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Weekly Iron Supplementation in 2-Year-Olds is Effective in Combating Anaemia

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AMM and FPNA designed the study. Authors AMM, FPNA, PGO, CPCA, FBDS, KMTP and KCAC conducted the study and analyzed the data. Authors AMM and FPNA wrote the paper. Authors FPNA had primary responsibility for the final content. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Iron deficiency anaemia 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 sulphate supplementation on haemoglobin (Hb) levels and the prevalence of anaemia 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 sulphate once a week (intervention). In the other school, the children received a 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 anaemia 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

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decrease of 0.74g/dL (p=0.0001) in the control group. The prevalence of anaemia 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 anaemia.

Keywords: Iron-deficiency anaemia; haemoglobins; ferrous sulphate; preschool child; clinical trial.

1. INTRODUCTION

The World Health Organization (WHO) defines anaemia as a condition in which the serum concentration of haemoglobin is below the reference values, to the point of not meeting the physiological needs according to age, sex, pregnancy, and altitude [1]. Of the causes of anaemia, 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 five years of age (preschoolers), women of childbearing age, pregnant and lactating women, in greater numbers in developing countries [2,3].

Iron is a widespread metal in the human body, playing a crucial role in all phases of protein synthesis, cellular respiration, and oxidative and immunological processes [4,5,6]. Iron deficiency is associated with bone fragility and distortions, hepatosplenomegaly (possibly from extramedullary haematopoiesis), 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 anaemia close to 40% [9,10]. Our study used weekly iron supplementation in public schools as a strategy to try to improve children's haematimetric levels without the need for family adherence since it is often difficult to understand how important iron is for the development and homeostasis of these children.

2. METHODOLOGY

2.1 Study Design

The authors designed and conducted a cluster randomized clinical trial study to address the research goal. In the north-eastern Brazilian municipality of Sobral - Ceará, a medium-sized city, between August and December 2019, the study sample was drawn from the population of preschoolers aged between 24 and 36 months from public Infant Education Centres.

Using a table of random numbers, three public Infant Education Centres were selected prior to the intervention; the first constituted Group A, and the second Group B. Once a week, Group A received 6 mg/kg of elemental iron (the intervention group); Group B served as the control group.

All preschoolers from the two Infant Education Centres between the ages of 24 and 36 months were invited to take part in the study. Infants who were already receiving iron supplements and those whose parents' refused participation were excluded.

2.2 Intervention

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

2.3 Primary Outcomes and Other Variables

The study included two primary outcome variables: 1) change in Hb concentration measured in g/dL before and after intervention, and 2) anaemia prevalence before and after intervention. To define anaemia, a Hb concentration of 11.0g/dL was used as the cut-off point [10].

A standardized data sheet that contained information on (other research variables): age, gender, exclusive breastfeeding (EBF) up to 6 months, mother's education, and family income

was filled out based on information provided by the parents.

2.4 Sample Size

Anaemia prevalence in the study population was predicted to be between 40 and 50 percent based on earlier research done in this area [11]. Each group needed a minimum of 43 individuals to achieve a reduction in the global anaemia prevalence from 50% to 25% with an 80 percent power, 2-sided, type I error of 5%, and allowing for 10% losses to follow-up [12].

2.5 Data Collection

To compare Hb values before and after intervention, two biochemical analyses were carried out. A trained technician measured the Hb concentrations using a portable HemoCue B-hemoglobin photometer (Hb 301 - HemoCue AB, Ängelholm, Sweden). Using Carelet® Safety Lancets, finger-prick capillary blood was collected in an aseptic environment (Facet Technologies, Atlanta, GA, USA). Members of the study team who collected outcome data were unaware of the different interventions.

2.6 Data Analyses

The researchers utilized the Fisher's exact test to determine the difference between positive and negative outcomes, and the paired student's t-test to determine the difference in Hb concentration within the groups before and after the intervention (absence or presence of anaemia). Data were distributed normally. All analyses were performed using the statistical program SPSS for Windows, version 17.0. (SPSS Inc., Chicago, IL). P=0.05 was chosen as the threshold for statistical significance. Analyses were by intention to treat.

According to the ethical guidelines established by National Health Council Resolution #466/2012 and with the required prior written approval from school administrators and parents/guardians, this study was approved by the Ethics Committee for Research at the Universidade Federal do Ceará. On request, medical assistance was provided. Children with anaemia were referred for therapy after intervention.

3. RESULTS

At baseline, 14 preschoolers were excluded before blood analysis, nine from group A (three refused and six were already using iron supplementation), and five from group B (three refused and two already using iron supplementation) (Fig. 1).

There were ten dropouts from Group A prior to the second biochemical evaluation (at the end of the intervention) (five left the Infant Education Centre, two absentees, and three non-compliant); there were eleven dropouts from Group B (seven left the Infant Education Centre, two absentees, and two non-compliant) (Fig. 1).

Hb concentration and the other research variables were examined at baseline. Age, gender, EBF, mother's education, and household income did not differ statistically significantly. In group A, there were 27 male participants and 27 participants who were female. The mean age (in months) for group A was 29.9±3.51 and 30.4±3.36 for group B, p=.30. Twenty-eight male and 31 females made up group B, p=.96. EBF, mother's education, and family income had p-values of .96 and .90 between groups, respectively. However, there was a significant difference in the mean Hb levels between the groups, being 11.34 1.31 g/dL in group A and 11.88 0.78 g/dL in group B (p=.003). (Table 1).

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

When mean Hb concentrations were taken into account, Group A's mean Hb values increased (0.85±1.42); whereas Group B's mean Hb concentration decreased (-0.74±0.96), p.0001 (Table 3).

With regard to just the anaemic participants, Group A (n=20) had a mean Hb concentration of 9.82±0.60 at baseline and 11.58±0.45 after the intervention, both of which were statistically significant (p<.0001). At baseline, there were twenty anaemic participants, but after the

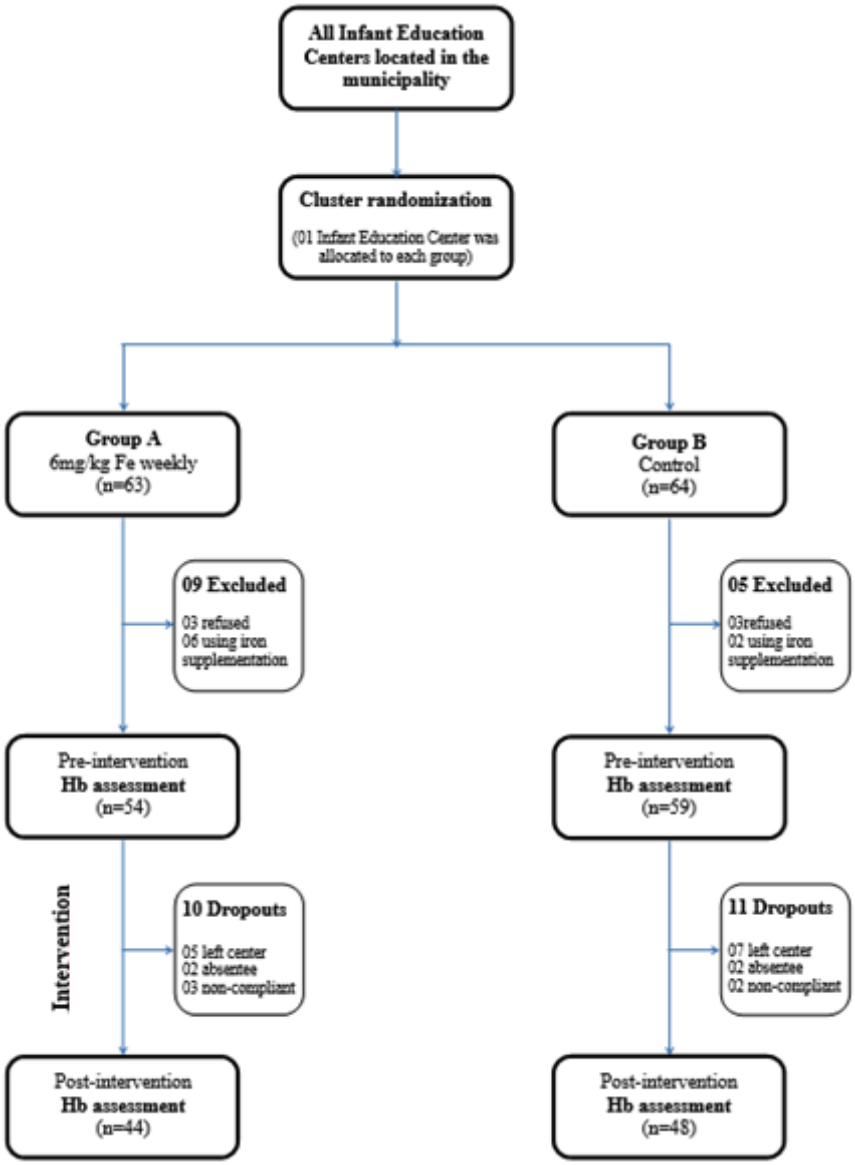

Fig. 1. Flow chart of study design

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]
Haemoglobin (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 of weekly iron supplementation and control on haemoglobin levels and anaemia prevalence before and after the 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	
Anaemia[b]	20 (45.5)	4 (9.1)	**.0002**[c]	8 (16.7)	12 (25.0)	.452[c]

All numbers are absolute except numbers in brackets, which represent percentages; Hb Haemoglobin; SD standard deviation; CI 95% Confidence interval; [a] Based on paired Student's t-tests; [b] Anaemia 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 haemoglobin levels and anaemia prevalence for anaemic preschoolers, before and after the intervention

	Group A (n=20) *Weekly iron*			Group B (n=8) *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	
Anaemia[b]	20	4	**<.0001**[c]	8	4	.077[c]

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

intervention, this number dropped to 4, also statistically significant (p<.0001). The mean Hb concentration in the control group (Group B) decreased from 10.78±0.14 g/dL at baseline to 10.60±1.27 after the intervention, without statistical significance, (p=.077). The mean Hb concentration increased in the intervention group (1.76±0.85 g/dL), but it marginally declined in the control group (Group B), p=.677 (Table 3).

Indicators predicting a positive or negative outcome were compared between intervention group A and the control group in this study (absence of anaemia versus anaemia). Twenty percent of experimental subjects and 100 percent of control subjects had the unfavourable outcome at the endpoint. For group A, the reduction in absolute risk (RAR) difference was 80%. The 95% confidence interval for this discrepancy varied from 62.5 to 97.5 percent (group A). The weekly supplementation group's relative risk (RR) was 0.36. The number needed to treat (NNT) was 2. This indicates that the intervention was successful for one out of every two preschoolers in the group. The 95% confidence interval for the NNT ranged from 1.0 to 1.6.

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 anaemia, through preventive iron supplementation in children aged six months to 2 years, and 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 [14,15].

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

In the present study, the weekly use of iron led to a significant decrease in the prevalence of iron deficiency anaemia in children, from 45.5 to 9.1%. Whereas there was a non-significant increase in the anaemic population from 16.7 to 25.0% in the control group. When analysing only anaemic participants, a large reduction of iron deficiency anaemia was observed, 80%, in the group that had weekly iron supplementation. We achieved an NNT of 2; that is, for every two children exposed to the intervention, one child was recovered from the condition of anaemic. Such data show that weekly iron supplementation in the anaemic participants was very effective.

Still analysing these same groups, a significant increase in serum Hb levels was verified in the group that received weekly ferrous sulphate supplementation (0.85g/dL) compared to the control group (-0.74g/dL) 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 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 to increase patients' patients' adherence to treatment and reduce the costs that daily supplementation demands.

Numerous studies have analysed the specific benefits of preventive iron supplementation in children. The convergence in the reduction of the prevalence of anaemia, in the reduction of the morbidity of infectious diseases and infant mortality, ,and the contribution to the integral development of the tissues has been observed [7,9,10]. However, few studies analyse practically 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 anaemia do not specifically analyse the 2-year-old age group addressed in the present study. Generally, they assess older children [11,14,16-19,21]. It is observed in these studies, including a systematic review, randomized clinical trials and community trials, that it is frequent to increase Hb levels and

reduce iron deficiency anaemia with weekly supplementation, as verified in the present study, in addition to increasing iron deposits [11,14,16-19,22-24].

As potential weaknesses to this study, the investigators make some considerations, first as the study was cluster randomized the prevalence of anaemia would not necessarily be similar between the groups, it is believed that the group with lower levels of Hb and higher prevalence of anaemia may have presented a better response due to possible lower ferric status. This cannot be confirmed as this study only analysed Hb concentrations, iron deficiency through ferritin or transferritin receptors was not assessed, which would make iron assessment more reliable. Although in the anaemic groups under intervention, there was a considerable decrease (from twenty to four) in the number of anaemic children at the end of the study, the investigators believe that the short study duration (only 14 weeks) may have led to a smaller result, and perhaps a greater effect could be attained with a longer intervention period.

5. CONCLUSION

In our study, we have some approaches that make it innovative: low cost due to the weekly use of ferrous sulphate, 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 the intent to treat, with significant results in the short period 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 iron deficiency anaemia.

CONSENT

Informed consent forms (ICF) were distributed to parents or guardians, per 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 parents/guardians. Medical support was available upon request. After the intervention, anaemic 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.

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COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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