

Effective community intervention to improve hemoglobin status in preschoolers receiving once-weekly iron supplementation¹⁻³

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ABSTRACT The effect of weekly iron supplementation with and without deworming on hemoglobin was investigated in a double-masked, placebo-controlled field trial. Subjects were 289 preschoolers who were randomly divided into three groups. Groups 1 and 2 received 30 mg Fe once weekly and group 3 received a placebo. Group 1 additionally received anthelmintic treatment. Supplements were administered by the mothers, who were educated about iron deficiency beforehand. In the iron-supplemented groups prevalence of anemia decreased from 37.2% to 16.2% ($P < 0.001$). Hemoglobin increased by an average of 6.9 ± 9.8 g/L in the two iron-supplemented groups ($n = 191$), which was greater ($P < 0.001$) than the increase of 1.9 ± 8.0 g/L in the placebo group. None of the subjects had hookworm, and anthelmintic treatment did not have an additional effect. Iron supplements administered once weekly by mothers reduced anemia without major involvement of health staff. *Am J Clin Nutr* 1997;65:1057-61.

KEY WORDS Anemia, iron supplementation, preschoolers, anthelmintic treatment, anemia

INTRODUCTION

Iron deficiency anemia is highly prevalent in developing countries (1, 2). To reduce the high prevalence rates of iron deficiency many countries have initiated intervention programs that are primarily targeted to pregnant women because this population is at high risk (2). These intervention programs are part of the prenatal care program, and iron supplements for daily ingestion throughout the second and third trimesters of pregnancy are distributed to the women through the public health system (2, 3).

Another population group, besides pregnant women, at high risk for iron deficiency is preschool children. Young children in developing countries generally have a low dietary iron intake on one hand and high iron requirements on the other hand because of rapid growth (4). The situation is often aggravated by parasitic infestations (5, 6). The consequences are serious because iron deficiency in young children is associated with poor school performance (7, 8), a decreased growth rate, and impaired motor development (9, 10). However, large-scale programs to combat iron deficiency among preschoolers do not generally exist because of the costs involved and the extra managerial burden for the health sector (2).

Therefore, to improve the iron status of children, alternative approaches are needed that will burden the health sector as little as possible while keeping the costs low. Supplementation using intermittent dosing schedules may offer such an alternative for large-scale programs targeted to children. Studies in rats (11, 12), preschool children (13, 14), nonpregnant women (15), and pregnant women (16) showed that intermittent iron supplementation had an effectiveness in improving iron status similar to that of daily supplementation. Supplementation on a weekly instead of a daily basis would decrease the costs of supplementation programs and possibly increase subject compliance.

However, although weekly supplementation was successfully used to improve iron status under closely supervised conditions in field trials, the efficiency of this approach remains to be proven when used on a larger scale in communities. Therefore, this study investigated whether once-weekly iron supplementation would reduce the prevalence of anemia in preschool children under real-life community conditions, and whether anthelmintic treatment would have an additional effect on iron status. In addition, the effect of treatment on physical growth was also measured.

SUBJECTS AND METHODS

The study was carried out in the West Javanese village of Setia Asih, which has a population of ≈ 8100 individuals. All village children aged 2-5 y who were registered at the village health centers were approached for participation. Of 344 potential subjects, parental permission was obtained for 299 children. At baseline, stool samples from all children were collected and analyzed for the type and intensity of helminthic infestation (17). The children were randomly divided into three, equal-sized treatment groups. The first group received

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iron supplements once per week and anthelmintic treatment, the second group also received iron supplements once per week and a placebo for anthelmintic treatment, and the third group received placebo only. Anthelmintic treatment consisted of a single dose of albendazole (400 mg). The anthelmintic tablets as well as the placebos were ingested under supervision of the researcher (LP) 1 wk before iron supplementation started. Before the start of supplementation the mothers of the children were informed by one of the researchers (LP) and by health center staff about the causes and consequences of iron deficiency for their children, and the importance of treatment was made clear to them. The explanations were made orally in combination with written information distributed in the form of pamphlets. After these explanations were given all mothers received a bottle with 100 mL glucose syrup. They were instructed to give their children 5 mL syrup using a standardized spoon each Friday (Muslim prayer day) for 9 wk. For groups 1 and 2 the syrup contained ferrous sulfate, and one weekly dose of 5 mL syrup was equivalent to 30 mg elemental iron. The placebo syrup did not contain ferrous sulfate, but was similar in taste and appearance to the iron-containing syrup. Iron supplements and anthelmintic tablets were distributed in a doubly masked fashion.

At the start and finish of the supplementation period, hemoglobin concentration and body weight and height were measured. It was decided to only measure hemoglobin as an indicator of iron status because previous studies in similar population groups had shown that iron deficiency was the main cause for low hemoglobin concentrations (10, 13), and because the primary aim was to decrease the prevalence of low hemoglobin concentrations rather than to build iron stores. Hemoglobin was determined in fingerprick blood samples by the cyanomethemoglobin method (18) with a Compur Minilab (Bayer Diagnostic, Leverkusen, Germany). Duplicate measurements were done in 15% of the samples, and variability based on these duplicate measurements was 1.3 g/L (SD). The body weight of the children was measured by using a platform model electronic weighing scale (Seca, Hamburg, Germany). Weight was recorded to the nearest 0.1 kg while children were minimally clothed. Height was measured to the nearest 0.1 cm by using a microtoise on the same occasion as the weight measurements. Z scores of the indicators weight-for-age, height-for-age, and weight-for-height were calculated by using the National Center for Health Statistics reference data (19). Stool samples from all children were again collected at the end of the supplementation period. Stool samples were collected in small plastic containers, transported in a cool box, and stored at 4 °C in the laboratory where they were analyzed within 1 wk for the presence and degree of helminthic infestation (17).

To collect information on the eventual use of self-bought supplements, mothers were questioned about whether the children already took vitamin or mineral supplements besides the provided syrup. Furthermore, mothers were asked whether their children had received a large dose of vitamin A up to 6 mo before the study.

Syrup intake was not supervised by health center staff or the researchers, but compliance was controlled by checking the iron content in the stool (20) of randomly selected subsamples of children (12–21 children per group). Stool samples were collected 1 d after the prescribed supplement intake on weeks 3 and 6 of the trial for this purpose. At the end of the supple-

mentation the quantity of remaining syrup was also checked as a further control of compliance.

All parents gave written informed consent for their children's participation, and at the end of the study those children who still had helminths or who were still anemic received treatment. At the end of the trial, 289 children remained; 10 dropped out because they had either moved or had become ill. The research proposal was approved by the Ethical Review Committee of the SEAMEO-TROPED Center at the University of Indonesia, Jakarta, and conformed with the International Guidelines for Ethical Review of Epidemiological Studies (21).

Within-group changes in hemoglobin and between-group differences as a result of treatment were first tested by using the multivariate analysis of variance (MANOVA) repeated-measures design of SPSS/PC+ 4.0 (SPSS Inc, Chicago) (22). For significant *P* values, differences were further investigated by using ANOVA with post hoc multiple-comparison tests (Tukey and Scheffé). Differences between groups in the prevalence of anemia or worm infestation were tested by using a chi-square test.

RESULTS

At baseline, hemoglobin concentrations were similar in the three treatment groups (Table 1), with a mean value for the whole group of 112 ± 10 g/L. At the end of the supplementation period the hemoglobin concentration had increased significantly in both iron-supplemented groups ($P < 0.001$). In the placebo group the hemoglobin concentration showed a small but significant increase of 1.9 ± 8.0 g/L ($P = 0.02$). In the two iron-supplemented groups the treatment effect on hemoglobin was similar ($P = 0.53$), and it was significantly larger than the change in the placebo group ($P < 0.05$).

The distribution of hemoglobin concentrations in the two iron-supplemented groups before and after treatment are shown in Figure 1. The distribution curve after supplementation shifted to the right in comparison with the curve before supplementation, indicating an overall improvement in iron status in the supplemented children.

Anemia prevalence (hemoglobin < 110 g/L) among all children at the start of the study was 36.7%, and no significant difference existed between the treatment groups. In the iron and deworming group, prevalence decreased from 37.9% at the beginning of the study to 14.7% at the end ($P < 0.001$); in the iron-only group the prevalence decreased from 36.5% to 17.9%

TABLE 1
Hemoglobin concentration at the beginning and end of a 9-wk supplementation period in three groups of children¹

Treatment group	Hemoglobin		
	Beginning	End	Change
	g/L		
Iron and deworming (<i>n</i> = 95)	112.6 ± 10.4	120.1 ± 9.7	7.5 ± 8.8 ²
Iron (<i>n</i> = 96)	112.1 ± 10.4	118.6 ± 11.4	6.4 ± 10.6 ²
Placebo (<i>n</i> = 98)	113.3 ± 9.9	115.2 ± 9.4	1.9 ± 8.0 ^{2,4}

¹ $\bar{x} \pm SD$.

^{2,3} Significant within-group change: ² $P < 0.001$, ³ $P = 0.02$.

⁴ Change smaller than in iron group ($P < 0.05$) and in iron and deworming group ($P < 0.05$).

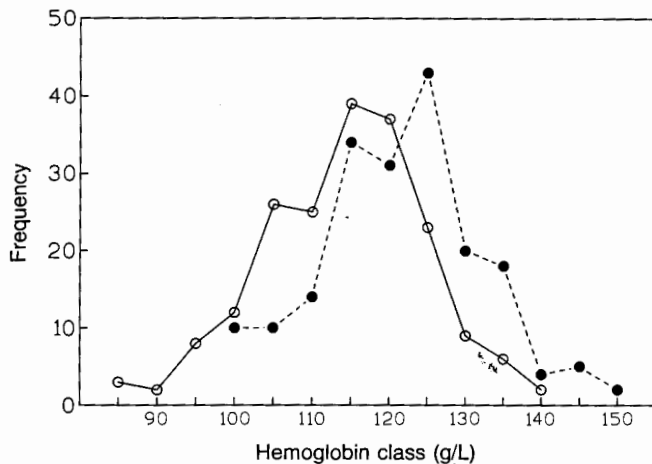


FIGURE 1. Distribution of hemoglobin values in subjects who were supplemented with iron only or with iron plus an anthelmintic agent ($n = 191$) at the beginning (○) and end (●) of the supplementation period.

($P < 0.01$) whereas in the placebo group the prevalence decreased from 35.7% to 26.5% ($P = 0.17$). At the end of the study the prevalence of anemia in the placebo group was significantly higher ($P = 0.04$) than that in the combined iron-treated groups ($n = 191$).

Hemoglobin concentrations of iron-supplemented children who were anemic at baseline increased by 12 ± 9 g/L, which was significantly higher ($P = 0.01$) than the increase of 5 ± 9 g/L among anemic children in the placebo group. A significant negative correlation ($r = -0.412$, $P = 0.001$) existed between initial hemoglobin concentration and the change in hemoglobin for the iron-supplemented groups, indicating that subjects with the lowest initial hemoglobin concentrations had the largest changes.

From subsamples of subjects, stool was collected at weeks 3 and 6 to check compliance with the prescribed supplement intake. The stool of 63–72% of sampled children from the iron-supplemented groups contained a large amount of iron, indicating that they ingested the supplement Figure 2. The stool of 15–24% of the sampled children in the placebo group contained iron; the hemoglobin concentration of those with stool positive for iron increased by 4.0 ± 9.3 g/L, suggesting that they indeed had a relatively high iron intake even though they were in the placebo group. No side effects related to supplement intake were registered among the children.

Fifty mothers indicated that their children took other vitamin or mineral supplements (equally divided over the three groups). ANOVA indicated that children who took these additional supplements had a significantly higher increase in hemoglobin concentration ($P = 0.02$) than did those who did not take additional supplements. Of the whole group of children, 47.9% had received a large dose of vitamin A up to 6 mo before the study. Supplementation of preschoolers with vitamin A is a national program in Indonesia. Reported previous intake of vitamin A supplements was neither associated with the initial concentration nor with changes in hemoglobin.

At the start of the study, 55.5%, 29.3%, and 0% of all children were infected with *Ascaris lambricoides*, *Trichuris trichiura*, and hookworm, respectively, whereas 19.3% suffered from both ascariasis and trichuriasis (Table 2). Median

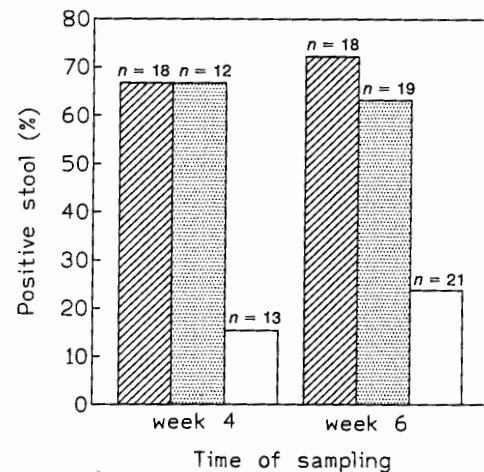


FIGURE 2. Children with a high amount of iron in their stool, indicating intake of iron supplements. n values indicate the total number of children sampled: (▨), iron supplementation plus anthelmintic treatment; (▩), iron supplementation only; (□), placebo.

egg counts per gram feces in infected children were 1245 and 38 for *A. lambricoides* and *T. trichiura*, respectively. Prevalence and severity of infection were similar in the three groups. At the end of supplementation, the prevalence of *A. lambricoides*, *T. trichiura*, and hookworm in the group treated for helminths was 2.2%, 16.1%, and 0%, respectively. Prevalence and severity of infestation were not significantly associated with either hemoglobin at baseline nor with treatment effect. The hemoglobin concentration of iron-supplemented subjects who still suffered from trichuriasis at the end of the study had increased by 6.7 ± 9.4 g/L ($n = 41$); the hemoglobin concentration of those without trichuriasis had increased by 6.9 ± 10.0 g/L, whereas both subgroups had similar initial hemoglobin concentrations.

At baseline, 40.1% of the entire group of children were stunted (height-for-age Z score < -2), 39.4% were underweight (weight-for-age Z score < -2), and 6.9% were wasted (weight-for-height < -2). Anemic children tended to have lower anthropometric values. The mean height-for-age Z scores at baseline for children who were anemic and nonanemic were -1.98 ± 1.25 and -1.69 ± 1.38 , respectively ($P = 0.08$). These weight-for-age values were -1.93 ± 0.92 and -1.61 ± 0.98 , respectively ($P = 0.007$), and weight-for-height values

TABLE 2

Prevalence of helminthic infection at the start and end of supplementation in subjects from whom two stool samples were obtained

	<i>Ascaris</i>	<i>Trichuris</i>	Hookworm
	%		
Start			
Iron and deworming ($n = 93$)	54.8	29.0	0.0
Iron ($n = 93$)	54.8	21.5	0.0
Placebo ($n = 94$)	55.3	33.0	0.0
End			
Iron and deworming ($n = 93$)	2.2	16.1	0.0
Iron ($n = 93$)	47.3	28.0	1.1
Placebo ($n = 94$)	37.2	31.9	4.3

were -0.90 ± 0.76 and -0.73 ± 0.88 , respectively ($P = 0.101$). The prevalences of stunting, underweight, and wasting were similar in the three treatment groups. The average weight and height values in all three groups increased significantly from the beginning to the end of the study as was expected in these young children (Table 3). There were no between-group differences in changes in weight and height. Significant within-group changes occurred in weight-for-age and weight-for-height in both iron-supplemented groups. In the group only supplemented with iron, height-for-age also increased significantly ($P < 0.02$), suggesting not only an improved trend in weight but also in height. In the placebo group no significant changes occurred over time in any of these anthropometric indicators. The changes in the iron-supplemented groups, however, were not significantly different from those of the placebo group.

Further investigation of interactions between growth status, micronutrient status, and worm infestation showed that neither the baseline values of any of the anthropometric indicators nor their changes were associated with worm infestation or reported vitamin A supplement intake. Multiple-linear-regression analysis indicated that changes in all three anthropometric indicators were negatively associated ($P < 0.01$) with the baseline values of the respective indicators, but not with changes in hemoglobin, worm infestation at the end of the study, age, or treatment group.

DISCUSSION

The study was carried out among children of whom 40.1% were stunted, 36.7% were anemic, and 64.5% suffered from at least one type of helminthic infestation. Through unsupervised, once-weekly supplementation for 9 wk, the prevalence of anemia was reduced from 37.2% to 16.2% in the children supplemented with iron. The hemoglobin concentration of anemic children who were supplemented increased on average by 12 g/L. This increase was similar to previously reported increases among preschoolers who were supplemented daily (10) and twice weekly (13). This similarity in results compared with previous studies (10, 13) among Indonesian preschool children is encouraging because supplementation in these previous studies was done with supervision. In the current study, no treat-

ment group received iron supplements daily because previous studies had shown that weekly and daily supplementation improved hemoglobin status similarly. Furthermore, our aim was to investigate a manageable intervention and it is unrealistic to expect that a large-scale iron-supplementation program involving daily supplementation would ever be implemented.

In the current study the supplements were given to the children by their mothers. The mothers received information about causes, consequences, and treatment of iron deficiency at the start of the study, whereafter they were no longer supervised by the health staff. The significant increase in hemoglobin and the high percentage of stool samples containing iron indicated that compliance with syrup intake was relatively high. Apparently, the information provided motivated the mothers sufficiently to give the supplements to their children, and not to forget the once a week time of supplementation. The high compliance rate was an important aspect of this study because low compliance is a problem with established iron-supplementation programs for pregnant women (2, 23, 24).

Besides the highly significant increase in hemoglobin in the iron-supplemented children, a small but significant increase in hemoglobin also occurred in the placebo group. This was partially caused by the fact that 17 (17.3%) of these children took additional vitamin or mineral supplements, and probably because some children consumed some form of iron supplements or iron-enriched foods as indicated by the positive stool samples in 15–24% of the sampled children. Furthermore, mothers were informed about the causes and consequences of iron deficiency at the start of the study, which raised the awareness of the mothers leading to better nourishment of their children.

Worm infestation was not associated with hemoglobin concentration at baseline. Albendazole treatment effectively reduced the prevalence of ascariasis, but was less effective in reducing trichuriasis. Similar observations on the effect of albendazole on trichuriasis were made among children in Zanzibar (25). Although the prevalence of helminths had decreased markedly after treatment, the increase in hemoglobin was not significantly higher in the children treated with both albendazole and iron compared with those who had received iron only. However, none of the children suffered from hookworm infes-

TABLE 3
Baseline values and changes in anthropometric indicators¹

	Iron and deworming	Iron	Placebo
Values at start			
Age (m)	43.5 ± 10.9	41.1 ± 11.1	42.0 ± 11.6
Weight (kg)	12.6 ± 2.0	12.2 ± 2.1	12.5 ± 2.1
Height (cm)	91.9 ± 7.5	89.9 ± 8.3	91.1 ± 7.3
Height-for-age (SD score)	-1.74 ± 1.26	-1.92 ± 1.29	-1.71 ± 1.12
Weight-for-age (SD score)	-1.76 ± 0.88	-1.84 ± 0.93	-1.69 ± 0.84
Weight-for-height (SD score)	-0.93 ± 0.73	-0.85 ± 0.80	-0.81 ± 0.79
Change			
Weight (kg)	0.51 ± 0.73 ²	0.45 ± 0.58 ²	0.34 ± 0.63 ²
Height (cm)	1.2 ± 0.9 ²	1.4 ± 1.0 ²	1.2 ± 1.0 ²
Height-for-age (SD score)	0.03 ± 0.24	0.07 ± 0.27 ³	0.03 ± 0.26
Weight-for-age (SD score)	0.16 ± 0.46 ⁴	0.14 ± 0.36 ³	0.06 ± 0.41
Weight-for-height (SD score)	0.20 ± 0.65 ⁴	0.12 ± 0.49 ³	0.03 ± 0.56

¹ $\bar{x} \pm SD$.

²⁻⁴ Within-group change over time: ² $P < 0.001$, ³ $P < 0.02$, ⁴ $P < 0.005$.

tation at the start of the study and the additional effect of anthelmintic treatment may be different in populations in whom hookworm infection is an important problem.

The results of the present study indicate that among populations not suffering from hookworm, anthelmintic treatment in combination with iron supplementation does not result in additional improvements in hemoglobin status.

Previous studies reported positive effects of iron supplementation on the growth of anemic children (9, 10, 26), but it was also reported that iron supplementation of iron-replete young children may retard growth (27). The present study indicated that weekly iron supplementation on a community basis did not negatively influence growth. Iron supplementation seemed to improve growth, but multiple linear regression indicated that growth changes were not associated significantly with changes in hemoglobin concentration.

The mothers were able to improve the iron status of their children through once-weekly supplementation after having received clear instructions. Considering that 17.3% of the children had already been receiving some form of self-purchased supplement, improvement in iron status may be achieved through home supplementation without the classic intervention efforts of the health sector.

Several issues need further attention. Although the prevalence of anemia was markedly reduced, $\approx 16\%$ of the children remained anemic after 9 wk of supplementation. Whether a prolonged period of supplementation would be beneficial to further reduce the prevalence of anemia, or whether the treatment needs to be modified such that other micronutrients, such as vitamin A (28, 29), be added to improve the treatment effect needs to be investigated. Furthermore, the current intervention was aimed at children aged 2–5 y; however, the population group most at risk of iron deficiency is infants aged 6–12 mo. These children depend completely on diet for iron because their iron stores are low or depleted and their iron requirement is very high because of their rapid growth rate (4). The diet of many infants in developing countries contains an insufficient amount and quality of iron; therefore, weekly supplementation may provide them with sufficient iron to prevent deficiency. An optimal supplementation regimen for infants would therefore also require investigation.

We conclude that once-weekly iron supplementation was an effective, cheap, and simple intervention that improved iron status in preschoolers in an Indonesian community. The treatment caused no side effects and involved little chance of overdose. Once the iron status of these children is restored, chances are favorable that it will remain adequate for a prolonged period of time (30). ■

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