocrit may prevent some deaths from severe malarial anemia on a population level. The prevalence of iron deficiency in our community is unknown, but investigators from other parts of the country have reported an overall prevalence of 34% in healthy children less than five years of age in southeastern Nigeria[27] and 15% in healthy children 6–24 months of age in Lagos.[28]

Several limitations of this study bear mention. Patients were not screened for sickle cell anemia or hookworm ova in their stool. Two children had sickle cells on a Giemsa-stained blood film, which is not sensitive for the detection of sickle cell disease. We did not perform a sickle cell preparation or hemoglobin electrophoresis to identify children with sickle cell disease. In Nigeria, the prevalence of sickle cell disease is 3% and that of the sickle cell trait is 21% based on newborn screening.[29] The prevalence of hookworm in our population is approximately 5%.[30] Other potential contributors to anemia were not evaluated, such as infection with human immunodeficiency virus, micronutrient deficiencies, and glucose-6-phosphate dehydrogenase deficiency. Blood hemoglobin, serum iron, total iron binding capacity, and ferritin to assess iron deficiency were not measured. However, the diagnosis of iron deficiency in acute malaria is problematic because serum iron is acutely reduced and serum ferritin is elevated by the inflammatory response.[8,21] Hepcidin is an acute-phase reactant produced by the liver that inhibits iron absorption and release of iron from macrophages. It has a crucial role in the anemia associated with the inflammatory response and chronic disease.[8] Definitive diagnosis of iron deficiency requires assessment of bone marrow–stainable iron.

Evaluation for persistent malaria was not assessed at four weeks, and differences in the rates of persistent or recurrent malaria could have accounted for the observed difference between the two groups. The greater parasite density in the folate alone group than in the iron plus folate group at baseline may have resulted in a greater delay in the clearance of malaria parasitemia in the folate alone group. However, the lack of difference hematocrit between the two groups at baseline and the randomized design would likely balance the risk of parasite resistance and demonstrate the effect of iron on the hematocrit at four weeks.

Because we did not include cases of children with severe malaria, the beneficial effect of iron should not be generalized to this group of children without further study to exclude the potential for harm from augmentation of parasite growth from iron. Further research is needed to determine if iron supplementation ultimately reduces mortality from severe malarial anemia. Whether efforts to distinguish those with or without iron deficiency at the time of malaria diagnosis would improve the outcome of iron supplementation is uncertain. Examination of the effect of iron in combination with current artemisinin-based combination therapy for malaria is also warranted.

This study showed that four weeks of iron plus folate supplementation produced a significant improvement in hematocrit than folate alone after malaria treatment. We found no evidence of harm associated with iron administration in conjunction with folate and antimalarial agents in acute malaria. This finding challenges the common practice in Nigeria of withholding iron supplementation in acute malaria for fear of worsening malaria infection.

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