Once Weekly Is Superior to Daily Iron Supplementation on Height Gain but Not on Hematological Improvement among Schoolchildren in Thailand[1]

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ABSTRACT Intermittent iron supplementation has been suggested as a replacement for daily iron supplements for reducing anemia in developing countries. The effects of once weekly and daily iron supplementation on hemoglobin (Hb), serum ferritin (SF), prevalence of anemia, weight and height are compared in this study. Primary schoolchildren ($n = 397$) from two selected schools in the Hat Yai rural area, southern Thailand, were recruited in 1999. All children received Albendazole and then randomly received ferrous sulfate (300 mg/tablet) either daily or weekly, or a placebo for 16 wk. The average increase in Hb was not significantly different between the daily (mean $\pm$ SD; 6.5 $\pm$ 6.0 g/L) and weekly (5.7 $\pm$ 6.3 g/L) groups. However, the average increase in SF was greater ($P < 0.01$) in the daily (mean $\pm$ SD; 39.8 $\pm$ 30.3 μg/L) than the weekly (13.4 $\pm$ 17.3 μg/L) group. All cases of iron deficiency anemia were abolished in both daily and weekly groups, whereas no reduction in prevalence occurred in the placebo group. Height gain was greater in children who received weekly (mean $\pm$ SD; 2.6 $\pm$ 0.9 cm) than in those who received daily iron (mean $\pm$ SD; 2.3 $\pm$ 0.8 cm), ($P < 0.01$). Weight gain, weight-for-age and height-for-age were not significantly different among the intervention groups. It is concluded that a weekly iron dose is more effective than a daily dose in height gain but not in hematological improvement over 16 wk of supplementation. J. Nutr. 132: 418–422, 2002.

KEY WORDS: • *iron supplementation* • *iron status* • *growth* • *schoolchildren*

In children, the seriousness of iron deficiency anemia (IDA) arises from its consequences for health, including changes in immune function, growth and cognitive development (1–3). The WHO recommends large-scale programs of daily iron supplementation to reduce the prevalence of anemia in high risk areas (4). However, IDA remains common in many parts of the world, particularly among children in developing countries (5–7). Insufficient supply of iron tablets, low coverage of the target population and poor compliance with tablet intake are among the main reasons for the ineffectiveness of supplementation programs (8,9).

Administration of weekly iron as a replacement for the existing daily iron supplement programs has been discussed widely in developing countries (10–14) due to greater iron absorption in animal studies (15–17), fewer side effects in humans (15) and potentially greater cost-effectiveness. However, field studies have yielded controversial results. Several studies have reported comparable effects between intermittent and daily iron supplementation on improvement of iron status and growth among anemic young children and adolescents (10–12); however, a subsequent comparative study (13) showed significantly greater efficacy of daily over twice weekly iron supplementation in adolescents.

In Thailand, where the nature of anemia includes not only iron deficiency but also thalassemia (18,19), a once daily iron supplementation program has been carried out among anemic children since 1988, and a once weekly dose administered through a school-based program among primary schoolchildren will soon be implemented. It is essential to conduct a randomized controlled trial to assess the efficacy of once weekly iron supplementation before the large-scale program is launched. The main objective of this study was to compare the results of once weekly and daily iron supplementation on hemoglobin (Hb), serum ferritin (SF) and physical growth among primary schoolchildren in southern Thailand.

SUBJECTS AND METHODS

Study site and study subjects. Data collection was carried out from June to December 1999 in a socioeconomically disadvantaged community in Songkhla Province, southern Thailand. The two (public) schools were selected because they had at least 150 pupils with a high prevalence of underweight children according to previous school records, were accessible by automobile and had teachers who were willing to cooperate in the study. These two schools were located ~35 km from the research center and had a mixture of Buddhist and Muslim students. Family occupation was mainly as rubber plantation workers. This area was free from malaria and no previous large-scale program of iron supplementation had been implemented.

The sample size was calculated to provide a power of 95% in

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[3] Abbreviations used: Hb, hemoglobin; IDA, iron deficiency anemia; SF, serum ferritin.

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detecting a difference at $\alpha = 0.05$ between daily and weekly supplements, and between either of these iron doses and a placebo of 1 SD in the pre- to post-treatment measurements of iron status and growth. At least 62 subjects per group were required.

An invitation letter and consent form were sent to the parents whose children were in primary school. All subjects who received parental consent had their baseline data measured. We excluded those with severe malnutrition (weight for height ≤ 3rd percentile of the Thai reference), chronic illness such as obvious thalassemia or hemolytic disease, high iron storage (SF > 100 μg/L), physical handicaps or no baseline laboratory assessment. The children were stratified by anemic status to balance the proportion of anemic and nonanemic children across the intervention groups. Anemic children were defined as Hb < 115 g/L among children 5–11 y and Hb < 120 g/L among children 12–13 y. These cut-off levels are recommended by the WHO (20). The children were then assigned by simple random allocation within each stratum using a computer to daily or once weekly iron supplemented or placebo groups.

Measurement of variables. School, class, sex, age, ethnic group and socioeconomic status (parents' education, father's and mother's occupations and family monthly income) data were collected via a questionnaire completed by parents before the intervention started.

At baseline and the end of the study, weight and height were measured with subjects wearing school uniforms without belts and shoes and with empty pockets using a beam balance Detecto scale and stadiometer (Detecto Scales, Brooklyn, NY) to the nearest 0.1 kg and 0.5 cm, respectively.

Before supplementation, well-trained nurses drew a 5-mL blood specimen from the cubital vein. A 2-mL portion of the blood was transferred to an EDTA-prepared tube and then stored in an ice box for subsequent Hb determination, blood morphology examination and screening for thalassemia. The remaining 3 mL of the blood was kept in a sealed plastic test tube at ambient temperature for SF assessment.

Hb level was assessed with an automated machine (Technicon H*1E system, Tarrytown, NY) using the cyanmethemoglobin method (CV = 0.6–3.4%). The One Tube Osmotic Fragility Test combined with the Dichlorophenol Indophenol Precipitation Test was used to screen for potential thalassemic disease (19). Children with a positive One Tube Osmotic Fragility Test < 85% or Dichlorophenol Indophenol Precipitation Test had further examination of blood cell morphology by a hematologist and were excluded from the study if there was evidence of thalassemia or hemolytic diseases such as ovalocytosis, which is common in the study area (19,21). There was no attempt to exclude the thalassemia trait in this study. SF was assessed by the IMx assay (IMx Ferritin assay, Abbot Park, IL) using The Microparticle Enzyme Immunoassay method (CV = 4.4–6.4%). SF ≤ 20 μg/L was used to define anemia due to iron deficiency. At the end of intervention, a new 3-mL specimen of blood for Hb and SF testing was taken.

Intervention. All eligible children were given a single dose of 400 mg Albendazole at the beginning of the study and again 11 wk later to eliminate hookworm infection. Ferrous sulfate 300 mg tablets (60 mg elemental iron) (Government Pharmaceutical Organization, Bangkok, Thailand) were used in this study because these will be used in the real supplementation program. Placebo tablets, produced by the Faculty of Pharmacy, Prince of Songkla University, Thailand, were similar in color, shape, size and taste to the iron tablet. The tablets were placed in bottles, which were labeled only with the subject's name. Their content was unknown to any of the project personnel. Each child received 2 bottles. The first was to be taken on Monday only. The second was to be taken for the remaining days of the week. The daily group had iron in all the bottles, whereas the once weekly group had iron in the Monday bottle and placebo in the rest. The placebo group had placebo tablets in all of the bottles. After packing, the codes were kept secret throughout the supplementation process. All oral administrations were strictly observed by either the principal investigator or the research assistant on each school day to ensure that the tablets were swallowed.

Ethical consideration. The research proposal was approved by the Ethical Review Committee of Faculty of Medicine, Prince of Songkla University, Thailand. Children with severe IDA (Hb ≤ 80 g/L and SF ≤ 20 μg/L) were excluded from the study and treated immediately to prevent unnecessary delay. Children who had hemolytic disease or relatively high iron storage (SF >100 μg/L) were also excluded to prevent the risk of iron overload. Children who continued to have IDA at the end of the study received appropriate iron supplementation.

Data analysis. The balance of baseline measurements across the interventions was examined. The effects of iron supplementation were analyzed on an intention-to-treat basis. The change of Hb from pre- to post-treatment was examined and compared across the interventions using Student's paired *t* test and ANOVA with Bonferroni's multiple comparison tests. Due to a problem of nonnormal distribution with SF, nonparametric statistics were used in the comparison. The Wilcoxon signed-rank test was used to see the change of SF from pre- to postintervention and the Kruskal-Wallis test was used to compare the effect across interventions. Mann-Whitney tests were performed for multiple pair-wise comparisons only when the Kruskal-Wallis test suggested a significant difference of SF among interventions. The reduction in prevalence of IDA was also compared across the interventions by using the Z-test applied to the McNemar's χ-squares for each intervention.

Anthropometric indices used in assessing growth were weight gain, height gain, change in weight-for-age and change in height-for-age. Z-scores of weight-for-age and height-for-age were calculated using the National Center for Health Statistics growth references for weights and heights using the EPI INFO software, version 6 (Centers for Disease Control, Atlanta, GA). These constitute the international growth reference curves recommended by WHO. Anthropometric indices were compared across interventions using ANOVA. Weight and height gain were also adjusted for age using multivariate regression analysis.

RESULTS

Overall, 61% of the parents consented to the study, resulting in 462 study subjects; 65 of these children were excluded from the study before randomization due to thalassemic disease ($n = 3$), ovalocytosis ($n = 18$), high iron storage ($n = 6$), severe malnutrition ($n = 9$), severe IDA ($n = 1$), partial blindness ($n = 1$) or no baseline laboratory investigation ($n = 27$). The excluded and the remaining children were otherwise comparable in all sociodemographic characteristics.

Eventually, 397 primary schoolchildren, aged ranging from 6 to 13 y, participated in the study; of these, 140, 134 and 123 children were allocated to daily, weekly and placebo groups, respectively. Most of the children belonged to socioeconomically deprived families as indicated by low parental education and income. Approximately 80% of family monthly incomes were ≤5000 baht (125.00 US$) per month compared with the Thai national average of 12,729 baht (318.00 US$) for the same year reported by the Household Socioeconomic Survey, National Statistical Office. The prevalence of anemia was 27% but only 21.5% of these anemic children were iron deficient. Children from the two schools had similar distribution of the above-mentioned socioeconomic variables; thus, no stratification by school was used in the analysis. Baseline measurements were similarly distributed among intervention groups as summarized in **Table 1**.

Over the 16 wk of intervention, 93.8 and 93.5% children in the daily and weekly groups received iron tablets as planned. Six children ($n = 1$, 4 and 1 in the daily, weekly and placebo groups, respectively) moved to other schools out of the study site during the study period and were thus excluded from the analysis of outcome. Means of Hb, SF, weight and height increased significantly from pre- to postintervention measurements except SF in the placebo group. Means of Hb change in the daily and weekly supplemented groups were similar but both were greater than that in the placebo group ($P < 0.001$ and $P = 0.026$, respectively). The mean increase in SF con-

TABLE 1

Baseline variables of primary schoolchildren among intervention groups given 300-mg tablets of ferrous sulfate (daily or weekly) or a placebo for 16 wk[1,2]

Variables	Intervention		
	Daily	Weekly	Placebo
n	140	134	123
Hemoglobin, *g/L*	121.3 ± 10	121.2 ± 9	121.8 ± 10
Anemic, *n*	39	40	28
Nonanemic, *n*	101	94	95
Serum ferritin, *μg/L*	39.9 ± 20.4	39.9 ± 19.3	38.5 ± 19.3
Sex (male:female)	69:71	64:70	52:71
Age, *y*	9.6 ± 1.7	9.7 ± 1.9	9.7 ± 1.7
Ethnic group, *n*			
Thai-Buddhist	41	47	34
Thai-Muslim	99	86	89
Weight, *kg*	25.5 ± 7.1	26.3 ± 8.0	26.4 ± 6.5
Height, *cm*	126.7 ± 10.7	128.5 ± 10.9	127.4 ± 10.3
Father's occupation, *n*			
None	3	1	0
Casual/farmer/seller	130	122	112
Government/private	7	8	9
Mother's occupation, *n*			
None	2	4	7
Casual/farmer/seller	134	126	111
Government/private	3	1	5
Parents' education, *y*	6 ± 3	6 ± 3	6 ± 3
Family monthly income, *n*			
≤5000 baht[3]	114	108	93
>5000 baht	25	21	27

[1] Values are means ± SD or numbers of children.
[2] The numbers for some variables do not equal the column totals because of missing data.
[3] 1 baht = 0.025 U.S. $ at the time of data collection.

centration in the daily group was greater than that in the weekly group ($P < 0.001$), which in turn was greater than that in the placebo group ($P < 0.001$). All IDA children in the weekly and daily groups became nonanemic ($P = 0.001$ and 0.025, respectively), whereas only one of the six IDA children in the placebo group had improved SF but were still anemic, and two children in the placebo group developed IDA by the end of the study ($P = 0.56$). These reductions of IDA in the daily and weekly groups did not differ, but each was different from the placebo group ($P = 0.006$ and $P = 0.047$, respectively, **Table 2**). Weight gain, change of weight-for-age and change of height-for-age among intervention groups were not significantly different across the groups. The increase in height of children in the weekly group was greater than that in the other two groups, but the only significant difference was between the daily and the weekly groups ($P = 0.02$, **Table 3**). This significance of height gain difference persisted after adjustment for age.

TABLE 2

Change in hematological variables in each intervention group among schoolchildren given 300-mg tablets of ferrous sulfate (daily or weekly) or a placebo for 16 wk[1,2]

Variables	Intervention		
	Daily	Weekly	Placebo
n	138	130	121
Hemoglobin (Hb), *g/L*			
Before	121.3 ± 10	121.2 ± 9.1	121.8 ± 9.8
After	127.8 ± 9.2	126.9 ± 9.2	125.3 ± 9.3
Change	6.5 ± 6.0[a]	5.7 ± 6.3[a]	3.4 ± 5.5[b]
n	137	123	117
Serum ferritin (SF), *μg/L*			
Before	39.9 ± 20.5	40.6 ± 19.6	38.5 ± 19.4
After	79.7 ± 36.6	54.0 ± 24.2	37.4 ± 18.9
Change	39.8 ± 30.3[a]	13.4 ± 17.3[b]	−1.1 ± 17.1[c]
n	140	134	123
IDA,[3] *n*			
Before	11	6	6
After	0	0	7
Change	11[a]	6[a]	−1[b]

[1] Values are means ± SD. Means in a row without a common letter differ, $P < 0.05$.
[2] The numbers of children do not equal the total eligible subjects (see Table 1) because of missing data.
[3] IDA, iron deficiency anemia, is defined as Hb < 115 g/L and SF ≤ 20 μg/L for children <12 y old or Hb <120 g/L and SF ≤20 μg/L for children >12 y old.

DISCUSSION

In this supplementation experiment, in which iron was given to primary schoolchildren in southern Thailand for 16 wk, comparable effects between once weekly and daily supplementation were found in both change in Hb and reduction of the prevalence of IDA. The daily group had a significantly greater SF than the other two groups, but significantly lower height gain than the weekly group. Neither supplementation regimen showed an effect on weight gain, change in weight-for-age or change in height-for-age.

During the supplementation period, the mean Hb improvement seen in the placebo group may have been due to various

TABLE 3

Change in growth variables in each intervention group among schoolchildren given 300-mg tablets of ferrous sulfate (daily or weekly) or a placebo for 16 wk[1,2]

	Intervention		
Variables	Daily	Weekly	Placebo
n	139	129	122
Weight, *kg*			
Before	25.5 ± 7.1	26.4 ± 8.0	25.4 ± 6.5
After	26.8 ± 7.8	27.8 ± 8.5	26.9 ± 7.2
Change	1.3 ± 1.6	1.4 ± 1.6	1.5 ± 1.6
Height, *cm*			
Before	126.6 ± 10.7	128.6 ± 10.8	127.4 ± 10.3
After	128.9 ± 10.8	131.2 ± 10.8	129.8 ± 10.2
Change	2.3 ± 0.8[b]	2.6 ± 0.9[a]	2.4 ± 0.9[ab]
Weight-for-age, *Z-score*			
Before	−1.30 ± 0.9	−1.25 ± 1.0	−1.32 ± 0.9
After	−1.32 ± 0.9	−1.27 ± 1.0	−1.34 ± 0.9
Change	−0.02 ± 0.30	−0.02 ± 0.20	−0.02 ± 0.20
Height-for-age, *Z-score*			
Before	−1.55 ± 0.9	−1.44 ± 1.0	−1.54 ± 0.9
After	−1.62 ± 0.9	−1.47 ± 1.0	−1.59 ± 0.9
Change	−0.07 ± 0.14	−0.03 ± 0.15	−0.05 ± 0.15

1 Values are means ± SD. Means in a row without a common letter differ, $P < 0.05$.

2 The numbers of children do not equal the total eligible subjects (see Table 1) because of missing data.

causes such as deworming, shift in age among children or some unknown effect of the follow-up. After allowing for the placebo effect, the net gain of Hb in the daily and weekly groups was 3.1 and 2.3 g/L, respectively, in 16 wk. The poor response to iron supplementation in these subjects may be attributable to the low prevalence of IDA or to the thalassemia trait, which exists in the southern Thai population (19).

Our study was confined to 16 wk of supplementation. However, the real supplementation program will be implemented year round. The findings that the daily dose yielded a higher SF than the weekly dose may simply reflect a slower increase of SF. Prolonged weekly dosing may eventually lead to adequate saturation of iron in blood and in tissue.

To our knowledge, only two previous studies (13,14) have assessed intermittent iron supplementation as a blanket supplementation, that is, including both anemic and nonanemic subjects as in our study. A study of weekly iron supplementation among Tanzanian adolescents (14) found a significantly greater increase in serum ferritin compared with a vitamin B-12 control group, but there was no significant difference in change in Hb. However, a study in Peru (13) found that a 17-wk daily supplementation led to significantly higher Hb increases than twice weekly supplementation; however, SF and free erythrocyte protoporphyrin were similar in the two groups. It is possible that the 60 mg iron/d given to adolescents whose average weight was almost 50 kg may be too small a dose to improve Hb and correct anemia in the intermittent schedule; the actual values of SF were not shown in that paper.

Our study found no significant difference in weight gain, change of weight-for-age, or change of height-for-age among weekly, daily and placebo groups, but a significantly greater height gain among children receiving once weekly iron supplementation than that in the daily group. The patterns of height gain and change of height-for-age were consistent (i.e., worst in the daily group and best in the weekly group), but a significant difference was detected only in height gain. The lack of significance in height-for-age may be due to the lower precision of this variable. Almost 50% of our subjects had a height exceeding the limit for calculation of weight-for-height; thus, we omitted this anthropometric index.

Studies regarding the effects of daily iron deficiency upon growth have shown inconsistent results. Studies in India, Kenya and Indonesia found an improvement in growth after iron supplementation (22–25). Improved appetite and decreased morbidity were the explanations given in those studies for enhanced growth after iron supplementation. Studies in Mexico, Bangladesh and Thailand, however, reported no benefit of iron supplementation on growth (26–28). One proposed explanation is that deficiency of multiple micronutrients such as zinc and vitamin A could have limited the growth response to iron (27). Furthermore, a report of the adverse effect of iron on weight gain in children with adequate iron status has raised concerns among public health researchers about giving supplemental iron to children (29).

We could find only one previous study comparing weekly iron supplementation with daily dosing on growth. This study on Indonesian primary schoolchildren (10) reported no significant differences in increases of weight-for-age, weight-for-height or height-for-age after 3 mo of weekly and daily iron supplementation among anemic schoolchildren.

Using subjects in a different age group, a study among Tanzanian adolescent girls comparing weekly iron supplementation and a vitamin B-12 control group reported a significantly greater weight gain in the weekly iron supplemented group than in the vitamin B-12 control group after 4 mo of supplementation (14).

Iron intake in our study was observed closely, and >90% of children received complete iron supplementation. Thus, the lack of significant difference in some of the outcome measurements among the groups cannot be explained by low compliance.

The immediate goal of the iron supplementation program in Thailand is to reduce the prevalence of anemia and increase tissue iron concentration, on the assumption that this will improve the health and performance of the children. Our data suggest that the goal of iron saturation is better achieved with daily rather than weekly supplementation but the potential adverse effect on growth (height gain) should be taken into consideration.

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