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ORIGINAL ARTICLE

Impact of weekly treatment with ferrous sulfate on hemoglobin level, morbidity and nutritional status of anemic infants

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Abstract

Objective: To evaluate the impact of weekly treatment with ferrous sulfate on hemoglobin level, morbidity and nutritional status in a sample of anemic infants from Zona da Mata Meridional in the state of Pernambuco, Brazil.

Methods: A controlled, community-based intervention was carried out with 378 infants who were followed-up for 18 months. Hemoglobin level was measured at 12 months in a total of 245 children randomly selected. Participating infants were divided into three groups: two received 45 mg of elemental iron weekly, from 12 to 18 months of life (69 children with moderate/severe anemia, and 111 with mild anemia); the third group was composed of 65 non-anemic children, who received no intervention. The remaining 133 children constituted the control group, for comparisons on nutritional status and morbidity.

Results: The prevalence of anemia was 73.5% at 12 months of life. After 6 months of treatment, 42.3% of anemic children reached hemoglobin levels ≥ 11.0 g/dL. The mean increase was 1.6 g/dL, being higher (2.5 g/dL) in the group with lower levels of hemoglobin at baseline. Children without anemia at baseline received no treatment, and 40.3% of them became anemic at the end of follow-up, with a mean decrease of 0.5 g/dL in hemoglobin levels. A significantly greater weight gain was observed in the two treated groups, while no significant improvements were seen in linear growth and duration of diarrhea.

Conclusions: The fact that less than half the children receiving ferrous sulfate recovered from anemia at the end of follow-up, along with the development of anemia in many untreated, previously non-anemic infants, suggests the need for effective control strategies.

J Pediatr (Rio J). 2006;82(6):452-7: Anemia, hemoglobin level, iron, weekly treatment, infant.

Introduction

Currently, iron deficiency anemia is considered one of the main public health problems worldwide, affecting people in almost every country, including developed nations, where more than 2 billion suffer from iron deficiency. The prevalence of anemia remains high and has even progressed over the years, influencing morbidity and mortality rates, ability to perform physical labor and child development. Anemia affects mainly infants from 4 to 24 months, school age children, teenagers, pregnant, and breastfeeding women.[1]

In Brazil, studies carried out over the last decades have shown a significant increase in the prevalence and severity of iron deficiency anemia in at-risk groups, in all parts of the country, regardless of socioeconomic status, with greater impact on children under 2 years of age.[2-5]

The public health approach to the treatment of anemia supports the use of iron salts, preferably by oral route, since these are low cost and rapidly absorbed drugs. Nevertheless, at population level, conventional treatment with daily doses has a limited impact on the prevalence of anemia (around 50%), and side effects lead to low maternal adherence to treatment.[6]

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New perspectives in the management of iron deficiency anemia include the prescription of weekly doses, in order to minimize possible side effects of treatment and increase maternal adherence. There is an ongoing debate on the effectiveness of the conventional model as the only valid alternative for facing the problem at population level.[7-13]

Considering the magnitude of iron deficiency anemia in the state of Pernambuco, Brazil,[4] the present study aims at assessing the impact of treatment with ferrous sulfate, administered on a weekly basis to anemic infants from 12 to 18 months of life, on the level of hemoglobin (Hb), morbidity, and nutritional status.

Methods

A controlled, community-based intervention was carried out in a sample of 378 infants, recruited between January and October, 1998, who were followed-up from birth to 18 months of life. All infants were from one of four urban areas (Palmares, Catende, Joaquim Nabuco, and Água Preta), situated in the Zona da Mata Meridional, part of the state of Pernambuco, northeast Brazil.

Children were recruited from six maternities located in the above mentioned towns, which respond for approximately 90% of deliveries in the area. Inclusion criterion was the intention to remain living in the community for at least 18 months following birth; exclusion criteria were multiple gestation, congenital anomalies, neurological problems, and/or need of intensive care in the immediate post-partum period.

Sample size was determined based on data from previous studies on the prevalence of anemia in regional urban areas of the state of Pernambuco,[4] using a test to compare two means. The sample was calculated assuming a mean Hb level of 9.4 g/dL (standard deviation or SD = 1.6 g/dL) for infants, and estimating an increase of 1.0 g/dL after 6 months of iron supplementation. Assuming a power of 0.90 and a significance level of 0.05, the minimum sample size was estimated in 54 subjects in each group.

From the 378 children included in the cohort, 245 were drawn for Hb measurement (study group); the remaining 133 constituted the control group for comparison of nutritional state and morbidity (Hb was not measured in this group). Therefore, 245 infants were divided into three study groups: two received treatment (69 infants with moderate/sever anemia – Hb < 9.0 g/dL, and 111 infants with mild anemia – Hb between 9.0 and 10.9 g/dL), while the third group, composed of 65 non-anemic children (Hb ≥ 11.0 g/dL), received no intervention. A total of 35 children (9.35%) were lost to follow-up after 6 months, distributed as follows: six (8.7%) in the moderate/severe anemia group; 11 (9.9%) in the mild anemia group; eight (12.3%) in the non-anemic, untreated, group; and 10 (7.5%) in the control group. Classification of anemia was based on criteria defined by the World Health Organization (WHO).[14]

Hb levels were measured at 12 and 18 months, through capillary blood samples, collected at home by a trained technician, using HemoCue. Children who presented Hb levels < 11.0 g/dL were treated with 45 mg of elemental iron, administered by the research assistants in the presence of the mother and/or guardian, in weekly doses, for 6 months. Children who remained anemic by the end of the study period received enough ferrous sulfate to last for the next three months, and mothers were encouraged to take their children to a local health care unit.

Weight and length were measured at 12 and 18 months, at the child's home, by two specially trained anthropometrists, using standardized techniques and equipments, in accordance with procedures established by the WHO.[15] For weight measurements, 10 and 25 kg scales (models MP10 and MP25, CMS Ltd., London) were used, with a precision of 10 g. Length was measured using a wooden anthropometer with a range of 0 to 130 cm in 0.1 cm increments. To reassure the quality of the data collected, the two research assistants independently checked 10% of the weight and length measurements throughout the study period. No systematic interrater differences were found (reproducibility coefficient = 0.96). Nutritional status was evaluated by weight/age, length/age, and weight/length relationships, which were expressed by mean z score, using the standard of reference set by the National Center for Health Statistics (NCHS).[15]

Occurrence and duration of diarrhea were reported by the mothers during home visits made by one of the 15 interviewers of the research team; these visits took place twice a week during the first 12 months and weekly from 12 to 18 months.

Two research supervisors monitored daily the quality of the information collected, which was analyzed in weekly meetings with the whole field staff. Data collected were codified and registered in specific forms and, after being reviewed, were double entered in a database built with Epi-Info, version 6.04 (CDC, Atlanta). Statistical analyses were performed with SPSS, version 8.0 for Windows (SPSS Inc., Chicago, USA). Paired *t* test, Wilcoxon test and medians were used to evaluate the impact of the intervention, assuming a significance level of 5%.

The research was approved by the Ethics Research Committee of the Centro de Ciências da Saúde from Universidade Federal de Pernambuco. In case any morbidity was observed, criteria were adopted for directing cases for medical assistance.

Results

A high prevalence (73.5%) of Hb levels < 11.0 g/dL was found among the 245 infants evaluated at 12 months of life. Among these, 28.2% had moderate/severe anemia. The mean Hb level for the entire sample was 9.8 g/dL (SD = 1.6 g/dL). Analysis of nutritional status, determined by mean z score for weight/age, length/age, and weight/length relationships, indicated that, at 12 months, there were no statistically significant differences between study and control groups. In regard to diarrhea, a median of 7 days was found for both groups (quartiles 1-3 = 2-17 and 2-15 days, respectively) from birth to 12 months, without statistically significant difference.

Throughout the 6 months of investigation, 25 children (10.2%) in the study group and 10 (7.5%) in the control group were lost to follow-up, because of family relocation to other geographic areas. Thus, a total of 220 children had their Hb levels measured at 12 months and later completed the study: 63 in the moderate/severe anemia group, 100 in the mild anemia group, and 57 in the non-anemic, untreated, group. Characteristics of children who were lost to follow-up did not differ from those who completed treatment in terms of morbidity and nutritional status.

Results presented in Table 1 refer to the 220 infants whose hemoglobin levels were measured both at 12 and 18 months. For anemic children treated with ferrous sulfate, mean Hb increase was 1.6 g/dL, with 42.3% reaching values ≥ 11.0 g/dL. The percentage of children with moderate/severe anemia at baseline who remained in this group by the end of the study period was 14.3%; 57.1% and 28.6% evolved to Hb levels between 9.0-10.9 g/dL and ≥ 11.0 g/dL, respectively, with mean Hb increase of 2.5 g/dL ($p < 0.001$). In the group of children with mild anemia at baseline, mean Hb increase was 1.1 g/dL ($p < 0.001$). Among non-anemic, untreated, children levels of Hb decreased by 0.5 g/dL by the end of the follow-up period ($p = 0.009$). In this group, 40.3% of the infants became anemic, with 33.3% showing Hb levels between 9.0-10.9 g/dL and 7% with Hb < 9.0 g/dL.

Possible side effects, mentioned by 12 mothers (5.5%), included diarrhea, nausea, vomiting and, in only one case, superficial teeth staining. All of these children were seen by a pediatrician, and maternal consent was obtained prior to continuing the treatment.

Table 2 presents weight/age, length/age, and weight/length relationships at 12 and 18 months of life, in mean z scores, for the 123 infants in the control group and the 220 in the study groups. At 18 months, an increase in the weight/age relationship was seen in the study groups, while no difference was observed in the control group. Mean z scores did not differ between groups for length/age and weight/length relationships.

The median duration of diarrhea, in days (Table 3), showed a statistically significant difference from 12 to 18 months of life when compared to the previous period

Table 1 - Mean and percentages of hemoglobin in treated and untreated groups at 12 and 18 months of life

Groups			Hemoglobin level (g/dL)		
		Mean (SD)	< 9.0 (%)	9.0 - 10.9 (%)	≥ 11.0 (%)
Moderate/severe anemia treated	12 m	7.7 (1.0)	100.0	0.0	0.0
(n = 63)	18 m	10.2 (1.3)	14.3	57.1	28.6
	Dif.	2.5 *	–	–	–
Mild anemia treated	12 m	10.0 (0.6)	0.0	100.0	0.0
(n = 100)	18 m	11.1 (1.2)	5.0	44.0	51.0
	Dif.	1.1 *	–	–	–
Anemia treated	12 m	9.1 (1.3)	38.7	61.3	0.0
(n = 163)	18 m	10.7 (1.3)	8.6	49.1	42.3
	Dif.	1.6 *	–	–	–
Non–anemic, untreated	12 m	11.7 (0.6)	0.0	0.0	100.0
(n = 57)	18 m	11.2 (1.4)	7.0	33.3	59.7
	Dif.	−0.5 †	–	–	–

Dif. = difference; SD = standard deviation; m = months.
* $p < 0.001$ (paired *t* test).
† $p = 0.009$.

(0-11 months), both for anemic children and those in the control group (p < 0.001). The median in the non-anemic, untreated, group was similar in both periods, from birth to 11 months and from 12 to 18 months. However, the median number of days with diarrhea in groups with and without anemia prior to intervention showed an inverse correlation, with lower Hb levels being associated with greater duration of the diarrhea (p = 0.04).

Discussion

The present study indicated a prevalence of anemia of 73.5% in infants at 12 months, with mean Hb levels of 9.8 g/dL (SD = 1.6 g/dL). The study also showed that 28.2% of infants have Hb levels < 9.0 g/dL. These results are in accordance with a 1997 study carried out in the state of Pernambuco that demonstrated a prevalence of anemia of 62% in children from 6 to 23 months of age.[4] These numbers are also compatible with those found in a sample representative of Brazilian northeast population, which showed a prevalence of anemia of 82.8% for infants at 12 months of life (± 2 months), with mean Hb levels of 9.38 g/dL (SD = 1.6 g/dL).[1] These findings highlight the magnitude of the problem of iron deficiency anemia in Pernambuco and northeast Brazil.

Since 2000, the Brazilian Ministry of Health has been implementing and supporting a program to prevent iron deficiency in high risk groups (children from 6 to 18 months of life) by offering weekly iron supplementation. Nevertheless, the weekly strategy, which is part of the

Table 2 - Nutritional status of children in treated and untreated groups at 12 and 18 months of life

Nutritional status (z score)		Control (n = 123)*	Treated		Untreated
			Moderate/severe anemia (n = 63)	Mild anemia (n = 100)	No anemia (n = 57)
Weight/age					
Mean (SD)	12 m	-0.32 (1.2)	-0.36 (1.3)	-0.32 (1.1)	-0.20 (1.0)
	18 m	-0.36 (1.2)	-0.18 (1.2)	-0.19 (1.1)	-0.09 (1.0)
	p *	0.41	0.002	0.003	0.09
Length/age					
Mean (SD)	12 m	-0.70 (1.1)	-0.75 (1.1)	-0.55 (1.0)	-0.31 (0.9)
	18 m	-0.67 (1.1)	-0.72 (1.2)	-0.49 (0.9)	-0.27 (1.0)
	p *	0.56	0.58	0.21	0.49
Weight/length					
Mean (SD)	12 m	0.16 (1.0)	0.29 (1.0)	0.14 (1.0)	0.10 (1.1)
	18 m	0.17 (1.0)	0.30 (1.0)	0.12 (1.0)	0.10 (1.0)
	p *	0.76	0.78	0.70	0.99

SD = standard deviation; m = months.
* Paired *t* test.

Table 3 - Median of days with diarrhea in treated and untreated groups during the first 18 months of life

Diarrhea (days)	Age (months)	Control (n = 123)*	Treated			Untreated
			Anemia (n = 163)	Moderate/severe anemia (n = 63)	Mild anemia (n = 100)	No anemia (n = 57)
Md (Q1-Q3)	0 - 11	7 (2-16)	8 (2-18)	10 (2-22)†	8 (2-17)†	4 (2-11)†
	12 - 18	3 (0-10)	5 (0-11)	5 (2-14)	4 (0-9)	4 (1-7)
p		< 0.001*	< 0.001*	0.06*	0.01*	0.24*

Md = median; Q1-Q3 = quartile 25 and 75.
* Wilcoxon test.
† Median test (p = 0.04).

Community Health Worker Program, still causes some controversy regarding its efficacy and efficiency.[9] This scenario has motivated the development of the interventional program here presented, in which ferrous sulfate was administered during 6 months, in weekly doses, under the supervision of research assistants, for a group of infants who were anemic at 12 months of life.

Regarding the efficacy of the current intervention, results indicated a mean increase in Hb levels of 1.6 g/dL. In the city of São Paulo, the efficacy of weekly iron supplementation for 6 months was four times lower, increasing mean Hb levels by only 0.4 g/dL. This can be explained by the fact that children with low adherence to the intervention were not excluded from the analysis in that study. Additionally, the population investigated in that study had a prevalence of anemia of approximately 50%, which may also help to explain such results.[16]

When groups were analyzed based on the severity of anemia, a higher increase in mean Hb levels (of approximately 2.6 g/dL) was seen in children with more significant baseline deficits (Hb < 9.0 g/dL). These findings are in accordance with previous studies that demonstrated greater iron absorption in the intestinal lumen of subjects with more significant deficits.[17] For children with mild anemia, mean Hb increase was 1.1 g/dL. For this group, false-positive and false-negative results may have occurred, especially because Hb levels were used as the only marker for anemia; if this was true, the efficacy of iron supplementation may have been underestimated.[18,19] In regard to the prevalence of anemia, a recovery to Hb levels ≥ 11.0 g/dL was seen in 28.6% of children with moderate/severe anemia, and in 51% of the children with mild anemia at baseline.

The absence of a placebo group, due to ethical reasons, was a limitation of the present study, which has restricted the possibility of assessing the effect of regression to the mean. Such effect was evidenced by the analysis of the non-anemic, untreated, group, which showed a 0.5 g/dL mean reduction in Hb levels during follow-up, with 40% of subjects reaching Hb levels < 11.0 g/dL. Therefore, the impact of treatment may not have been a direct consequence of the intervention. The development of anemia and/or reduction in Hb levels during the study period in non-anemic children suggests the need for preventive iron supplementation in this risk group.

In this study, possible side effects most frequently included diarrhea, nausea, and vomiting, which were observed in 5.5% of children. Similar findings were described for Vietnamese children receiving iron supplementation once or twice a week who showed a 0 and 8% prevalence of side effects, respectively, contrasting with the 35% prevalence of side effects in children who received daily supplementation.[8]

On the issue of a possible impact of iron supplementation on nutritional status, only the weight/age relationship had a significant increase in children who received ferrous sulfate, an effect that was not observed in the control group. Data from the literature indicate similar results in developed[20,21] and developing[22-24] countries, where anemic children receiving iron supplementation and/or treatment show a significant improvement in body weight. Only two of these studies[22,23] evaluated gains in length, one of them showing a positive effect.[22] The brief course of iron supplementation may help explain its inconsistent impact on linear growth.

Recently a randomized, placebo-controlled interventional study with elemental iron was carried out in Sweden and Honduras, involving children from 4 to 9 months. In the study, children received half the daily dose recommended by the WHO for infants (6-24 months). Results indicated a reduction of 0.4 cm in mean length gain when compared to placebo.[13] However, other researches have not found a statistically significant association between Hb levels and nutritional status.[25,26] Most of these studies are designed to evaluate only improvements in Hb levels and, therefore, do not allow time to observe variations on nutritional status in terms of linear growth and weight gain.

Morbidity due to diarrhea was similar for intervention and control groups. Both groups showed a reduction in the duration of diarrhea (in days) in both periods analyzed, before (0-11 months) and during the intervention (12-18 months), suggesting that supplementation of ferrous sulfate has no impact on diarrhea. Absence of a placebo group may have limited a more conclusive analysis of this issue, as well as the natural course of diarrhea, which becomes less prevalent as the child grows. It is important, however, to highlight the inverse correlation observed between Hb level and morbidity due to diarrhea, as the median duration was 10 days for children in the moderate/sever anemia group and 4 days in the non-anemic group.

Predisposition for development of anemia after an acute infection is high, varying according to the duration and severity of the disease.[27] Childhood infections, which occur at least once in approximately 60% of children from 9 to 12 months of life, are clearly associated with low Hb levels. These association is even higher in the presence of persistent or recurrent infections, especially diarrhea, combined with a reduction in the amount of iron in the diet of children in this age group.[28] A recent report by the WHO[28] indicates that patients with moderate/severe iron deficiency anemia show a higher prevalence of infections, due to the adverse effects of iron deficiency on the immune system.

The results obtained in this study, with recovery to normal Hb levels in less than half of children with mild anemia and in only 28.6% of children with moderate/

severe anemia, suggest the need to consider other drug intervention strategies for controlling anemia, also highlighting the need of a more unified approach, such as nutritional education and improved diet quality for children. In this context, breastfeeding must be encouraged, as well as diet fortification and infection control, especially for infants from low socioeconomic backgrounds.

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