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Weekly iron supplementation is as effective as 5 day per week iron supplementation in Bolivian school children living at high altitude

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Objective: To compare the efficacy of a daily and a weekly iron supplementation on the hematological status of anemic children living at high altitude.
Design: Double blind iron supplementation trial including a placebo control group.
Setting: A socioeconomically disadvantaged district of La Paz, Bolivia (altitude of 4000 m).
Subjects: Anemic (hemoglobin concentration ≤ 144 g/L), 3.3–8.3 y old children of both sexes.
Intervention: Children received a placebo ($n=57$) or a dose of 3–4 mg of elemental iron per kg body weight (FeSO4 tablets) 1 d per week ($n=58$) or 5 d per week ($n=58$) for 16 weeks.
Results: Hemoglobin and zinc erythrocyte protoporphyrin concentrations improved significantly in supplemented groups but not in the placebo group. Changes in hemoglobin during the study were not significantly different between supplemented groups (weekly group: 15.2 ± 6.9 g/L and daily group: 18.6 ± 11.1 g/L) but were different from the placebo group (0.5 ± 7.1 g/L, $P < 0.001$). At the end of the supplementation period, the hemoglobin distribution was Gaussian, and similar in both supplemented groups. Adjusting for the initial hemoglobin concentration, final hemoglobin and its changes were similar in both supplemented groups.
Conclusion: Weekly iron supplementation is as efficacious as daily iron supplementation in improving iron status and correcting moderate iron deficiency anemia in Bolivian school children living at high altitude.
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Descriptors: anemia; iron; weekly supplementation; school children; altitude

Introduction

Iron deficiency anemia is a major health problem worldwide especially in developing countries where two billion individuals are concerned (CIN, 1992). Iron deficiency anemia is particularly prevalent among infants and children. A recent study conducted in Bolivia shows a prevalence ranging from 22.4–70.0% in a population of 0.5–9 y old children, living in the bolivian altiplano (Berger, 1996). Therefore the implementation of controlling strategies is urgent because of the negative consequences of iron deficiency anemia on many body systems and functions, including child development: disturbed behaviour (Johnson *et al*, 1992), impaired psychomotor development (Walter *et al*, 1983; Pollitt *et al*, 1986; Lozoff *et al*, 1991) and decreased growth rate (Fairweather-Tait, 1992; Angeles *et al*, 1993).

Iron supplementation has proven to be a useful strategy to produce a rapid improvement of the iron status of individuals when the iron deficit is important and has to be corrected rapidly (Hercberg, 1988; Horn, 1988). Short term iron supplementation can also reduce the prevalence of iron deficiency anemia in a population (Dawson *et al*, 1989; Angeles *et al*, 1993; Schultink *et al*, 1993).

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In terms of public health, daily iron supplementation is the most frequent strategy to control iron deficiency. Several short-term studies in children show a significant improvement of the hemoglobin concentration in response to daily iron supplements (Aukett *et al*, 1986; Chwang *et al*, 1988; Mejia & Chew, 1988; Latham *et al*, 1990).

The effectiveness of antenatal supplementation is not always satisfactory because of factors related to the available iron supplements in the poorest countries (United Nations, 1991; Stephenson, 1995), the motivation of the target population (Paita *et al*, 1987; WHO, 1992) and the lack of compliance due in part to side effects (Chareoenlarp & Dhanamitta, 1988; Schultink *et al*, 1993; Liu *et al*, 1995a).

Recent studies in animal models show that the intermittent administration of iron has a similar (Wright & Southon, 1990) or better effect (Viteri, 1995) on the iron status than the daily iron supplementation. This may be explained by the time needed for the turnover of intestinal cells (Fairweather-Tait *et al*, 1985; Viteri, 1995).

These results have prompted their authors to encourage intermittent iron supplementation trials in humans with the idea that an intermittent iron supplementation could have as similar an effect on the hematological status as the daily iron supplementation, reducing the side effects (Viteri *et al*, 1994) and the interaction of a daily iron dose with the absorption of other nutrients (Solomons, 1986).

A study conducted in China with preschool children

shows that the administration of twice-weekly or weekly iron doses are as effective as daily supplementation with the benefit of markedly reduced incidence of side effects (Liu *et al*, 1995b). Another study conducted on young Indonesian children show that a twice-weekly dose has as similar an effect as a daily dose (Schultink *et al*, 1995). A study on anemic women (Gross *et al*, 1994) and two studies on pregnant women (Ridwan *et al*, 1996; Liu *et al*, 1995b) also show similar results. WHO (1993) has promoted field studies in different environmental settings and in different population groups in order to evaluate the efficacy of intermittent iron supplementation as a general strategy.

The goal of this study was to compare the efficacy of a daily and a weekly iron supplementation on the hematological status of anemic Bolivian school children living at high altitude (4000 m above sea level).

Subjects and methods

The study was carried out between March and November 1995 in a socioeconomically disadvantaged district of La Paz, Bolivia, located at an altitude of 4000 m above sea level.

Subjects

Subjects were healthy children of both sexes, aged 3.3–8.3 y, attending the schools administered by the Non-Governmental Organization 'Fe y Alegria'. Sample size calculation indicated that at least 49 children were required in order to distinguish a difference in hemoglobin equal to or greater than 10 g/L between groups with a significance level of 5% and a 95% power. Because of anticipated dropouts, the sample size was established to be 59 subjects per group.

The inclusion criterion was a hemoglobin concentration equal to or lower than 144 g/L. A recent study conducted by our team on children living at high altitude (Berger, 1996) allowed us to define the hemoglobin cut-off value of 144 g/L for the diagnosis of anemia for children of this age living at 4000 m. The study was approved by the Technical Committee of the Instituto Boliviano de Biologia de Altura (IBBA); only children with parent's consent were included in the study.

Out of 260 children measured, 176 (67.7%) had a hemoglobin concentration ≤ 144 g/L. These 176 children were randomly assigned to three groups:

(1) Control group (58 children) received a placebo, once a week, every Tuesday;
(2) Group 1 (59 children) received a dose or iron, once a week, every Tuesday;
(3) Group 2 (59 children) received a daily dose of iron, 5 d per week, Monday to Friday.

Thus, in each week, and over the course of the study, the children of Group 1 received one-fifth the total dose received by those of Group 2.

Supplementation

According to previous studies (Margolis *et al*, 1981; Paiti *et al*, 1987), the iron dose was calculated to provide between 3–4 mg of iron per k of body weight to the children of both supplemented groups. The supplement consisted of two types of tablets of similar size and aspect, made mainly of lactose, containing either 20 mg or 36 mg of elemental iron in form of FeSO4 (IFA Laboratories, Santa Cruz, Bolivia) used in combination to adjust the dose for the child's weight. The placebo consisted of same tablets without iron. The tablets were given to children at school, with clean boiled water, at mid-morning (one and a half hours after breakfast and one and a half hours before lunch), by trained school assistants, under the supervision of a member of the research team.

Methods

Hemoglobin concentration (Hb) and zinc erythrocyte protoporphyrin (ZPP) were determined in finger-prick blood in all children. Hemoglobin concentration was measured using a Hemoglobin Photometer HemoCue (HemoCue AB, Angelholm, Sweden) and the zinc erythrocyte protoporphyrin using a hematofluorometer (AVIV Biomedical, model 206). Hemoglobin screening was performed at the beginning of the study (T0), tablet administration for selected children started the following day. Hemoglobin concentration was determined again 5 weeks (T5), 10 weeks (T10) and 16 weeks (T16) after the beginning of the study whereas the zinc erythrocyte protoporphyrin concentration was determined only at T0 and T16. At the end of the study, all children still anemic were supplemented. Iron supplements were given to the mothers taught to give the supplement to their children 5 d per week, Monday to Friday.

Standard anthropometric assessment was performed by a trained member of the team both at T0 and T16. Body height was expressed as mean of three consecutive measures taken with a precision of 1 mm by using an accurate handcrafted microtoise. Body weight was measured to the nearest 0.2 kg with an electronic scale (TEFAL, France). The anthropometric indicators, weight-for-age, height-for-age and weight-for-height were expressed in Z scores according to the National Center for Health Statistics (NCHS) reference using EPI-INFO 6.0 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA).

Statistical analysis

The statistical analysis of data sets was performed using STATISTIX 4.1 (Analytical software, PO Box 12185, Tallahassee, FL, USA), and SAS (SAS Institute, Cary, N.C., USA). Data analysis included descriptive statistics, Pearson correlations, paired t-test, and analysis of variance with the Scheffe's multiple comparison test. Analysis of covariance was also used to adjust comparison of the three experimental groups for initial values of hemoglobin.

Results

The sample size and composition by sex in each group are presented in Table 1. A complete data set was obtained for 57 children of the control group and 58 children for both groups 1 and 2. Children were 3.3–8.3 y old but 96.3% of them were between 4.0–6.9 y old. Only 3 children (1 boy and 2 girls) dropped out during the study, one in each group (initial hemoglobin: 135, 136, 143 g/L respectively for the children from the placebo group, group 1 and group 2). Dropouts were due to migration of the family out of the area of study. At the beginning of the study, mean age, sex distribution, and nutritional and hematological status were not statistically different among the three groups (Table 1).

Table 1 Hematologic and anthropometric values at the beginning of the study[a]

	Control group (n=58)[c]	*Group 1 (n=59)*	*Group 2 (n=59)*	P^b
Girls (%)	52.6	48.3	53.4	0.94
Boys (%)	47.4	51.7	46.6	0.94
Age (months)	67.2±9.3	67.8±7.6	69.6±12.2	0.40
Age groups (%)				
40–47 months	3.5	1.7	1.7	0.77
48–59 months	14.0	15.5	19.0	0.82
60–71 months	49.1	55.2	50.0	0.92
72–83 months	33.3	25.9	19.0	0.40
≥ 84 months	0	1.7	10.3	0.12
Hemoglobin (g/L)	131.6±11.4	135.3±8.6	131.5±12.6	0.11[e]
ZPP[d] (μg/g Hb)	4.54±1.74	4.12±1.00	4.80±1.67	0.06[e]
Height (cm)	105.1±5.5	105.8±4.7	105.9±5.6	0.66
Weight (kg)	17.94±2.10	17.93±1.95	18.33±2.6	0.56
Height-for-Age (*Z* score)	−1.61±0.92	−1.54±0.89	−1.65±0.80	0.81
Weight-for-Height (*Z* score)	0.51±0.74	0.38±0.71	0.55±0.79	0.46

[a]Mean±s.d. Group 1 was supplemented once weekly and group 2, five days per week.
[b]*P*: difference between groups, One-way ANOVA or *chi*-square test.
[c]By the end of the study only one child in each group had dropped out. Total number at beginning of study: 176 children.
[d]ZPP: zinc erythrocyte protoporphyrin.
[e]Non parametric Krukal-Wallis test Hb, $P=0.09$; ZPP, $P=0.08$.

Table 2 presents the evolution of the hematological values during the study. At the end of the supplementation period (T16), the hemoglobin concentration in both supplemented groups was significantly higher than in the control group whereas no significant difference was detected between the two groups receiving either the weekly or the 5 d per week supplementation. The mean zinc erythrocyte protoporphyrin (ZPP) concentrations were not different between both supplemented groups but significantly lower than in the control group. Anthropometrical indicators were not statistically different among the three groups (*Z* scores: Height-for-age: −1.54±0.89, −1.46±0.89, −1.57±0.78 s.d. and weight-for-height: 0.62±0.77, 0.44±0.80, 0.57±0.88 respectively for the control group, group 1 and group 2).

Between T0 and T16 the hemoglobin concentration increased 15.2±6.9 g/L ($P<0.0001$) in group 1 and 18.6±11.1 g/L ($P<0.001$) in group 2. The control group increased only 0.5±7.1 g/L ($P=0.56$). Neither mean hemoglobin concentrations nor hemoglobin increments were statistically different between groups 1 and 2 at the four phases of the supplementation period. They differed from the placebo group as early as the 5th week of supplementation.

Between T0 and T16 the mean concentrations of ZPP decreased in group 1 (−0.25±1.07 μg/g Hb, $P=0.08$) and in group 2 (−0.74±1.37 μg/g Hb, $P=0.001$) whereas ZPP did not change significantly in the control group (0.10±1.43 μg/g Hb, $P=0.60$).

Even though children were allocated randomly to the three groups, the proportion of children with lower hemoglobin values was higher in the group receiving the supplementation 5 d per week. Figure 1 shows the changes in hemoglobin according to three classes of initial hemoglobin concentration; class (1) Hb < 125 g/L, class (2) 125 ≤ Hb < 135 g/L and class (3) 135 ≤ Hb < 144 g/L. In class 1 the increase of hemoglobin during the supplementation period was 23.9±8.4 g.L in the weekly group ($n=8$) and 37.0±12.3 g/L ($n=9$) in the 5 d per week group ($P<0.05$). In class 2 the changes in hemoglobin were 18.6±5.3 g/L in the weekly group ($n=8$) and 18.5±6.6 g/L in the 5 d per week group ($n=22$) and in class 3, 12.9±5.2 g/L ($n=42$) *vs* 12.6±5.9 g/L ($n=27$). The mean hemoglobin at T0 in children in class 1 was

Table 2 Variation of hematological values during the study period[a]

Groups	*Control*	*Group 1*	*Group 2*	P^b
Hemoglobin (g/L)				
T0	131.6±11.4a	135.3±8.6a	131.5±12.6a	0.11
T5	131.0±10.0a	142.6±9.1b	142.8±9.8b	<0.0001
T10	131.5±8.4a	146.6±9.6b	148.2±8.2b	<0.001
T16	132.2±8.1a	150.5±6.9b	150.1±6.7b	<0.001
Changes in hemoglobin (g/L)				
between T0-T5	−0.7±6.4a	7.3±8.3b	11.3±10.6b	<0.001
between T5-T10	0.5±6.7a	4.0±8.9ab	5.7±8.3b	<0.01
between T10-T16	0.7±6.1a	3.9±6.5b	1.7±6.5ab	0.03
between T0-T16	0.5±7.1a	15.2±6.9b	18.6±11.1b	<0.001
Zinc Protoporphyrin (μg/g Hb)				
T0	4.54±1.74a	4.12±1.00a	4.80±1.67a	0.06
T16	4.64±1.30a	3.87±0.80b	4.06±1.03b	0.02
Changes in zinc protoporphyrin (μg/g Hb)				
between TO-T16	0.10±1.43a	−0.25±1.07ab	−0.74±1.38b	0.003

[a]Mean±s.d. Group 1 was supplemented once weekly and group 2, five days per week.
[b]*P*: difference between groups, One-way ANOVA + Scheffe's test: different when letters differ.

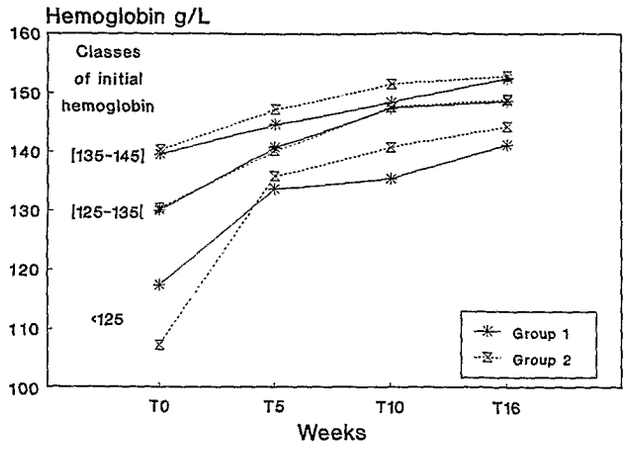

Figure 1 Changes in hemoglobin concentration according to initial hemoglobin concentration. Group 1 was supplemented once weekly and Group 2, five days per week. No difference between groups (One-way ANOVA).

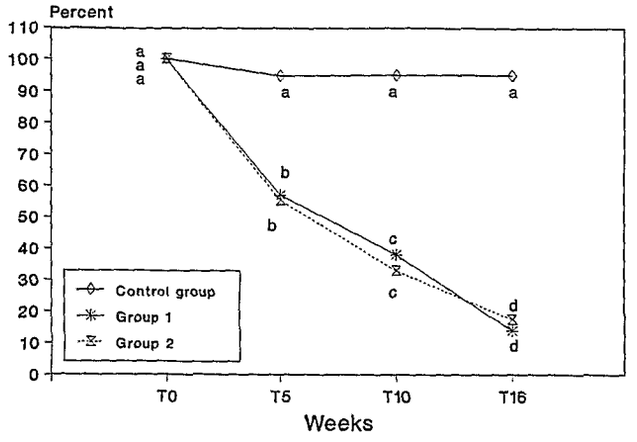

Figure 2 Prevalence of anemia. Group 1 was supplemented once weekly and Group 2, five days per week. Difference between groups and within groups was tested by Chi-square test. Significance difference when letter differ.

lower in the 5 d per week than in the weekly group ($P=0.052$).

Changes in hemoglobin and in ZPP were correlated with the initial hemoglobin concentration (Hb: $r=-0.79$, $P<0.0001$; ZPP: $r=+0.38$, $P<0.0001$). Therefore the initial hemoglobin concentration had to be taken into consideration. After adjustment for the initial hemoglobin concentration by including it as a covariate in the analysis of covariance, the adjusted means for the hemoglobin concentration at the end of the supplementation period were 132.6 g/L for the control group, 149.5 g/L for the weekly iron group and 150.7 g/L for the 5 d per week iron group. The hemoglobin concentration was not statistically different between group 1 and 2 and lower in the control group ($P<0.05$). Similar results were obtained when initial ZPP concentration was included as a covariate. At T16, both hemoglobin distribution of supplemented groups fell within a normal Gaussian distribution (Wilk-Shapiro test: 0.95 for group 1 and 0.98 for group 2). These results indicate that the effect of the weekly iron supplementation was identical to the effect of the 5 d per week iron supplementation.

During the 16 weeks of the supplementation period the number of iron doses given were 16 for group 1 and 76 for group 2 (4 non-consecutive days of holidays without iron supplementation). Group 1 took on average 99.1% of the dose; 100% of the children received more than 80% of the dose. Group 2 took on average 92.2% of the dose; 96.6% received more than 80% of the dose.

At the beginning of the study all children were anemic according to the cut-off value of 144 g/L relevant for the altitude of the study (4000 m). Figure 2 shows that at the end of the supplementation period the proportion of anemic children decreased to 13.8% in group 1 and to 17.3% in group 2 ($\chi^2=0.26$, $P=0.61$ between groups). In contrast, 94.7% of children from the control group were still anemic at the end of the study.

At the end of the supplementation period, the proportion of children whose increase in hemoglobin concentration was equal to or higher than 10 g/L was 84.5% in the weekly group and 86.2% in the 5 d per week group. The corresponding proportion in the control group was 7.0%. Whereas no children of the experimental groups showed a decrease in hemoglobin concentration, 49.1% of the control group did.

Discussion

The proportion of anemia among the children of the three schools included in the study, defined by a cut-off value of 144 g/L to take into account the altitude of the study setting, namely 4000 m (Berger, 1996) was 67.7%. This high proportion may be related to the fact that the study took place in one of the poorest districts of La Paz, where most inhabitants are migrants who have left the surrounding rural areas of La Paz and come to the city looking for better living conditions. A socioeconomic survey conducted within the study families revealed that the economic resources, parental education level, and living and employment conditions of the majority of households were very unsatisfactory.

The hematological status of both supplemented (5 d or 1 d per week) groups improved significantly whereas it did not change in the control group. This shows the positive effect of both types of iron supplementation. The increase of hemoglobin concentration (adjusted for initial hemoglobin concentration) observed in both supplemented groups was in the range of the increases of hemoglobin obtained in other studies providing daily comparable iron doses to anemic children (Aukett *et al*, 1986; Chwang *et al*, 1988; Mejia & Chew, 1988).

The changes of hemoglobin and ZPP between the beginning and the end of the supplementation period were not significantly different between both supplemented groups. However the decrease in ZPP reached statistical significance with the control group only in the 5 d per week group. The decrements in ZPP in both supplemented groups suggests an improvement of the iron status of children receiving the iron supplementation either weekly or 5 d per week but not in the control group.

The rate of change in hemoglobin (Figure 1) show that, as expected, the greatest change is observed among the most anemic children and in the first five weeks of supplementation. This strongly suggests that the main cause of the low hemoglobin levels is iron deficiency. By the 16th week of supplementation the more anemic children were still increasing their hemoglobin levels, suggesting that a longer period of supplementation could be beneficial. The Gaussian distribution of final hemoglobin, together with the high proportion of children responding by 10 g/L

or greater, considered as a positive response to the supplementation (Hercberg & Galán, 1985; Estrella *et al*, 1987), and the significant decrease of ZPP concentration in both supplemented groups also strongly suggest that the etiology of anemia was iron deficiency. At first sight, the 5 d per week supplementation seemed to be more efficient than the weekly supplementation in improving iron status and to also have a more rapid effect on the hemoglobin increase. However, while not significantly different, the mean initial hemoglobin concentration was lower in the 5 d per week group compared to the weekly group.

When controlling for the initial hemoglobin concentration by covariance analysis, the 5 d per week and the weekly supplementation had the same effect on the increase of hemoglobin concentration. Furthermore, the final hemoglobin concentration of both supplemented groups were not significantly different, being expressed in mean or adjusted mean hemoglobin concentration. The final distribution of hemoglobin reached a normal Gaussian distribution in the two supplemented groups. The same results apply to changes in ZPP.

These results from a population of Bolivian school children living at high altitude are consistent with results of the study of Liu *et al* (1995b) in a 3–6 y old Chinese children and with the study of Schultink *et al* (1995) in a 2–5 y old Indonesian children.

Compared to the study conducted in Indonesia, our results are even more conclusive because the Indonesian children were dewormed prior to the supplementation and there was no control group; therefore, changes in hemoglobin concentration could be due in part to deworming. In this Indonesian study the iron supplementation lasted only eight weeks and the changes in hemoglobin concentration were 7 g/L for the group receiving a twice-weekly supplementation of 30 mg iron namely 2.2–4 mg per kg body weight. In Liu's study, changes in the twice-weekly supplementation were 31.8 g/L after three months of supplementation and 26.7 g/L for the weekly group with a dose of iron per kg of body weight, approximately two times the dose used in Bolivian and Indonesian children.

While a close comparison between the three studies is not feasible due to differences in iron dose, duration of the supplementation period, initial hemoglobin level and environmental settings, the findings from these three studies agree on the similar efficacy of an intermittent iron supplementation and a daily iron supplementation.

In our study, the choice to compare the weekly supplementation to the 5 d per week supplementation instead of a daily supplementation, was made in order to use the real school conditions in the Bolivian school milieu. The distribution of tablets by the school members, during school days was well accepted by the children and was conducted without disturbing normal school life.

One of the objectives of an iron supplementation is to reduce the prevalence of anemia (Dawson *et al*, 1989; Angeles *et al*, 1993). The definition of anemia for the Bolivian children living at 4000 m was based on the cut-off value of 144 g/L defined in a previous study conducted by our team on Bolivian children (Berger, 1996), a cut-off value similar to the one proposed by Yip (1993). All children were anemic at the beginning of the study. After 16 weeks of iron supplementation, 86.2% of the children receiving the weekly supplementation and 82.7% of the group receiving the 5 d per week supplementation became non-anemic whereas only 5.4% of the control group were non-anemic at the end of the supplementation period.

The strategy of long term weekly supplementation in preschool and school children should lead, primarily, to the prevention of iron deficiency (and correction of those deficient) including the progressive accumulation of adequate iron reserves which will insure protection from iron deficiency later in life, during adolescence and in the case of women, during their reproductive life. The study of Liu *et al* (1995b) shows the safety and excellent tolerance of the weekly dose. Studies where weekly supplements are given throughout the school year should be carried out to evaluate the rate of accretion of iron reserves.

Conclusions

The results of our study are therefore conclusive about the equivalent efficacy of the once-weekly and the five-day per week iron supplementation schedules and are in agreement with other studies realized in very different environments. These findings could lead to a revision of iron supplementation strategies for the prevention and control of iron deficiency and anemia if the global effectiveness of such a strategy is proven: compliance by children and cooperation of school staff and/or community members in practical field conditions under the supervision of national and local health authorities.

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