Original Research Article

Weekly iron supplementation in 2-year-olds is effective in combating anemia

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ABSTRACT

Introduction: Iron deficiency anemia is a serious public health problem in developing countries, especially among children, as it is associated with serious developmental problems. **Objective:** To assess the effects of weekly ferrous sulfate supplementation on hemoglobin (Hb) levels and the prevalence of anemia in children aged 2 to 3 years. **Methods:** A cluster randomized clinical trial was conducted, two schools were randomly chosen, in the first school the children received 6mg/kg of elemental iron in the form of iron sulfate once a week (intervention), in the other school the children received placebo (control). The intervention group had 44 participants at the end of the study and the control group had 48 children. Blood samples were taken at baseline and at the end of the study to assess serum Hb levels and anemia prevalence. The intervention lasted 14 weeks. **Results:** There was a mean increase in Hb of 0.85g/dL (p=0.0003) in the intervention group and a decrease of 0.74g/dL (p=0.0001) in the control group. The prevalence of anemia significantly decreased in the weekly supplementation group with p=0.0002. **Conclusion:** Weekly iron supplementation in preschool-age children promoted a significant increase in Hb levels and a decrease in the prevalence of anemia.

Keywords: Iron-deficiency anemia; Hemoglobins; Ferrous sulfate; Preschool child; Clinical trial.

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1. INTRODUCTION

The World Health Organization (WHO) defines the term anemia as a condition in which the serum concentration of hemoglobin is below the reference values, to the point of not meeting the physiological needs according to age, sex, pregnancy and altitude (1). Within of the causes of anemia, approximately 50% are attributed to a diet deficient in iron, which is considered the most prevalent nutritional deficiency in the world, affecting mainly children under 5 years of age (preschoolers), women of childbearing age, pregnant and lactating women, in greater numbers in developing countries (2,3).

Iron is the most found metal in the human body, playing a crucial role in all phases of protein synthesis, cellular respiration, oxidative and immunological processes (4,5,6). Iron deficiency is associated with bone fragility and distortions, hepatosplenomegaly (possibly from extramedullary hematopoiesis), delayed growth and puberty, neurodevelopmental changes, cardiomegaly, and electrocardiographic abnormalities (7). A recent study associated iron deficiency in childhood and adolescence with the increased prevalence of Attention Deficit Hyperactivity Disorder (ADHD), Anxiety Disorder and Bipolar Mood Disorder, highlighting the long-term importance of iron deprivation (8).

In this sense, one of the strategies recommended by the WHO to control iron deficiency is the use of weekly (intermittent) supplementation for risk groups, infants and preschoolers, which worldwide have a prevalence of anemia close to 40% (9,10). Our study

used weekly iron supplementation in public schools as a strategy to try to improve children's hematimetric levels without the need for family adherence, since it is often difficult to understand how important iron is for the homeostasis and development of these children.

2. METHODOLOGY

2.1. Study design

To address the research purpose, the authors designed and implemented a cluster randomized clinical trial study. The study sample was derived from the population of preschoolers aged between 24 and 36 months, from public Infant Education Centers, in the municipality of Sobral - Ceará, a middle-sized city, in the northeast of Brazil, between August and December 2019.

Prior to intervention, three public Infant Education Centers were chosen using a table of randomized numbers; the first formed Group A, the second Group B. Group A received 6 mg/kg of elemental iron once weekly (intervention); and Group B was designated as control.

All preschoolers aged 24 to 36 months from the two Infant Education Centers were invited to participate in our study. Exclusion criteria were parents' refusal to participate and infants already using iron supplementation.

2.2. Intervention

The preschoolers in Group A received 6 mg/kg elemental iron once weekly (Mondays); intervention was administered using an individual plastic medical syringe with scale, previously prepared according to child's weight, to gently squirt the solution into the side of the child's mouth by graduate medical trainees. Intervention lasted 14 weeks, beginning and ending on the same date for all groups.

2.3. Primary outcomes and other variables

The study included 2 primary outcome variables: 1) change in Hb concentration measured in g/dL; and 2) anemia prevalence before and after intervention. Hb concentration <11.0g/dL was used as cutoff point to define anemia (10).

According to information provided by parents, a standardized data sheet was filled in containing information on (other study variables): age, gender, exclusive breastfeeding (EBF) up to 6 months, mother's schooling, and family income.

2.4. Sample size

According to previous studies conducted in this region anemia prevalence in the study population was estimated at 40-50% (11). To achieve a reduction in global anemia prevalence from 50 to 25%, with 80% power, 2-sided, type I error of 5 %, accounting for 10% losses to follow-up, each group required a minimum of 43 participants (12).

2.5. Data collection

Two biochemical evaluations were performed, to determine Hb concentrations, before and after intervention. Hb concentrations were promptly analyzed with a portable HemoCue B-hemoglobin photometer (Hb 301 - HemoCue AB, Ängelholm, Sweden) by technician. Finger prick capillary blood was collected under aseptic conditions using Carelet® Safety Lancets (Facet Technologies, Atlanta, GA, USA). Members of the study team who collected outcome data were blinded to the different interventions.

2.6. Data analyses

To compare means we used, the paired student's t-test to assess the difference in Hb concentration before and after intervention within the groups, and Fisher's exact test to assess the difference between good and bad outcomes (absence or presence of anemia).

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Data had normal distribution. The statistical software package SPSS for Windows, version 17.0, was used for all analyses (SPSS Inc., Chicago, IL). The limit for statistical significance was set at p=0.05. Analyses were by intention to treat.

This study was approved by the Ethics Committee for Research at the Universidade Federal do Ceará following the ethical principles established by the National Health Council Resolution #466/2012, with necessary prior written consent from school directors and parents/guardians. Medical support was available upon request. After intervention, anemic children were referred for treatment.

3. RESULTS

At baseline, 14 preschoolers were excluded before blood analysis, nine from group A (3 refused and 6 already using iron supplementation), and five from group B (3 refused and 2 already using iron supplementation) (Figure 1).

Before the second biochemical evaluation (at the end of the intervention), there were 10 dropouts from Group A (5 left Infant Education Center, 2 absentee, 3 non-compliant); in Group B there were 11 dropouts (7 left Infant Education Center, 2 absentee, 2 non-compliant) (Figure 1).

At baseline, Hb concentration and the other study variables were analyzed. There were no statistically significant differences for age, gender, EBF, mother's schooling, and family income. Mean age (in months) for group A was 29.9±3.51for group A, and 30.4±3.36 for group B, p= .30; in group A, 27 participants were male and 27 were female, in group B 28 were male and 31were female, p= .96. The p-values between groups for EBF, mother's schooling and family income were .96, and .90, respectively. However, there was a significant difference between the groups for mean Hb values; mean Hb for group A was 11.34±1.31 for group A, and 11.88±0.78 g/dL for group B, p= .003 (Table 1).

In Group A, mean baseline Hb concentration was 11.19±1.42 g/dL, and after intervention mean Hb concentration increased to 12.04±0.96 g/dL, p= .0003; and anemia prevalence was 20 out of 44, 45.5% at baseline, and 4 out of 44 (9.1%) at the end of the study, p= .0002. In the control group (Group B), mean baseline Hb concentration was 11.85±0.86 g/dL, and after intervention mean Hb concentration decreased to 11.11±0.87 g/dL, p< .0001; and anemia prevalence was 8 out of 48, 16.7% at baseline, increasing to 12 out of 48, 25.0% at the end of the study, without statistical difference, p= .452. (Table 2).

When considering alterations in mean Hb concentrations, there was an increase in mean Hb values for Group A (0.85±1.42); however, Group B registered a reduction in mean Hb concentration (-0.74±0.96), p< .0001 (Table 3).

When considering only the anemic participants, in Group A (n=20), mean Hb concentration was 9.82±0.60 at baseline and 11.58±0.45 after intervention, p< .0001; at baseline 20 participants were anemic; however, after intervention this number reduced to 4, p< .0001. In the control group (Group B), mean Hb concentration was 10.78±0.14 g/dL at baseline, decreasing to 10.60±1.27 after intervention, without statistical significance, p= .077. Intervention group presented an increase in mean Hb concentration, 1.76±0.85 g/dL, while the control group (Group B) presented a slight decrease in mean Hb concentration, p= .677. (Table 3).

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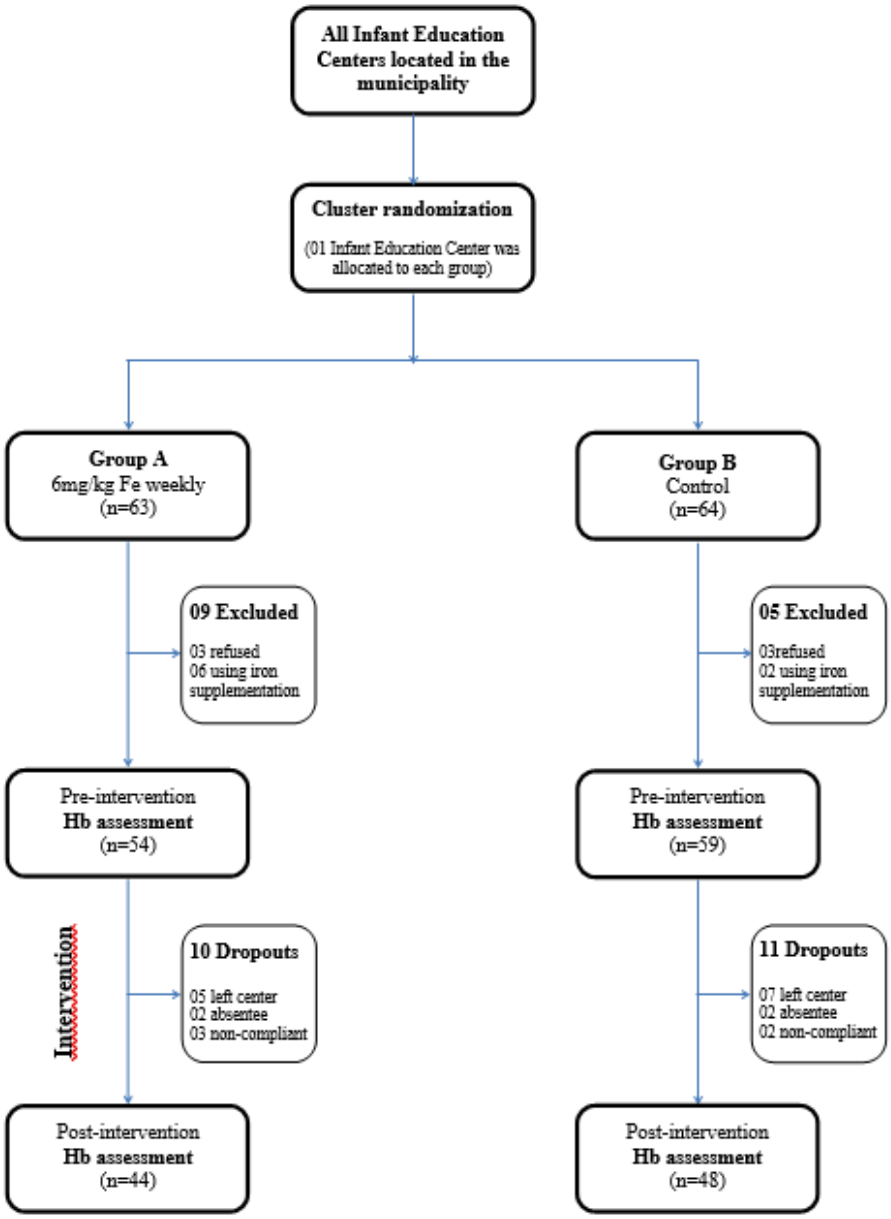

Figure 1. Flow chart of study design

In this study the following indicators were compared: intervention group A versus control, for a favorable or adverse outcome (absence of anemia versus anemia). At the endpoint, adverse outcome was present in 100% of control subjects and 20% (group A) of experimental subjects. The difference, the Reduction of Absolute Risk (RAR), was 80% for group A . The 95% confidence interval for this difference ranged from 62.5 to 97.5% (group A). Relative Risk (RR) was 0.36 for weekly supplementation group. The Number Needed to Treat (NNT) was 2 for group A. This means that one in every 2 preschoolers in the intervention group benefited from the intervention. The 95% confidence interval for the NNT ranged from 1.0 to 1.6 (group A).

Table 1. Baseline characteristics of study participants, by intervention group and control

Variables	**Group A** (n=54) *Weekly iron*	**Group B (**n=59) *Control*	p-value[a]
Age (months) *Mean±SD*	29.9±3.51	30.4±3.36	.30[a]
Hemoglobin (g/dL)	11.34±1.31	11.88±0.78	**.003[a]**
Gender M:F	27:27	28:31	.96[b]
EBF	25	24	.46[b]
Mother with ≥9y schooling	22	23	.96[b]
Family income ≥300USD	23	25	.90[b]

All numbers are absolute; SD standard deviation; M:F male:female; EBF exclusively breastfed up to 6 months of age; [a] Based on unpaired Student's *t*-tests; [b] Based on Fisher's exact test (2-tailed).

Table 2. Effects weekly iron supplementation and control on hemoglobin levels, and anemia prevalence before and after intervention.

	Group A (n=44) *Weekly iron*			**Group B** (n=48) *Control*		
Variables	Before	After	*p*	Before	After	*p*
Hb (g/dL) *Mean±SD*	11.19±1.42	12.04±0.96	**.0003**[a]	11.85±0.86	11.11±0.87	**<.0001**[a]
CI	10.76, 11.62	11.75, 12.33		11.60, 12.10	10.85, 11.36	
Mean increase in Hb *Mean±SD*		0.85±1.42			-0.74±0.96	**<.0001**[a]
CI		0.413, 1.278			-1.020, -0.463	
Anemia[b]	20 (45.5)	4 (9.1)	**.0002**[c]	8 (16.7)	12 (25.0)	.452[c]

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All numbers are absolute except numbers in brackets, which represent percentages; Hb Hemoglobin; SD standard deviation; CI 95% Confidence interval; [a] Based on paired Student's *t*-tests; [b] Anemia defined as Hb concentration <11.0 g/dL; [c] Based on Fisher's exact test (2-tailed).

Table 3. Effects of weekly iron supplementation and control on hemoglobin levels, and anemia prevalence for anemic preschoolers, before and after intervention.

	Group A (n=20)			**Group B** (n=8)		
	Weekly iron			*Control*		
Variables	Before	After	*p*	Before	After	*p*
Hb (g/dL) *Mean±SD*	9.82±0.60	11.58±0.45	**<.0001**[a]	10.78±0.14	10.60±1.27	.677[a]
CI	9.58, 10.06	11.34, 11.82		10.09, 11.46	9.91, 11.29	
Mean increase in Hb *Mean±SD*		1.76±0.85			-0.18±1.14	**<.0001**[a]
CI		1.363, 2.157			-1.126, 0.776	
Anemia[b]	20	4	**<.0001**[c]	8	4	.077[c]

All numbers are absolute; Hb Hemoglobin; SD standard deviation; CI 95% Confidence interval; [a] Based on paired Student's *t*-tests; [b] Anemia defined as Hb concentration <11.0 g/dL; [c] Based on Fisher's exact test (2-tailed).

4. DISCUSSION

In Brazil, in 2005, the Ministry of Health implemented the National Iron Supplementation Program, which aimed to reduce the prevalence of iron deficiency anemia, through preventive iron supplementation in children aged 6 months to 2 years, pregnant women, and women in the postpartum period (13). This type of program has been conducted for more than 60 years in developed countries, but only in the last decade has it been implemented on a larger scale in the rest of the world (14,15).

Even with these interventions, we still have anemia as a public health problem in our country. In our study, the prevalence of anemia was 30.4% , classified as moderate, unlike the prevalence found in a recent systematic review on the prevalence of anemia in preschool children in Brazil, 40.2%, a level considered to be a severe public health problem (10). Our study, despite being conducted in a poor region, presented a lower prevalence of anemia than the more developed regions of the country (38.7%) (11). This perhaps may be explained by effective local public policies, iron-rich school lunch menus and extra-governmental interventions carried out locally (16-18).

In the present study, the weekly use of iron led to a significant decrease in the prevalence of anemia in children, from 45.5 to 9.1%. Whereas, in the control group, there was an increase in the anemic population from 16.7 to 25.0%. When analyzing only anemic

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participants, a large reduction of anemia was observed, 80%, in the group that had weekly iron supplementation. We achieved an NNT of 2, that is, for every 2 children exposed to the intervention, 1 child was recovered from the condition of anemic. Such data show that weekly iron supplementation in the anemic participants was very effective.

Still analyzing these same groups, a significant increase in serum Hb levels was verified in the group that received weekly ferrous sulfate supplementation (0.85g/dL) compared to the control group (-0.74g/dL), which presented a decrease in Hb levels. This result agrees with the systematic review by De-Regil (2011) who found a mean increase in Hb of 0.5g/dL when compared to placebo. In this review, greater adherence to treatment was found with weekly supplementation when compared to the daily use of iron (19). It is understood that intermittent supplementation may be an alternative both to increase patients' adherence to treatment and to reduce the costs that daily supplementation demands.

Numerous studies have analyzed the specific benefits of preventive iron supplementation in children. The convergence in the reduction of the prevalence of anemia, in the reduction of the morbidity of infectious diseases and of infant mortality, in addition to the contribution to the integral development of the tissues has been observed (7,9,10). However, there are few studies that analyze in a practical manner the possible damage from this conduct, such as possible losses in the absorption of some micronutrients, such as zinc, and the possibility of excessive accumulation of iron in the body, which could be maximized with the daily use of iron and perhaps minimized with intermittent supplementation (20).

Most of the studies that relate iron supplementation with the reduction of anemia do not specifically analyze the 2-year-old age group that was addressed in the present study, generally, they assess older children (11,14,16-19,21). It is observed in these studies, which include a systematic review, randomized clinical trials and community trials, that it is frequent to increase Hb levels and reduce anemia with weekly supplementation, as verified in the present study, in addition to increasing iron deposits (11,14,16-19,22-24).

5. CONCLUSION

In our study, we have some approaches that make it innovative: low cost due to the weekly use of ferrous sulfate, use of supplementation in a community manner with the school lunch space in schools, reducing the chances of failures that could occur in the family environment, and intervention conducted with intent to treat, with significant results in the short time span of just 14 weeks. Thus, it becomes a plausible strategy to be implemented on a large scale in developing countries with a high prevalence of anemia.

CONSENT

Informed consent forms (ICF) were distributed to parents or guardians, in accordance with Resolution Nº 466, of December 12, 2012. All students who signed the assent term and whose ICF was completed and signed by their parents or guardians were included in the study.

ETHICAL APPROVAL

This study was approved by the ethics committee for research at the Universidade Federal do Ceará following the ethical principles established by the National Health Council resolution #466/2012, with necessary prior written consent from school directors and

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parents/guardians. Medical support was available upon request. After intervention, anemic children were referred for treatment.
All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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