WEEKLY AS EFFECTIVE AS DAILY IRON SUPPLEMENTATION TO CONTROL IRON DEFIENCY ANEMIA IN CHILDREN LIVING AT HIGH ALTITUDE

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INTRODUCTION

Iron deficiency anemia is particularly prevalent among infants and children of the Bolivian altiplano, ranging from 22.4 to 70.0 % in 0.5-9 year-old children and may have negative consequences on many body systems and functions, including child development.

The effectiveness of iron supplementation is not always satisfactory because of factors related to the available iron supplements in the poorest countries, the motivation of the target population and the lack of compliance due in part to side effects.

Recent studies in animal models show that the intermittent administration of iron has a similar16 or better effect on the iron status than the daily iron supplementation. This may be explained by the time needed for the turnover of intestinal cells.

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. Another study conducted in young Indonesian children show that a twice-weekly dose has as similar an effect as a daily dose. A study on anemic women, and two studies on pregnant women, also show similar results.

However, despite these first attractive results, the efficacy of weekly and intermittent iron supplementation needs to be confirm in more studies conducted in different settings and vulnerable groups.

OBJECTIVE

The goal of this study was to compare the efficacy of a weekly and a 5-day per week iron supplementation on the hematological status of anemic Bolivian school children living at high altitude (4000 m above sea level).

SETTING

Socioeconomically disadvantaged district of La Paz, Bolivia, located at an altitude of 4000 m above sea level.

SUBJECTS

Inclusion criteria:
- schoolchildren of both sexes
- hemoglobin concentration < 144g/L. (taking in account the altitude of 4000 m of the setting).
- parent's consent.

Sample size: 59 children
- difference in hemoglobin between groups > 10 g/L
- significance level of 5% and a 95% power
- 20 % anticipated dropouts

The children were randomly assigned to three groups:
- Control group (58 children) received a placebo once a week, every Tuesday
- Group 1 (59 children) received a dose of iron once a week, every Tuesday
- Group 2 (59 children) received a daily dose of iron 5 days per week, Monday to Friday.

Thus, Group 1 received one-fifth the total dose received by those of Group 2.

Anthropometric values at the beginning of the study[1]

Table 1

	Control groupe (n=58)3	Group 1 (n=59)	Group 2 (n=59)	p2
Age (months)	87.2 ± 8.3	87.8 ± 7.6	89.8 ± 12.2	0.40
Height (cm)	105.1 ± 5.5	105.8 ± 4.7	105.9 ± 5.6	0.66
Weight (kg)	17.84 ± 2.10	17.83 ± 1.95	18.33 ± 2.8	0.58
Height-for-Age (Z-s)	-1.61 ± 0.92	-1.54 ± 0.69	-1.65 ± 0.80	0.81
Weight-for-Height (Z-s)	0.51 ± 0.74	0.39 ± 0.71	0.55 ± 0.79	0.45

[1] Mean ± SD. Group 1 was supplemented once weekly and group 2, five days per week
[2] p: difference between groups, One-way ANOVA

SUPPLEMENTATION

- Iron dose: 3 to 4 mg of iron per kilogram of body weight
- supplement: FeSO4 tablets.
- placebo: tablets of identical aspect without iron.
- distribution: at school, with clean boiled water, at mid-morning between breakfast and lunch, by trained school assistants, under supervision.

METHODS

Hemoglobin: at the beginning of the study (T0) and again 5 weeks (T5), 10 weeks (T10) and 16 weeks (T16) after.
Zinc erythrocyte protoporphyrin: at T0 and T16.
- blood finger-prick.
- hemoglobin concentration: HemoCue (HemoCue AB, Angelholm, Sweden).
- zinc erythrocyte protoporphyrin: hematofluorometer (AVIV Biomedical, model 206).

Anthropometric assessment : at T0 and T16.
- body height: microtoise, precision of 1 mm.
- body weight: electronic scale, precisionof 0.2 Kg.
- anthropometric indices : weight-for-age, height-for-age, weight-for-height (Z scores, NCHS reference).

The study was approved by the Technical Committee of the Instituto Boliviano de Biologia de Altura.

RESULTS

At the begining of the study (T0)

* Children were 3.3 to 8.3 years old (96.3% between 4.0 to 6.9 y. old)
* Mean age, sex distribution, nutritional and hematological status were not statistically different among the three groups (table 1).
* All children were anemic according to the cut-off value of 144 g/L relevant for the altitude of the study (4000 m).

At the end of supplementation period (T16)

* Only 3 children (1 boy and 2 girls) dropped out.
* Final hemoglobin concentration was significantly higher in both supplemented groups than in the control group and no significant difference between the two groups receiving the iron supplementation. The hemoglobin concentration increased 15.2 ± 6.9 g/L (p<0.0001) in group 1, 18.6 ± 11. 1 g/L (p<0.000 1) in group 2 and 0. 5 ± 7.1 g/L (p=0.56) in control group (table 2).

Table 2
Variation of hemoglobin concentration during the study period [1]

	Control	Group 1	Group 2	p [2]
	Hemoglobin (g / L)			
T0	131.6 ± 11.4 a	135.3 ± 8.6 a	131.5 ± 12.6 a	0.11[4]
T5	131.0 ± 10.0 a[3]	142.6 ± 9.1 b	142.8 ± 9.8 b	<0.0001
T10	131.5 ± 8.4 a	146.6 ± 9.6 b	148.4 ± 8.2 b	<0.001
T16	132.2 ± 8.1 a	150.5 ± 6.9 b	150.1 ± 6.7 b	<0.001
	Changes in hemoglobin (g / L)			
Between T0-T5	-0.7 ± 6.4 a	7.3 ± 8.3 b	11.3 ± 10.6 b	<0.001
Between T5-T10	0.5 ± 6.7 a	4.0 ± 8.9 ab	5.7 ± 8.3 b	<0.01
Between T10-T16	0.7 ± 6.1 a	3.9 ± 6.5 b	1.7 ± 6.5 ab	0.03
Between T0-T16	0.5 ± 7.1 a	15.2 ± 6.9 b	18.6 ± 11.1 b	<0.001

[1] Mean ± SD, Group 1 was supplemented once weekly and group 2, five days per week
[2] p: difference between groups, One-way ANOVA + Scheffe's test
[3] significantly different when letters differ
[4] Non parametric Kruskal-Wallis test, p=0.09

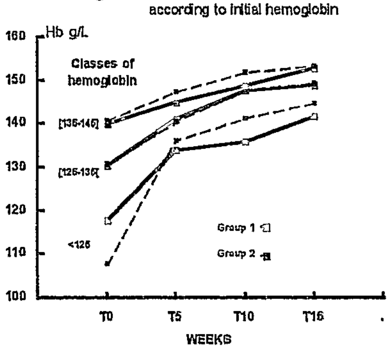
* Greatest changes in hemoglobin were observed among the most anemic children and in the first 5 weeks of supplementation (table 3, figure 1).

Table 3
Hemoglobin increments according to initial hemoglobin concentration[1]

Initial Hemoglobin (g/L)	Hemoglobin increment (g/L) Control group	Group 1	Group 2
<125	9.3 ± 9.2 a	23.9 ± 8.4 b	37.0 ± 12.3 c
[125-135[	-1.04 ± 4.5 a	18.6 ± 5.3 b	18.5 ± 6.6 b
[135-145[	-1.96 ± 4.6	12.9 ± 5.2 b	12.6 ± 5.9 b

[1] Mean ± SD. Group 1 was supplemented once weekly and group 2, five days per week
[2] p: difference between groups, One-way ANOVA + Scheffe's test, p<0.05
[3] significantly different when letters differ

Figure 1: VARIATION OF HEMOGLOBIN according to initial hemoglobin



When controlling for the initial hemoglobin concentration by covariance analysis the 5-day per week and the weekly supplementation had the same effect on the increase of hemoglobin (adjusted means: 132.6 g/L for the control group, 149.5 g/L for the weekly group and 150.7 g/L for the daily group). Similar results were obtained when initial ZPP concentration or iron dose were included as a covariate.

* Hemoglobin distributions of supplemented groups fell within a normal Gaussian distribution (Wilk-Shapiro test: 0.95 for group 1 and 0.98 for group 2).
* Neither mean hemoglobin concentrations nor hemoglobin increments were statistically different between groups 1 and 2 at the four time points of the supplementation period. They differed from the placebo group as early as the 5th week of supplementation (table 2, figure 2).
* 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 (figure 1).
* Mean zinc erythrocyte protoprophyrin (ZPP) concentrations were not different between both supplemented groups but significantly lower than in the control group (table 4).
* The mean concentrations of ZPP decreased in group 1 (-0.25 ± 1.07 æg/g Hb, p=0.08) and in group 2 (-0.74 ± 1.38 æg/g Hb, p=0.001) whereas ZPP did not change significantly in the control group (0. 10 ± 1.43 æg/g Hb, p=0.60) (table 4).
* Proportion of anemic children decreased of 86.2 % in group 1, of 82.7 % in group 2 and of only 5.3 % in control group (figure 3).
* Proportion of children whose increase in hemoglobin concentration was equal to or higher than 10g/L was 84.5% in group 1, 86.2 % in group 2 and 7.0% in the control group.
* Anthropometrical indices were not statistically different among the three groups.

Figure 2 :HEMOGLOBIN INCREMENTS

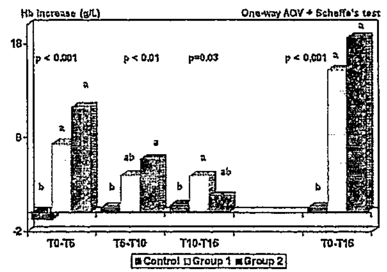
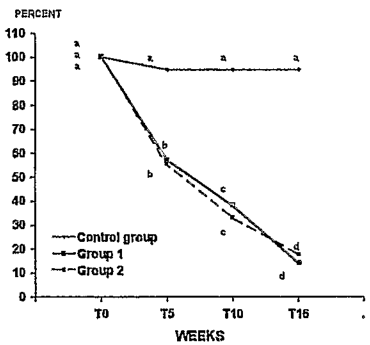


Table 4
Variation of erythrocyte protoporphyrin values during the study period

	Control	Group 1	Group	p
	Zinc Protoprophyrin (µg/g Hb)			
T0	4.64 ± 1.74 a	4.12 ± 1.00 a	4.50 ± 1.67 a	0.06
T10	4.04 ± 1.30 a	3.67 ± 0.90 b	4.06 ± 1.03 b	0.02
	Changes in zinc protoporphyrin (µg/g Hb)			
Between T0-T10	0.10 ± 1.43 a	-0.25 ± 1.07 ab	-0.74 ± 1.30 b	0.003

[1] Mean ± SD. Group 1 was supplemented once weekly and group 2, five days per week
[2] p. difference between groups, One-way ANOVA + Scheffe's test
[3] significantly different when letters differ
[4] Non parametric Kruskal-Wallis test, p=0.08

Figure 3:PREVALENCE OF ANEMIA



CONCLUSION

The rate of change in hemoglobin higher among the most anemic children and in the first 5 weeks of supplementation, the Gaussian distribution of final hemoglobin, the high proportion of children responding by 10g/L or greater, considered as a positive response to the supplementation and the significant decrease of ZPP concentration in both supplemented groups suggest that the main cause of the low hemoglobin levels in Bolivian children was iron deficiency.

This study indicates the equivalent efficacy of the once-weekly and the five-day per week iron supplementation schedules in Bolivian children living at high altitude.

This study is 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 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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