Preliminary findings on iron supplementation and learning achievement of rural Indonesian children[1–3]

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ABSTRACT The effects of oral iron supplementation on blood iron levels and learning achievement in 130 rural Indonesian school children were assessed in this double-blind study. The children were classified into anemic and nonanemic groups according to their initial hemoglobin and transferrin saturation levels and were randomly assigned to either iron or placebo treatment for 3 mo. Hematological, anthropometric, and learning-achievement data were collected before (T1) and after (T2) the treatment period and 3 mo later. The means and standard deviations suggest that supplementation with 10 mg ferrous sulfate per kilogram body weight per day for 3 mo resulted in an apparent improvement in anemic subjects' hematological status and learning-achievement scores. No tests of statistical comparisons are reported. *Am J Clin Nutr* 1989;50:698–702.

KEY WORDS Iron, anemia, learning, school, Indonesia

Introduction

Numerous studies on the effect of iron deficiency (ID) and anemia have focused on the cognitive function of infants and preschoolers or on physical work productivity of adults (1, 2; K Darwin, unpublished observations, 1984). Studies related to behavior and achievement in formal educational settings have also been done by Webb and Oski (3–5) and others (6; AG Soemantri, unpublished observations, 1978) on school-aged children. Reports on younger and older children indicated the deleterious effects of anemia and ID in iron-deficient anemic (IDA) subjects when compared with a well-matched control group. In a previous study in Indonesia (6, 7), administration of 10 mg ferrous sulfate per kilogram body weight per day resulted in a significant improvement in school achievement of anemic subjects. Growth rate reached an almost normal value compared with the anemic control group. Reduced morbidity was found.

These results led to the conclusion that iron supplementation on IDA children during a treatment period of 3 mo was able to improve hematological status, school achievement, growth velocity and morbidity.

The objective of this study was to investigate the effect of 3-mo iron supplementation on the learning achievement of IDA children. One important difference in comparison with the previous study is that in this one the effect on learning achievement was observed during the 3 mo after iron supplementation.

Methods

The study was conducted in the district of Gunungpati, an agricultural area with a tropical climate and located about 20 km southwest of Semarang. It has a population of ~30 000, 42% of which are < 15 y old. Procedures followed were in accord with the Helsinki Declaration of 1975 as revised in 1983.

Agriculture is the main source of income. Agricultural produce is marketed in Ungaran, which is ~17 km from the area, or in Semarang. The primary staple foods are rice, corn, and cassava. Side dishes are vegetables and sometimes meal and eggs. Fruit consumption varies with the seasons.

Electricity is available, although not all families have made use of it yet. Health facilities consist of one health station with one physician assisted by a midwife and other paramedical personnel and supported by a mobile health unit.

A total of 491 children from two primary schools in district Gunungpati served as the potential target population for the study. Selection of the schools was based on the similarity of health programs in the two schools and the willingness of the teachers to cooperate.

The following criteria were used to select the children in the study: *1*) > 80th percentile of weight (wt) and height (ht) and mid-arm circumference > 85th percentile of Indonesian growth standards; *2*) negative parasite egg count by stool examination after deworming treatment; *3*) no evidence of acute or chronic illness, clinical

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TABLE 1
Comparative statistics of age and anthropometric measurements of anemic and control children before supplementation*

	Anemic (n = 58)	Nonanemic (n = 72)	p value
Age (y)	10.4 ± 1.57	10.5 ± 1.48	0.1
Anthropometry			
Weight (kg)	27.20 ± 3.60	28.79 ± 3.49	0.04
Height (cm)	132.35 ± 3.60	134.70 ± 5.43	0.01
Arm circumference (cm)	18.60 ± 0.90	19.50 ± 0.70	0.01

* $\bar{x}$ ± SD.

signs of malnutrition, physical handicaps, mental retardation, neurological dysfunction, or hematological disorders; *4*) consent of parent to participate in the study; *5*) IQ > 75; and *6*) absence of acute or severe morbidity. The procedures followed were in accordance with the National Standards of the Indonesian Department of Health. A total of 210 children, aged 8.1–11.6 y, met the selection criteria.

The study design was that of a double-blind, randomized clinical trial. From the 210 subjects meeting the selection criteria, 130 were divided by random sampling into anemic (AN) and nonanemic (NA) groups. The study subjects chosen were those whose parents fully agreed to participate in the study, after having received a thorough explanation about the study.

Subjects

The sample of 130 children was divided into an anemic group (n = 58) and a nonanemic group (n = 72). Anemia was defined by a hemoglobin (Hb) value < 110 g/L and transferrin saturation (TS) < 12%. Nonanemia was defined as Hb > 120 g/L and TS < 20%. Those subjects with Hb 111–119 g/L and TS 13–19% were excluded to minimize the chances of an overlap between the AN and NA groups. The mean ages for the AN and control subjects were 10.4 ± 1.3 y (±SD) and 10.6 ± 1.4 y, respectively. The subjects included in the statistical analysis were those who consumed 80% of the tablets and completed the laboratory examinations and achievement tests.

Blood specimen and analysis

A 12-mL venous blood sample was taken from each child by a physician and kept in a freezer kit. The samples were sent to the hematology laboratory in Semarang and analyzed on the same day they were collected. The analysis included determination of Hb concentration, estimated as cyanmethemoglobin; serum iron (SI), tested with a method modified by Bothwell and Mallet; total iron binding capacity (TIBC), tested by a method differing slightly from the technique originally described by Ramsay, that is, using sulfonated sathophenanthroline for colimetric determination; and total protein, albumin, and globulin, calculated by dividing SI by TIBC and expressed as a percentage.

Iron supplementation

Children in both the AN and NA groups were randomly assigned to either iron supplementation (FE) or placebo (PL). Thus, four study subgroups were formed: anemic and placebo-treated (ANPL, n = 24), anemic and iron-supplemented (ANFE, n = 34), nonanemic and pla-

TABLE 2
Comparative statistics of Hb, hematocrit, and transferrin saturation for anemic and control groups before and after supplementation*

Group†	Time of evaluation‡ T1	T2	T3
Hemoglobin (g/L)			
NAPL (n = 35)	132.1 ± 4.4	133.3 ± 5.5	134.3 ± 5.0
NAFE (n = 37)	133.0 ± 3.3	136.0 ± 4.4	138.1 ± 4.1
ANPL (n = 24)	96.8 ± 5.1	95.0 ± 5.3	96.8 ± 4.3
ANFE (n = 34)	97.7 ± 4.0	130.6 ± 6.3	130.2 ± 4.8
Hematocrit			
NAPL (n = 35)	0.3885 ± 0.0164	0.3901 ± 0.0173	0.3904 ± 0.0136
NAFE (n = 37)	0.3894 ± 0.0171	0.3897 ± 0.0136	0.3888 ± 0.0130
ANPL (n = 24)	0.2795 ± 0.0164	0.2785 ± 0.0112	0.2790 ± 0.0087
ANFE (n = 34)	0.2953 ± 0.0175	0.3873 ± 0.0146	0.3880 ± 0.0123
Transferrin saturation (%)			
NAPL (n = 35)	24.85 ± 4.63	25.26 ± 4.45	24.34 ± 4.67
NAFE (n = 37)	25.34 ± 3.27	26.02 ± 2.82	25.32 ± 3.10
ANPL (n = 24)	10.47 ± 6.93	10.80 ± 1.10	10.60 ± 1.88
ANFE (n = 34)	11.15 ± 6.72	25.98 ± 3.10	25.28 ± 2.78

* $\bar{x}$ ± SD.
† NA, nonanemic; PL, placebo; FE, iron-supplemented; and AN, anemic.
‡ Evaluations were conducted immediately before (T1) and after (T2) treatment and 3 mo later (T3).

cebo-treated (NAPL, n = 35), and nonanemic and iron-supplemented (NAFE, n = 37).

Iron supplementation was given orally by ferrous sulfate tablets at a dosage of 10 $mg \cdot kg^{-1} \cdot d^{-1}$, which equals 2 mg elemental Fe. The placebo contained saccharin and tapioca and had the same size and color as the iron tablets. The parents, teachers, and subjects were blind to the difference between the iron tablet and the placebo.

Both iron and placebo tablets were given by school teachers on school days and the distribution was supervised by paramedical personnel. Whenever necessary, social workers made home visits to deliver the tablets. The supplementation period lasted 3 mo. After 3 mo the intervention was terminated. However, postintervention evaluations were conducted after an additional 3-mo period for all subgroups.

Treatment of ancylostomiasis

A preliminary survey in the study area showed a 63.1% incidence of ancylostomiasis, based on a positive parasite egg count by stool examination. About one-third of this percentage had a worm load of 200 eggs per gram stool. The finding led to a deworming treatment prior to iron supplementation.

All parasite-positive children were treated with pyrantel pemoate (combination) at a dosage of 10 mg/kg body wt for 2 d. Follow-up stool examination was indicated after 2 wk and therapy was repeated for those with a positive egg count. Stool examination was repeated on those children who received treatment. Once the children were considered to be free of parasites they were randomly assigned for the placebo or the iron-supplementation group.

Supplementation and specificity of diagnosis classification

A reference criterion of response to iron treatment as indicated by change of Hb value (> 10 g/L) (8) was used to assess the sensitivity and specificity of the diagnostic measures. The sensitivity was 100%, which means that all subjects diagnosed as anemic were truly anemic. The specificity was 94.6%, meaning that 94.6% of subjects classified as normal were truly nonanemic.

Behavioral tests

The color progressive matrices (9) were employed to test general intelligence of the children in the study. The test is easy to administer and the instructions were clearly understood by the children. The test was conducted before iron supplementation (T1), after the iron-supplementation period of 3 mo (T2), and after an additional 3-mo period postsupplementation (T3).

An educational achievement test prepared by officials of the Department of Education and Culture at the local level was administered to all children. The multiple-choice test was distributed confidentially to the school teachers in the area. It consists of four main areas: mathematics, biology, social science, and language. The test was constructed by the teachers and a psychologist.

TABLE 3
Comparative statistics of IQ and educational achievement test scores for anemic and control groups at T1, T2, and T3*

Groups†	T1	T2	T3
IQ			
NAPL (n = 35)	96.45 ± 6.10	96.90 ± 5.90	96.86 ± 5.80
NAFE (n = 37)	95.96 ± 6.30	97.30 ± 6.15	97.46 ± 7.20
ANPL (n = 24)	96.50 ± 5.85	95.98 ± 5.78	96.40 ± 6.30
ANFE (n = 34)	97.25 ± 7.20	98.97 ± 6.86	98.30 ± 7.30
Language scores			
NAPL (n = 35)	73.42 ± 6.87	72.70 ± 7.12	74.90 ± 7.08
NAFE (n = 37)	74.51 ± 6.43	73.53 ± 6.71	72.24 ± 7.48
ANPL (n = 24)	63.30 ± 3.97	65.83 ± 2.14	67.92 ± 2.77
ANFE (n = 34)	64.30 ± 3.97	73.82 ± 4.58	76.85 ± 3.16
Math scores			
NAPL (n = 35)	72.10 ± 4.12	74.41 ± 5.70	76.60 ± 0.45
NAFE (n = 37)	71.82 ± 5.39	73.24 ± 6.49	76.30 ± 4.91
ANPL (n = 24)	59.10 ± 3.96	59.52 ± 2.01	60.40 ± 2.27
ANFE (n = 34)	56.30 ± 2.71	62.03 ± 4.63	65.70 ± 3.71
Biology scores			
NAPL (n = 35)	71.50 ± 5.70	72.24 ± 6.49	71.61 ± 4.83
NAFE (n = 37)	70.52 ± 6.70	72.24 ± 6.49	76.60 ± 4.83
ANPL (n = 24)	63.32 ± 4.57	61.40 ± 3.30	62.32 ± 3.60
ANFE (n = 34)	61.60 ± 1.43	67.78 ± 2.33	69.13 ± 2.77
Social science scores			
NAPL (n = 35)	81.51 ± 6.36	87.71 ± 5.58	80.02 ± 3.74
NAFE (n = 37)	79.49 ± 6.30	81.72 ± 5.56	78.10 ± 3.74
ANPL (n = 24)	58.42 ± 2.63	59.14 ± 2.28	61.52 ± 2.92
ANFE (n = 34)	58.90 ± 2.50	70.22 ± 2.70	73.90 ± 3.03

* $\bar{x}$ ± SD.
† See Table 2 for abbreviations.

Results

Anthropometry

As shown in **Table 1,** the children in the NA group were significantly taller and heavier than the AN group at T1. The same result was obtained previously (6).

Hematologic evaluation

After iron supplementation the Hb of the AN groups reached the same value as the NA group at T2 (**Table 2**). Three-month posttreatment (T3), that is, without additional iron supplementation, showed the same result as at T2. The pattern of hematocrit values was similar to the pattern of Hb values (Table 2).

There was a nonsignificant increase of TS in the NAFE group. It was expected that TS at T2 would show a more significant increase compared with TS at T1.

IQ

As indicated in **Table 3,** no significant differences were found in IQ between T1, T2, and T3.

IQ and learning achievement

Table 3 presents the IQ and achievement scores for the four groups.

Discussion

The results of the study indicated that iron supplementation restored the hematological status of children. The nonsignificant difference of TS in the iron-supplemented group may be explained by several factors such as mucosal block or other unidentified causes that were not detected during the study (eg, genetic factors that control absorption). The mucosal-block theory put forward that iron absorption may have reached its highest level and consequently iron supplementation will not have any effect.

The positive effect of iron treatment on learning in the ANFE group was observed in the four subject areas. An improvement in scores was also observed in the NAFE group for mathematics and biology.

In an endemic area of worm infestations accompanied by a high prevalence of IDA, iron supplementation improved the hematologic variables and learning achievement. It is expected that this positive effect would be much higher if the iron treatment was followed by an improvement of other variables such as socioeconomic level and environmental sanitation.

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Comments

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How relevant was the study?

The study is relevant because school-age children (6–15+ y) by and large suffer from nutritional anemia in Third World countries. The functional area of ID and cognition needs to be studied in this age group as well. Up to now attention has been focused on infants and preschoolers.

How appropriate were the use and measurement of the independent variable?

The independent variable is the ID in children. The recommended method for measuring ID is two or more of the following variables: serum iron, transferrin saturation, serum ferritin, and erythrocyte protoporphyrin. In the development of ID in an individual, the tissue stores of iron are depleted, leading to a lowering of serum iron, a decrease in transferrin saturation, a decrease in serum ferritin, and an increase in erythrocyte protoporphyrin. When tissue stores are seriously depleted, the Hb levels start declining. Thus, low levels of Hb may be taken to indicate ID, although the arbitrary cutoffs may not be entirely satisfactory. A therapeutic response in Hb to Fe supplements is considered a better criterion for establishing ID.

In this study ID has been established through a combination of measures such as reduced transferrin saturation (< 12%) and Hb levels < 110 g/L. Further, the ability of this Hb cutoff to identify the truly anemic children was also established through a response to iron supplementation of > 10 g Hb/L. Therefore, measurement of the independent variable is adequate.

How appropriate were the use and measurement of the dependent variable?

The dependent variable in the study was the learning achievement of the children in mathematics, biology, social science, and language. Although the same test was used at T1 and T2, a different test was used at T3. However, performance at T1 and T2 is more relevant to the present issue. The tests need to be described in more detail for an assessment. However, because learning achievement is usually measured in terms of tests in schools, this approach may be considered appropriate.

How appropriate were the use and measurement of intervening variables?

Nutritional status is one of the intervening variables, which in this study may be considered to be controlled because all children included were above the 80th percentile of weight and height, and above the 85th percentile for mid-arm circumference. However, the use of international standards would have helped in comparing this data with data from other countries.

Another intervening variable is the socioeconomic sta-

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tus of the subjects, which has not been clarified in this study. Should it be presumed that the socioeconomic status of the children selected from the two primary schools was similar?

Also, it has not been mentioned whether the study included both sexes. If so, then "girl/boy" becomes another intervening variable and data could have been presented for these subsets as well.

Methods

Selection criteria

The selection criteria used are rigorous but why are the rather high cutoffs being used? Were only nonmenstruating girls included in the study? When do children start school in Indonesia? How did all 210 subjects fall into the narrow age range of 8.1–11.6 y?

Selection of IDA and nonanemic children

Standards and cutoffs used for the above are okay. However, in India, children seldom have Hb of ≥ 120 g/L; hence, we have used 110 g/L as our cutoff.

Selection of dose

Why was 10 mg ferrous sulphate per kilogram body weight (or 2 mg elemental Fe) per day chosen as the dose level? At mean body weight of ~28 kg, children were getting ~280 mg $FeSO_4$, or 56 mg elemental Fe, per day. That seems okay, too.

Records of iron-tablet consumption

Did teachers keep records? Did all children in the study receive the full dose? In the school setting children are absent 25% of the time in India, on average. What is the situation in Indonesia?

Treatment of worms

Our children suffer more from amebiasis than helminthiasis. We have used pyrantal pamoate as a one-dose drug in another study of ours. It did not work for our children.

Blood withdrawal

Did all children and parents agree to three withdrawals of 12 mL blood? Otherwise, iron status tests are okay. Data are presented later for Hb, hematocrit, and TS. All graphs bear out our hypothesis that just Hb estimation would have done as well.

Results

Results were well presented. Appropriate statistics were used.

Inferences

They are correct and acceptable and show that iron supplementation helps anemic, not nonanemic, children.

Comments

Ernesto Pollitt[1]

Dr Soemantri's preliminary findings on a clinical trial to assess the impact of iron supplementation on school achievement are interesting. The assessment of test performance 3 mo after the completion of the iron intervention is commendable. However, the absence of statistical test data to determine whether the magnitude of the differences between groups is significant or not precludes any critical comments regarding the meaning of the findings.

The statistics he reports raise questions about plausibility that will have to be addressed in a more complete report on this study. Among others, the following are crucial:

1) The posttreatment mean transferrin saturation values (26.02%) of the iron-replete children who received iron are closely similar to those before treatment (25.34%). Generally, iron supplementation of iron-replete subjects results in a significant increment in the mean values of transferrin saturation (*see*, for example, 1, 2). What could explain these differences?

2) The pre- and posttreatment standard deviations for Hb and hematocrit in the anemic group that received iron are small and almost identical. This similarity contrasts sharply with the large differences in mean Hb and suggests a negligible variability between subjects in the magnitude of the response to treatment. This finding goes against a basic principle of normal biological variability.

3) In most groups the changes in performance in the four achievement tests from T1 to T2 to T3 are small. This lack of improvement goes against a common-sense assumption that the children must have learned "something" in school over the 6 mo of the study. In fact, if we assume that they did not, then we must also assume that iron status is a greater determinant of school achievement tests than school learning.

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