

Randomized, Controlled Trial of Daily Iron Supplementation and Intermittent Sulfadoxine-Pyrimethamine for the Treatment of Mild Childhood Anemia in Western Kenya

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A randomized, placebo-controlled treatment trial was conducted among 546 anemic (hemoglobin concentration, 7–11 g/dL) children aged 2–36 months in an area with intense malaria transmission in western Kenya. All children used bednets and received a single dose of sulfadoxine-pyrimethamine (SP) on enrollment, followed by either intermittent preventive treatment (IPT) with SP at 4 and 8 weeks and daily iron for 12 weeks, daily iron and IPT with SP placebo, IPT and daily iron placebo, or daily iron placebo and IPT with SP placebo (double placebo). The mean hemoglobin concentration at 12 weeks, compared with that for the double-placebo group, was 1.14 g/dL (95% confidence interval [CI], 0.82–1.47 g/dL) greater for the IPT + iron group, 0.79 g/dL (95% CI, 0.46–1.10 g/dL) greater for the iron group, and 0.17 g/dL (95% CI, –0.15–0.49 g/dL) greater for the IPT group. IPT reduced the incidence of malaria parasitemia and clinic visits, but iron did not. The combination of IPT and iron supplementation was most effective in the treatment of mild anemia. Although IPT prevented malaria, the hematological benefit it added to that of a single dose of SP and bednet use was modest.

It is estimated that one-third to two-thirds of children <5 years of age in sub-Saharan Africa are anemic [1, 2], and severe anemia contributes substantially to child mortality in this region [3]. Although the etiology of childhood anemia is multifactorial, iron deficiency and malaria are predominant causes in most of sub-Saharan Africa [3].

New international guidelines recommend the use of iron supplementation in all areas with a high prevalence of iron-deficiency anemia [4]. Despite the well-recog-

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Written informed consent was obtained from the caretakers of each participant. The human experimentation guidelines of the following institutions were followed in conducting the clinical research: Kenya Medical Research Institute, Nairobi, Kenya; Centers for Disease Control and Prevention, Atlanta; and Academic Medical Centre at the University of Amsterdam, Amsterdam.

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nized public health burden of anemia, implementation of these guidelines continues to be hindered, partly as a result of controversy surrounding the use of iron supplementation in areas in which malaria is endemic [5, 6]. A recent meta-analysis of 13 clinical trials addressing this concern suggested that the hematological benefits of iron supplementation outweigh the clinically nonsignificant increase in the risk of malaria infection and symptomatic malaria that is associated with iron supplementation [5]. Conversely, another review of 8 studies suggested that the risk of symptomatic malaria increased as much as 50% when iron was given in doses >2 mg/kg/day [6].

Promising results with intermittent preventive treatment (IPT) in the control of malaria in pregnancy [7] have generated interest in the use of IPT for the prevention of malaria and malaria-associated severe anemia in young children [8]. In a recent study involving Tanzanian infants, conducted in the context of routine vaccinations, IPT with sulphadoxine-pyrimethamine (SP) halved the incidence of severe anemia in an area with intense malaria transmission [8]. However, the role of IPT in the treatment, rather than prevention, of all-cause anemia in young children in areas in which malaria is endemic remains to be established.

We assessed the efficacy of single and combined therapy with iron supplementation and IPT with SP in improving hemoglobin concentrations among anemic preschool children. We also assessed the effect of such therapy on the risk of malaria and hypothesized that any possible risk of malaria associated with iron supplementation could be reduced or prevented with combined therapy, while maximizing the hematological benefits.

METHODS

Study area and population. This study was conducted in 15 villages in Asembo, Bondo district, in western Kenya. The study site is described in detail elsewhere [9, 10]. This area has high mortality rates for infants and children <5 years of age (176/1000 and 257/1000 live births, respectively [11]). Malaria transmission is intense and perennial [12]; however, recent area-wide deployment of insecticide-treated bednets (ITNs) has substantially reduced the transmission pressure [13–15]. SP replaced chloroquine as first-line drug for the treatment of uncomplicated malaria in this area in January 1999 [16]. There were no standardized guidelines for the treatment or prevention of anemia in children in this area at the time of the study. Clinic-based surveillance indicated that iron supplementation was prescribed for only 12% of children <5 years of age who had clinically diagnosed anemia [17].

Study design and randomization. The study was a double-blind, randomized, placebo-controlled trial with a 2 × 2 factorial design. All resident children aged 2–36 months for whom consent was obtained were screened. Children were eligible for

enrollment if they had mild anemia (hemoglobin concentration, 7.0–10.9 g/dL), were a parasitemic or had parasite counts <20,000 parasites/mm³, had no reported iron supplementation, SP treatment, or blood transfusions within the last 2 weeks, and did not have the HbSS phenotype. Children were assigned sequentially (by M.R.D.) to 1 of 4 treatment groups, using balanced block randomization (8 children/block) and a random number listing generated independently before the study (by F.O.t.K.). All study drugs and identical placebos were manufactured by Laboratory and Allied Limited. The code to the true drug and placebo assignment was revealed only after closure of the data set and completion of preliminary analyses. It was estimated that a sample size of 600 would yield 90% power ($\alpha = 0.05$) to detect a 0.5-g/dL difference between the mean hemoglobin concentrations of the treatment groups at week 12, assuming a within-group SD of 1.8 g/dL and that 10% of the subject group would be lost to follow-up. Similarly, this would yield 80% power to detect a difference of ~33% in the incidence of malaria, assuming an event rate of 0.5 events/12 weeks in the group that received only placebo.

Interventions. All enrolled children were given a single presumptive treatment dose of SP [18] (Malodar [Laboratory and Allied Limited], which contains 500 mg of sulfadoxine and 25 mg of pyrimethamine per tablet; study dose was 25/1.25 mg/kg [subjects weighing ≤10 kg received one-half tablet, and subjects weighing >10 kg received 1 tablet]). Subsequent treatment regimens were IPT with SP at 4 and 8 weeks, combined with daily iron for 12 weeks (IPT + iron); daily iron and IPT with SP placebo; IPT and daily iron placebo; and daily iron placebo and IPT with SP placebo (double placebo). The target oral dose for iron supplementation was 3–6 mg/kg/day (ferrous sulphate in a 40-mg/mL suspension, 27.5% elemental) [19]. SP and SP placebo were given as crushed tablets mixed with water. The dose was repeated when spitting or vomiting occurred within 30 min. The quality of the SP and SP placebo was confirmed by high-performance liquid chromatography (Centers for Disease Control and Prevention, Atlanta).

Follow-up. In addition to daily home visits by staff to administer the iron or iron placebo, children were visited at home every 2 weeks for completion of a morbidity questionnaire and assessment of cutaneous reactions and axillary temperature. Fingerprick or heel-prick blood samples (250–500 μ L) were obtained every 4 weeks (just before the next dose of SP or SP placebo) for determination of hemoglobin concentrations and the presence of malaria parasites. The frequency of local clinic and hospital attendance was monitored using a passive surveillance system.

Children with uncomplicated symptomatic malaria (axillary temperature $\geq 37.5^{\circ}\text{C}$ with any malaria parasitemia or parasitemia >5000 parasites/mm³ [20]) received oral quinine (supervised; 10 mg/kg 3 times/day for 7 days). Children who de-

veloped severe malaria [21], severe anemia (hemoglobin concentration <5.0 g/dL), or other severe disease requiring hospitalization were referred for further treatment.

Laboratory methods. An AcT 10 Coulter Counter was used to obtain full blood counts. Malaria smears were Giemsa stained, and *Plasmodium* parasite densities were counted against 300 leukocytes and expressed per microliter, using the Coulter Counter leukocyte count. Before a slide was declared to be negative, 200 microscopic fields were read. Hemoglobin phenotype was determined by hemoglobin electrophoresis. In a subsample of the first 155 children enrolled, serum transferrin receptor (sTfR) concentrations were determined (EIA; Ramco Laboratories) at enrollment and at 12 weeks.

Statistical analysis. Statistical analyses were conducted in SAS (version 8.0; SAS Institute) on an intent-to-treat basis. Characteristics at enrollment were compared by analysis of variance or by the χ^2 or Fisher's exact test (table 1). Hemoglobin concentration measurements from scheduled follow-up visits

were modeled as a polynomial function of time, using repeated-measures analysis [22]. Reported confidence intervals are adjusted for within-subject correlation. Factors at enrollment were introduced into the initial model individually to assess possible confounding and/or effect modification. The effect of each intervention was first compared with data from the double-placebo group (table 2). The interaction between daily iron and IPT was tested in a full model using the -2 log likelihood ratio test. Because this result was not significant, the overall effect of iron was assessed with adjustment for the effect of IPT (table 3). Similarly, the overall effect of IPT was assessed with adjustment for the effect of iron (table 3). Least square means are reported for a child with a global mean hemoglobin concentration of 9.48 g/dL on enrollment. After we had verified that the proportionality of hazards assumption was met, Cox regression models were used to determine hazard ratios for adequate recovery from anemia during the intervention period, while controlling for the same covariates as in the model used

Table 1. Demographic characteristics and enrollment laboratory values, by treatment group, for 546 subjects enrolled in a trial of treatment of anemia with iron and sulfadoxine-pyrimethamine.

Variable	IPT + iron (n = 135)	Iron (n = 139)	IPT (n = 136)	Double placebo (n = 136)	P
Demographic characteristic					
Age, mean months (SD)	11.2 (7.2)	11.7 (7.5)	12.5 (8.0)	11.2 (7.6)	.45 ^a
Male sex	63/135 (46.7)	66/139 (47.5)	68/136 (50.0)	66/136 (48.5)	.89 ^b
Household wealth category ^c					.18 ^b
0–33rd percentile	35/128 (27.3)	37/130 (28.5)	44/125 (35.2)	41/127 (32.3)	
33rd–67th percentile	46/128 (35.9)	37/130 (28.5)	46/125 (36.8)	48/127 (37.8)	
67th–100th percentile	47/128 (36.7)	56/130 (43.1)	35/125 (28.0)	38/127 (29.9)	
Laboratory value					
Hemoglobin concentration, mean g/dL (SD)	9.48 (1.1)	9.58 (1.0)	9.34 (1.2)	9.59 (1.1)	.21 ^a
MCV, mean fL (SD)	71.1 (9.3)	71.0 (8.3)	70.9 (8.3)	72.2 (7.8)	.65 ^a
Microcytemia ^d	60/98 (61.2)	68/103 (66.0)	59/96 (61.5)	53/96 (55.2)	.49 ^b
sTfR concentration ^e					
Geometric mean, $\mu\text{g/mL}$	4.90	2.95	4.56	3.31	.52 ^a
Above threshold	15/40 (37.5)	11/39 (28.2)	12/38 (31.6)	9/38 (23.7)	.60 ^b
Parasitemia	38/133 (28.6)	30/135 (22.2)	36/132 (27.3)	34/134 (25.4)	.71 ^b
Parasite density, ^f geometric mean parasites/mm ³	1814	2087	2020	3442	.59 ^a
Hemoglobin phenotype ^g					.54 ^b
AA	105/130 (80.8)	98/133 (73.7)	102/130 (78.5)	103/130 (79.2)	
AS	25/130 (19.2)	35/133 (26.3)	28/130 (21.5)	27/130 (20.8)	

NOTE. Data are no. of subjects with characteristic/no. of subjects for whom data were available (%), unless otherwise indicated. IPT, intermittent preventive treatment with sulfadoxine-pyrimethamine; MCV, mean cell volume; sTfR, serum transferrin receptor.

^a By analysis of variance (*F* test).

^b By χ^2 or Fisher's exact test.

^c Data are for 510 households (546 children) and are based on type of house and ownership of livestock, radios, bicycles, and sofas. Data are no. of households in wealth category/total no. of households (%).

^d "Microcytemia" was defined as an MCV <70 fL (for subjects aged 2–5 months), <73 fL (for subjects aged 6–11 months), or <75 fL (for subjects aged \geq 12 months) [24].

^e Data are for the first 155 enrolled children. The sTfR concentration threshold associated with iron deficiency in children aged >12 months was \geq 11.2 $\mu\text{g/mL}$ [25].

^f Data are for the 137 children with parasitemia.

^g HbSS phenotype was a criterion for exclusion.

Table 2. Effect of anemia treatment or placebo on hematological, malaria, and nonmalaria outcomes by week 12 among 491 children aged 2–35 months with mild anemia.

Variable	IPT + iron (n = 129)	Iron (n = 127)	IPT (n = 127)	Double placebo (n = 108)
Hemoglobin concentration, g/dL				
Mean ^a	11.05	10.70	10.08	9.91
Difference in means (95% CI)	1.14 (0.82–1.47)	0.79 (0.46–1.10)	0.17 (–0.15–0.49)	Reference
Hematological recovery ^b				
n/N (%)	81/108 (75.0)	83/111 (74.8)	45/101 (44.6)	55/108 (50.9)
Hazard ratio (95% CI) ^c	1.83 (1.30–2.59)	1.65 (1.18–2.32)	0.90 (0.60–1.33)	Reference
Severe anemia ^d				
n/N (%)	2/108 (1.9)	5/111 (4.5)	9/101 (8.9)	8/108 (7.4)
Hazard ratio (95% CI) ^c	0.25 (0.05–1.18)	0.66 (0.22–2.03)	1.04 (0.40–2.72)	Reference
MCV, fL ^e				
Mean	73.89	74.96	69.06	70.40
Difference in means (95% CI)	3.49 (1.25–5.74)	4.56 (2.35–6.77)	–1.34 (–3.59–0.91)	Reference
Microcytemia, ^f n/N (%)	45/92 (48.9)	46/91 (50.6)	68/89 (76.4)	64/86 (74.4)
Prevalence PR for MCV above threshold (95% CI)	0.67 (0.50–0.84)	0.60 (0.46–0.76)	1.01 (0.89–1.15)	Reference
sTfR concentration ^g				
Geometric mean, µg/mL	1.19	1.73	2.31	3.83
Ratio of geometric means (95% CI)	0.31 (0.12–0.81)	0.45 (0.17–1.23)	0.60 (0.23–1.59)	Reference
Above threshold, n/N (%)	2/34 (5.9)	2/30 (6.7)	5/32 (15.6)	5/27 (18.5)
Prevalence PR for sTfR above threshold (95% CI)	0.28 (0.04–1.13)	0.32 (0.05–1.32)	0.82 (0.27–2.52)	Reference
Parasite density, ^h parasites/mm ³				
Geometric mean	1705	2569	2485	3778
Ratio of geometric means (95% CI)	0.45 (0.25–0.82)	0.68 (0.38–1.23)	0.66 (0.36–1.19)	Reference
Malaria parasitemia				
n/N (%)	11/104 (10.6)	22/111 (19.8)	17/114 (14.9)	20/95 (21.1)
Prevalence PR ⁱ	0.72 (0.45–1.11)	1.04 (0.72–1.51)	0.59 (0.38–0.91)	Reference
Incidence, no. of episodes (ID)	86 (2.86)	89 (2.92)	80 (2.72)	95 (3.19)
Hazard ratio (95% CI) ^j	0.79 (0.49–1.26)	1.06 (0.68–1.66)	0.63 (0.39–1.01)	Reference
Clinical malaria ^k				
Incidence, no. of episodes (ID)	16 (0.53)	20 (0.66)	26 (0.88)	30 (1.01)
Hazard ratio (95% CI) ^j	0.45 (0.19–1.05)	0.68 (0.32–1.43)	0.63 (0.30–1.30)	Reference
Clinic visits				
Incidence, no. of episodes (ID)	113 (3.69)	123 (4.02)	95 (3.23)	132 (4.38)
Hazard ratio (95% CI) ^j	0.89 (0.63–1.25)	1.04 (0.74–1.44)	0.61 (0.43–0.88)	Reference

NOTE. CI, confidence interval; ID, crude incidence density (no. of episodes/person-year); IPT, intermittent preventive treatment with sulfadoxine-pyrimethamine; MCV, mean cell volume; n/N, no. of subjects/no. for whom data were available; PR, proportion ratio.

^a Least square mean at week 12, obtained from repeated measures analysis, using a polynomial function of time and adjusted for enrollment hemoglobin concentration and enrollment parasitemia.

^b “Hematological recovery” was defined as a hemoglobin concentration ≥ 11 g/dL before or at week 12.

^c Cox proportional hazards analysis, adjusted for enrollment hemoglobin concentration and enrollment parasitemia.

^d “Severe anemia” was defined as a hemoglobin concentration < 7 g/dL before or at week 12.

^e At week 12; least square means are adjusted for enrollment MCV and compared using analysis of variance and log-binomial regression.

^f “Microcytemia” was defined as an MCV < 70 fL (for subjects aged 0–5 months), < 73 fL (for subjects aged 6–11 months), or < 75 fL (for subjects aged ≥ 12 months) [24].

^g Data are for the first 155 enrolled children. Differences in geometric means at week 12 from the double-placebo group are reported as ratios. Estimates are adjusted for enrollment sTfR concentration and compared using analysis of variance and log-binomial regression. The sTfR concentration threshold associated with iron deficiency in children aged > 12 months was ≥ 11.2 µg/mL [25].

^h Repeated measures analysis over the course of the 12-week intervention period. Differences in geometric means from the double-placebo group are reported as ratios.

ⁱ PR at week 12, adjusted for enrollment hemoglobin concentration, age, and enrollment parasitemia.

^j Cox proportional hazards analysis, adjusted for enrollment hemoglobin concentration, age, and parasitemia.

^k “Clinical malaria” was defined as an axillary temperature $\geq 37.5^\circ\text{C}$ with coexisting malaria parasitemia.

Table 3. Effect of intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine (with adjustment for iron supplementation) and iron supplementation (with adjustment for IPT) on hematological, malaria, and nonmalaria outcomes by week 12 among subjects receiving anemia treatment.

Variable	IPT	Iron
Hemoglobin concentration, g/dL		
Difference in means (95% CI) ^a	0.27 (0.03–0.51)	0.88 (0.65–1.10)
<i>P</i>	.03	<.0001
Hematological recovery ^b		
Hazard ratio (95% CI) ^c	1.07 (0.78–1.47)	1.83 (1.43–2.35)
<i>P</i>	.67	<.0001
Severe anemia ^d		
Hazard ratio (95% CI) ^c	0.78 (0.35–1.76)	0.44 (0.18–1.07)
<i>P</i>	.55	.07
Mean cell volume, fL		
Difference in means (95% CI) ^e	–1.20 (–2.76–0.36)	4.70 (3.13–6.26)
<i>P</i>	.13	<.0001
sTfR concentration, μ g/mL		
Ratio of geometric means (95% CI) ^f	0.64 (0.33–1.27)	0.49 (0.25–0.96)
<i>P</i>	.20	.04
Malaria parasitemia		
Hazard ratio (95% CI) ^g	0.55 (0.35–0.89)	1.14 (0.82–1.59)
<i>P</i>	.01	.44
Clinical malaria ^h		
Hazard ratio (95% CI) ^g	0.47 (0.20–1.06)	0.69 (0.39–1.22)
<i>P</i>	0.07	0.21
Clinic visits		
Hazard ratio (95% CI) ^g	0.38 (0.22–0.66)	1.04 (0.74–1.44)
<i>P</i>	.001	.84
Nonmalaria morbidity ⁱ		
Hazard ratio (95% CI) ^g	0.77 (0.56–1.05)	1.16 (0.90–1.48)
<i>P</i>	.10	.25

NOTE. Differences and hazard ratios compare subjects who received the intervention with those who did not. Separate full models containing the interaction term between iron and IPT showed that the effects of iron on hematologic responses or morbidity were independent of IPT and vice versa. $P > .40$ for all interaction terms, except severe anemia ($P = .30$) and clinic visits ($P = .19$). CI, confidence interval; sTfR, serum transferrin receptor.

^a Multivariate repeated measures analysis for mean hemoglobin concentration at week 12, using a polynomial function of time and adjusted for enrollment hemoglobin concentration, enrollment parasitemia, and either iron (for the effect of IPT) or IPT (for the effect of iron).

^b “Hematological recovery” was defined as a hemoglobin concentration ≥ 11 g/dL before or at week 12.

^c Cox proportional hazards analysis during the 12-week intervention, adjusted for enrollment hemoglobin concentration, parasitemia, and either iron (for the effect of IPT) or IPT (for the effect of iron).

^d “Severe anemia” was defined as a hemoglobin concentration < 7 g/dL before or at week 12.

^e Difference in means at week 12, calculated using analysis of variance and adjusted for mean cell volume at enrollment.

^f Ratio of geometric means at week 12, calculated using analysis of variance and adjusted for sTfR concentration at enrollment.

^g Cox proportional hazards analysis, adjusted for enrollment hemoglobin concentration, age, parasitemia, and either iron (for the effect of IPT) or IPT (for the effect of iron).

^h “Clinical malaria” was defined as an axillary temperature $\geq 37.5^\circ\text{C}$ with coexisting malaria parasitemia.

ⁱ “Nonmalaria morbidity” was defined as an axillary temperature $\geq 37.5^\circ\text{C}$ without coexisting malaria parasitemia.

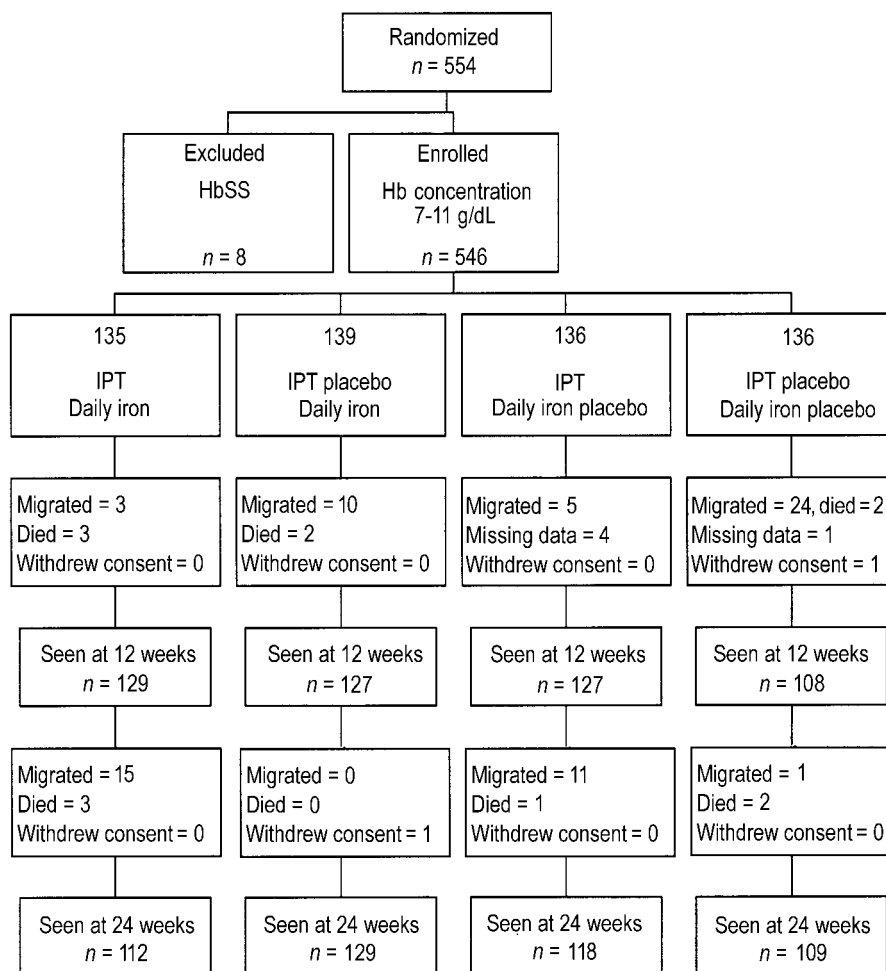


Figure 1. Subject distribution for a trial comparing the use of iron supplementation and intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine for treatment of mild anemia in children in Western Kenya. Some children seen at week 24 may not have been seen at week 12. Hb, hemoglobin.

to assess the effect on hemoglobin concentration as a continuous outcome.

Similar Cox regression models were used to compare the effects on time to first or only episode of malaria parasitemia, clinical malaria, clinic visit, or nonmalaria morbidity, respectively. The assumption was made that all parasitemic episodes occurring 4 weeks after the dose of SP on enrollment were new infections. Rate ratios for incidence of malaria and clinic visit outcomes in the postintervention period were obtained using a Poisson regression model. A repeated-measures model was fit to the log-transformed mean parasite densities. Because all children received a single dose of SP on enrollment but only one-half received additional doses at 4 and 8 weeks, the differential effect of IPT with SP in all models was assessed at 4–12 weeks after enrollment [23]. sTfR concentrations and mean cell volumes (MCVs) at 12 weeks after enrollment were compared with those for the double-placebo group (table 2), using multivariate analysis-of-variance models.

RESULTS

A total of 753 children were screened between April and November 1999; it was initially determined that 554 fulfilled the enrollment criteria, and these were randomly assigned to treatment groups. Eight of these children were excluded from the study before they received the first dose, because further investigation revealed that they had the HbSS phenotype (figure 1). The enrollment characteristics of the 546 enrolled children were similar across treatment groups (table 1). The mean amount of elemental iron received was 3.83 mg/kg/day (range, 2.75–5.5 mg/kg/day). All households had been issued ITNs.

Loss to follow-up by week 12 was 10% ($n = 55$) and did not differ significantly among the treatment groups (figure 1). The characteristics of the children who were lost to follow-up were similar to those of children who completed follow-up. Seven and 6 children died during the intervention (weeks 1–12) and postin-

tervention (weeks 12–24) periods, respectively (figure 1); these deaths were equally distributed among the treatment groups.

The mean hemoglobin concentration at 12 weeks was highest in the IPT + iron group, followed by the group of children who received iron alone, those who received IPT alone, and the double-placebo group (table 2). IPT + iron was more effective than iron alone (mean difference in hemoglobin concentration, 0.35 g/dL; 95% confidence interval [CI], 0.03–0.68 g/dL; $P = .03$), whereas IPT alone was not significantly more effective than double placebo (mean difference in hemoglobin concentration, 0.17 g/dL; 95% CI, -0.15 – 0.49 g/dL; $P = .30$) (figure 2). Iron supplementation (with adjustment for the effect of IPT) was associated with a mean hemoglobin concentration at week 12 that was 0.88 g/dL higher than that of iron placebo. IPT (with adjustment for the effect of iron) was associated with a more modest effect (0.27 g/dL higher than IPT with SP placebo) (table 3). The effect of iron supplementation was evident from week 4 onward (figure 2) and for up to 24 weeks (mean difference in hemoglobin concentration at week 24, compared with iron placebo, 0.61 g/dL; 95% CI, 0.30–0.92 g/dL), whereas the effect of IPT was not evident beyond week 12 (mean difference in hemoglobin concentration at week 16, compared with IPT with SP placebo, 0.15 g/dL; 95% CI, -0.07 – 0.37 g/dL). Separate models with interaction terms showed that the effects were independent of season, age group, or enrollment hemoglobin concentration (data not shown). Children who received iron supplementation were nearly twice as likely as those who received iron placebo to have an adequate hematological recovery (hemoglobin concentration ≥ 11 g/dL; table 3). The difference was still apparent at week 24 (hazard ratio, 1.63; 95%

CI, 1.31–2.03). In contrast, IPT did not increase the likelihood of recovery at either 12 or 24 weeks.

sTfR concentrations were high in 30.3% of subjects at enrollment, and 61.0% of subjects were microcytemic. No significant differences were observed among treatment groups at enrollment (table 1). Iron supplementation, but not IPT, was associated with significant improvements in sTfR concentration and MCV (table 3).

There was no significant interaction between the effect of iron supplementation and that of IPT on the risk of malaria or non-malaria morbidity during the intervention period. Between 4 and 12 weeks after enrollment, IPT was associated with significant reductions in malaria parasitemia and clinic visits and a nonsignificant reduction in clinical malaria ($P = .07$; table 3). Iron supplementation was not associated with malaria parasitemia or morbidity (table 3). There was no evidence that the risk of malaria in the postintervention period (12–24 weeks) was greater among those who received IPT (rebound effect) than among those who did not, when the analysis was adjusted for the effect of iron (data not shown). The sample size in our study was too limited to exclude with certainty the possibility that rare serious adverse effects associated with SP might occur, but none of the children included developed severe cutaneous reactions.

DISCUSSION

In the context of area-wide ITN use and administration of a single presumptive dose of SP on enrollment, 12 weeks of supervised daily iron supplementation in anemic children 2–36 months old was associated with an increase in hemoglobin

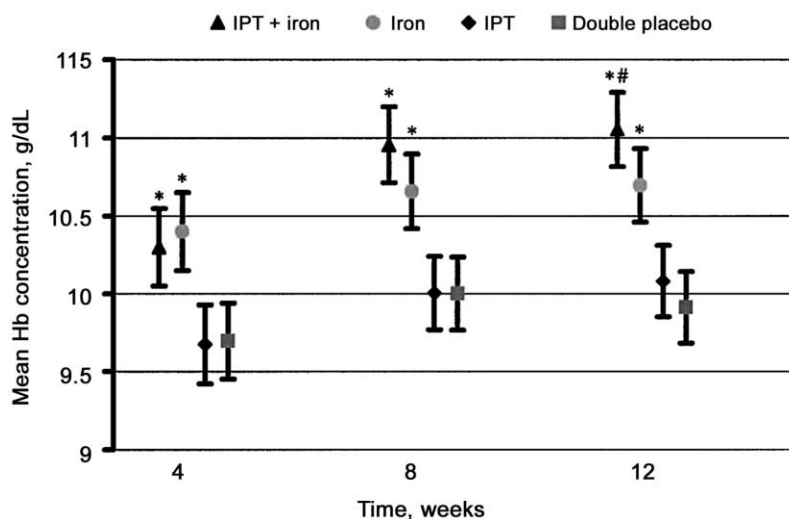


Figure 2. Multivariate repeated-measures analysis for mean hemoglobin (Hb) concentration, using a polynomial function of time and adjusted for enrollment hemoglobin concentration (global mean, 9.48 g/dL) and enrollment parasitemia. Error bars represent the 95% confidence intervals of the means. All children received a single dose of sulfadoxine-pyrimethamine (SP) on enrollment. In addition, groups received one of the following: intermittent preventive treatment (IPT) with SP, combined with daily iron; daily iron and IPT with SP placebo; IPT and daily iron placebo; or daily iron placebo and IPT with SP placebo (double placebo). *Significantly different from double placebo ($P < .05$). **Significantly different from iron ($P = .03$).

concentration that was 0.88 g/dL greater, compared with iron placebo, and a 1.8-fold greater probability of full hematological recovery. The beneficial effects were sustained for several months after the intervention ceased. The combination of iron and IPT resulted in the best treatment response, but the additional increase in hemoglobin concentration associated with IPT, although statistically significant, was modest. These results were similar in all age groups and were not affected by the degree of anemia at enrollment in this relatively homogeneous sample (more severely anemic children [hemoglobin concentration <7 g/dL] were excluded from the study).

This clear beneficial effect of iron supplementation on hemoglobin concentration in the treatment of all-cause anemia is consistent with the results of a similar treatment study in eastern Kenya in an area of seasonal malaria transmission [26] and with the findings reported in a meta-analysis involving 13 randomized, controlled iron supplementation trials [5]. Similarly, we found no indication that iron supplementation was associated with a clinically relevant increase in the risk of malaria [5, 26]. These findings were independent of age and, by proxy, the level of acquired immunity to malaria. However, malaria transmission and infection rates were low in all age groups, which reflects the area-wide impact of use of ITNs: >95% of households in this area had been issued ITNs [13], and ITNs were used in 70% of these households on a regular basis [27].

IPT further reduced the incidence of malaria parasitemia and clinical episodes by ~50%, but this resulted in only a modest hematological benefit. There are several likely reasons for this. First, although the children included in our study represent the age group at highest risk of malaria-associated anemia, the low incidence of malaria is likely to have reduced the relative causal contribution of malaria to anemia [20]. Second, all children received a single dose of SP on enrollment, in accordance with guidelines for integrated management of the sick child [18]. A marked increase in hemoglobin concentrations by week 4 was observed in all treatment groups, including the double-placebo group. This partly reflects regression toward the mean in this selected sample of anemic children but presumably also results from clearance of the initial nonresistant malaria parasitemia and subsequent resolution of the malaria-attributable component of the anemia. Thus, additional doses of SP at weeks 4 and 8 would only have treated and prevented further hematological insults associated with new malaria episodes. Third, parasitological resistance to SP is increasing rapidly in this study area, further reducing hematological efficacy, because of persistence of the initial infection and reduced prophylactic efficacy [28].

Thus, although our findings are representative for areas with similar transmission and widespread ITN use, they raise the question of whether IPT is more effective in treating anemia in children who do not use bednets and who live in areas with

less SP resistance or in treating more severe anemia (e.g., hemoglobin concentration <7.0 g/dL). The similarly limited hematological effect of IPT, however, found in 2 other randomized, controlled treatment studies involving young anemic children in eastern Kenya [26] and Tanzania [23] does not support a marked effect of IPT. These studies were conducted in areas with low bednet coverage and low levels of SP resistance and included children who had more severe anemia (hemoglobin concentration, 5–7 g/dL) than did the children in our study. All children in the Tanzanian study, which was conducted in an area with intense malaria transmission, also received presumptive treatment with SP on enrollment [23].

In most areas in which malaria is endemic, children <3 years of age represent ~9%–10% of the population, and mild anemia is the rule rather than the exception in this age group [10, 29, 30]. Routine use of IPT with SP in the treatment of mild anemia among these children is thus likely to increase drug pressure that could potentially affect the rate of development of SP resistance by *Plasmodium falciparum* in the population [31, 32]. Furthermore, although the short- and long-term consequences of iron-deficiency anemia are well documented [33–35], the public health benefits of preventing or treating asymptomatic nonsevere malaria or mild malaria-associated anemia are less clear. Available evidence from the present study and 2 other studies conducted to date [23, 26] suggests that the hematological benefit of 2 monthly doses of SP is limited, especially when these doses are in addition to a single presumptive dose of SP, and may not outweigh the potential risk of increased drug pressure if IPT were applied routinely in the treatment of mild all-cause anemia.

Thus, in contrast to the promising results obtained with use of IPT in the prevention of severe anemia in infants in areas with intense malaria transmission [8], the available evidence suggests that IPT with SP has only modest beneficial effects on hemoglobin concentrations when used for the treatment of moderate or mild all-cause anemia in addition to a single presumptive dose of SP. However, our study and that in eastern Kenya [26] clearly indicate that iron supplementation is efficacious in increasing hemoglobin concentrations in young children with mild anemia, and this is likely to outweigh any potential associated adverse effects caused by increased risk of malaria.

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