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Ferric Pyrophosphate-fortified Rice Given Once Weekly Does not Increase Hemoglobin Levels in Preschoolers

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Abstract

Background: The objective of this study was to evaluate the effect of rice fortified with iron (Ultrarice®), given once weekly, and on hemoglobin levels and anemia prevalence compared with standard rice.

Methods: In this prospective quasi-experimental study, we evaluated preschoolers aged 2 to 5 years (n=303) from 2 public schools in Sobral, Brazil. Intervention lasted 18 weeks. The once weekly 50 g individual portion (uncooked) of fortified rice provided 56.4 mg of elemental iron as ferric pyrophosphate. Capillary blood samples to test for hemoglobin levels were taken at baseline and after intervention. Student's *t*-test was used to assess the difference in hemoglobin within / between the groups.

Results: For fortified rice school: baseline mean hemoglobin was 12.06 ± 1.01 g/dL, and after intervention 12.14 ± 1.06 g/dL, p=0.52; anemia prevalence was 8.9% (11/120) at baseline, and 10.5% (13/120) at end of study, p=0.67. For the standard rice school: baseline mean hemoglobin was 12.40 ± 4.14 g/dL, and after intervention 12.29 ± 2.48, p=0.78; anemia prevalence was 20.8% (30/144) at baseline, and 37.5% (54/144) at the end of study, p=0.002. Considering only anemic participants, there was a significant increase in hemoglobin means before and after intervention, p=0.003 in the fortified rice school. Relative Risk was 0.29 and the Number Needed to Treat was 4.

Conclusions: This study shows that consumption of the iron-fortified rice compared to the control rice does not change hemoglobin or anemia prevalence in preschoolers.

Keywords: Anemia; Rice; Fortification; Iron; Preschoolers

Background

Iron deficiency (ID) has been identified as the most prevalent micronutrient deficiency in the world, afflicting over 50% of the world population. An estimated 47% of children under five years worldwide experience Iron Deficiency Anemia (IDA) [1-3] and poor and/or minority children are at increased risk [4]. Inadequate intake of iron and consumption of foods with low iron bioavailability are the major causes of this problem. Iron deficiency in the first years of life can cause serious consequences later in life including lack of concentration, behavioral and cognitive disorders, and growth impairment [5,6].

WHO regards food fortification as a safe and effective means to supplement diets with low-iron content [5], whereas international suggestions for food fortification often require changes in local diet habits and even the importation of foodstuffs not locally available. Interventions should focus on the fortification of locally consumed foodstuffs, as this type of fortification may be implemented sustainably on a large scale, allowing people to get more nutritional value from the food they already eat. This current study focuses on rice fortification, as in Brazilian households rice is probably the most widely consumed foodstuff. The impact of iron-fortified rice has already been the object of other studies and its effect on anemia and hemoglobin levels, but up-to-date no studies have investigated the use of ferric pyrophosphate in weekly dosages with preschoolers [7-13].

The objective of our study was to evaluate the impact of rice fortified with iron, given once weekly, in preschoolers aged 2-5 years compared with control (standard household rice) on hemoglobin values and anemia levels.

Materials and Methods

This prospective quasi-experimental study was conducted in the City of Sobral-Ceará, in the northeast of Brazil, between August and December 2010. The study population comprised of preschoolers (2 to 5 years) from two chosen public schools (n=303).

Prior to the study, each school was identified to receive one type of rice to avoid contamination between the different groups, as the meal was served at the same time in the same school refectory. The first school was designated to receive fortified rice once weekly in schools meals–School A, and the latter received standard rice-School B. The menus at the two schools were equal in content; the study rice was consumed with poultry, which was the customarily consumed meal for Tuesdays at the schools. Staff at the schools were not aware of the rice that was being served (fortified or standard) as the rice was provided by the study team in non-identifying packages. Data collection team was also unaware of intervention and control groups. Intervention period was adapted to the 20-week school semester, the first 2 weeks were used for intervention setup and training; the following 18 weeks constituted the study period, starting and ending on the same date.

All preschoolers from the two schools were invited to participate in our study. Exclusion criteria were parents' refusal to participate and

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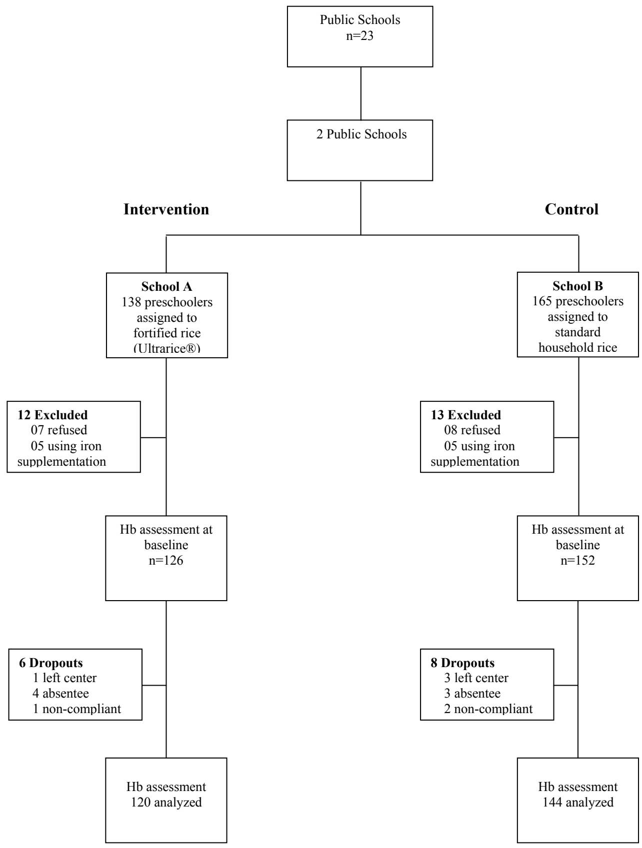

Figure 1: Study Profile.

preschoolers already using iron supplementation (Figure 1). Upon enrollment, baseline characteristics of participants were defined by means of questionnaire with the children's mothers. Characteristics analyzed for this study were age, gender, mother's schooling, and family income.

Ultra Rice grains (Adorella Alimentos LTDA, Indaiatuba, Sao Paulo, Brazil) are made with rice flour and selected micronutrients, which are combined and then extruded through a rice-shaped mold. Ultra Rice can be tailor made with different micronutrients, including iron, thiamin, zinc, and folic acid, while mimicking the look of standard rice.

In our nutritional intervention, Ultra Rice fortified with non-encapsulated ferric pyrophosphate with an average particle size of 3 microns in micronized form (donated to the Secretariat of Education–Sobral by the Program for Appropriate Technology in Health PATH) was used at 6%. This proportioned a weekly ingestion of 56.4 mg of elemental iron as ferric pyrophosphate per 50 g uncooked individual portion. The meals were prepared in the school kitchen and served at lunchtime (11 a.m.). This quantity of rice provided a satisfactory weekly amount of elemental iron considering dietary reference intakes (DRI) for this mixed age range (children aged 2 to 3 years=7 mg Fe/day and 4 to 5 years=10 mg) [14].

The main outcomes analyzed were hemoglobin values and anemia prevalence, by means of two biochemical evaluations, before and after intervention. Capillary blood samples were taken from a finger prick using aseptic techniques. Hemoglobin concentrations were promptly analyzed with a portable HemoCue B-hemoglobin photometer (Hb 301-HemoCue AB, Ängelholm, Sweden) by technician. Cutoff point to define anemia for children <5 years: Hb <11.0 g/dL [6].

Anemia prevalence in the study population was estimated at 20%, according to the global prevalence for anemia in this age range, in Brazil, is 20–25% (varies according to region) [15]. To achieve a reduction in global anemia prevalence from 20 to 10%, with 80% power, 2-sided, type I error of 1%, accounting for 10% losses to follow-up, each group required a minimum of 107 participants [16].

Data were entered into a database in double-entry EPI Info version 6.04 (Centers for Disease Control and Prevention–CDC, Atlanta, Georgia, USA). At baseline, the participants from the two schools were compared. To compare ratios and means we used, respectively, the χ^2-test and the paired student's t-test to assess the difference in hemoglobin within the groups, and unpaired student's t-test between the groups before and after intervention. Data had normal distribution. Processing and analysis of data was made using the statistics package PASW (Predictive Analytic Software, Windows Version 17.0, SPSS Inc., Chicago, IL). We considered $\alpha<0.05$. Analyses were by intention to treat.

Relative risk to anemia was calculated upon completion of intervention. The χ^2-test was used to compare the ratios between the study groups. The independent variable (intervention or control) was organized and examined in the form of a dichotomy: (a) fortified rice (intervention), (b) standard household rice (control). From this point, using 2x2 contingency tables, the following measures of association were calculated: reduction of absolute risk (RAR), relative risk (RR), reduction of relative risk (RRR) and number needed for treatment (NNT), which in this study is the number of preschoolers submitted to intervention for the prevention of unfavorable outcome (anemia).

Approval for this study was obtained from the Ethics Committee at the Federal University of Ceara, 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.

Results

At baseline, the following parameters were analyzed: age, gender, mother's schooling, and family income. However, there were no statistically significant differences between the two schools (Table 1). The mean hemoglobin values for the groups were 12.06 ± 1.01 g/dL for school A and 12.40 ± 4.14 g/dL for school B, p=0.38; anemia prevalence was 8.9% and 20.8%, for schools A and B, respectively, p=0.009. During our study, there were six dropouts from school A (1 left center, 4 absentee, 1 non-compliant); in school B there were eight dropouts (3 left center, 3 absentee, 2 non-compliant) (Figure 1and Table 1).

	School A (n=138)	School B (n=165)	p-value
Age in months	41.3 (10.1)	42.5 (9.96)	0.29[a]
Gender M:F	65:73	79:86	0.89[b]
Mother with ≤8y schooling	103	135	0.13[b]
Family income ≤300USD	126	154	0.50[b]

M:F male:female
( ) standard deviation
[a] descriptive level of unpaired student t-test
[b] descriptive level of chi-square.

Table 1: Baseline characteristics of study participants, by intervention center.

Mean hemoglobin value at baseline was 12.06 ± 1.01 g/dL for the fortified rice group (school A), and after intervention 12.14 ± 1.06 g/dL, p=0.52. For the standard household rice/control group (school B) mean hemoglobin value at baseline was 12.40 ± 4.14 g/dL, and after intervention 12.29 ± 2.48, p=0.78. In the intervention group (school A), there was no significant change in anemia prevalence during the study, p=0.67; however, there was a statistically significant increase in anemia prevalence for the control group (school B), from 20.8 to 37.5%, p=0.002 (Table 2).

At baseline, the groups were similar for hemoglobin means, p=0.38; after intervention, there was no significant difference between the schools, p=0.56 (Table 2). However, for anemia prevalence, the groups were different at baseline: 8.9% (11/120 were anemic) in school A, and 20.8% (30/144 were anemic) in school B, p=0.009; at the end of the study, the groups remained different, 10.5% (13/120) at school A, and 37.5% (54/144) at school B, p<0.001 (Table 2).

Considering only anemic participants, in school A before intervention mean hemoglobin value was 10.12 ± 0.85 g/dL (n=11) and 11.56 ± 0.86 after intervention, p=0.0003; in school B (n=30), mean hemoglobin values went from 10.83 ± 1.11 g/dL before intervention to 10.94 ± 1.18 g/dL after intervention, p=0.18 (Table 3). For non-anemic participants, there was no significant alteration in the mean hemoglobin values before and after intervention for schools A (12.20 ± 0.76 before and 12.24 ± 1.04 after) and B (12.44 ± 3.27 before and 12.48 ± 3.01 after), p=0.72 and 0.74, respectively (Table 3).

In this study, the following indicators were compared: fortified rice versus standard household rice, for a favorable (absence of anemia) or adverse (anemia) outcome.

After intervention, adverse outcome was present in 37.5% of control subjects and 10.8% of experimental subjects. The difference, the Reduction of Absolute Risk (RAR), was 26.7%. The 95% confidence interval for this difference ranges from 17.00 to 36.33%. The Number Needed to Treat (NNT) was 4. This means that about one in every 4 preschoolers will benefit from this anemia prevention intervention. The 95% confidence interval for the NNT ranges from 2.8 to 5.9. Measurements of efficacy were: Relative Risk (RR)=0.29; 95% Confidence Interval (CI)=0.166, 0.503; Relative Risk Reduction (RRR)=0.73, expressing that the preschoolers submitted to this intervention had 73% less likelihood of developing anemia.

Discussion

Main findings of this study

This 18-week study demonstrated that rice fortified with iron once weekly does not change hemoglobin and anemia in preschoolers; nevertheless, it was capable of preventing anemia in preschoolers. There was a statistically significant increase in anemia prevalence in the control group; however, the fortified rice group did not present a statistically significant alteration in the number of anemic children after intervention. Furthermore, it prevented anemia onset for 1 in every 4 preschoolers submitted to the intervention, preschoolers submitted to this intervention had 73% less likelihood of developing anemia (RRR), a significant result taking into consideration that the population submitted to the fortified rice intervention had low anemia prevalence, 8.9%. Additionally, when we analyzed only anemic participants there was a significant increase in hemoglobin means for the ´participants in the fortified rice school, compared to no change in the standard rice group, strengthening the results from the fortified rice.

In our study, low anemia prevalence and hemoglobin means above 12.0 g/dL probably represented a population with low iron deficit, situation that may have impeded a greater response from the proposed intervention. It is likely that the results from this kind of intervention would be more significant than in populations with more widespread ID, anemia prevalence and lower mean hemoglobin.

Our study was conducted in compliance with DRI recommendations for this age range [14] and also taking into consideration the low absorption of this iron composition [17], we used a once weekly

	School A – Fortified Rice (n=120)			School B – Standard Rice (n=144)				
	Before	After	p-value	Before	After	p-value	AxB[a]baseline p-value	AxB[a]after p-value
Hemoglobin (g/dL)	12.06	12.14	0.52[b]	12.40	12.29	0.78[b]	0.38[c]	0.56[c]
SD[d] CI[e]	1.01 11.87-12.25	1.06 11.96-12.33		4.14 11.84-12.96	2.48 11.73-12.84			
Anemia[f]	11 (9.2%)	13 (10.8%)	0.67[g]	30 (20.8%)	54 (37.5%)	0.002[g]	0.009[g]	<0.001[g]

[a]School A vs. School B
[b]Based on paired Student's *t*-tests
[c]Based on unpaired Student's *t*-tests
[d]SD = Standard deviation
[e] CI = Confidence interval
[f]Anemia defined as Hb concentration <11.0 g/dL
[g] Descriptive level of chi-square

Table 2: Effect of iron fortified rice, compared with standard rice before and after intervention and comparison of hemoglobin means and anemia prevalence between schools.

	School A – Fortified Rice (n=11)			School B – Standard Rice (n=30)		
	Before	After	p-value	Before	After	p-value
Hemoglobin (g/dL)	10.12	11.56	0.0003[a]	10.83	10.94	0.18[a]
SD	0.85	0.86		1.11	1.18	

[a]Based on paired Student's *t*-tests
SD = Standard deviation

Table 3: Effect of iron fortified rice, compared with standard rice before and after intervention on hemoglobin means for anemic participants.

56 mg elemental iron dosage; this was the amount offered to the preschooler and does not necessarily represent the amount consumed; individual ingestion was not measured in this study. Additionally, this intervention sought not to alter the established school menu where rice was consumed only once weekly.

What we already know

According to Hurrel and Egli [18], bioavailability of fortification iron varies widely with the iron compound used. Furthermore, iron status of the individual and other host factors largely influence iron bioavailability such as obesity, nutritional deficiencies, infection/inflammation, and genetic disorders. Additionally, iron status generally has a greater effect than the vehicle that is used in fortification.

Two recent studies conducted in infants with the similar intervention designs, have achieved statistically significant results increasing hemoglobin values and reducing anemia prevalence in the fortified rice groups when compared to the standard rice groups. In the first study [13] mean hemoglobin values increased from 11.37 to 11.95 g/dL, p<0.0001 and anemia prevalence reduced from 27.8 to 11.1%, p=0.012; in the second study [12] hemoglobin values rose from 11.44 to 11.67, p=0.029, and anemia prevalence decreased from 31.25 to 18.75%, p=0.045. In these studies, anemia prevalence at baseline in the intervention groups was higher than that of this intervention, which may have contributed to better results.

One 5-month home-based randomized controlled trial (RCT) conducted in Brazil with anemic infants used the same iron to fortify rice, comparing the daily consumption of iron-fortified rice with orally administered iron drops (10 mg iron/daily). The authors concluded that both interventions improved iron status, p<0.01 for hemoglobin and p<0.02 for serum ferritin, reducing anemia prevalence from 100 to 61.8% (fortified rice) and 85.6% (iron drops). It is likely that daily small doses will have a greater impact than the same quantity delivered once weekly [10]. However in a double-blind, 8-month, placebo-controlled trial using micronized ferric pyrophosphate (MFP) in extruded rice kernels mixed in a rice-based meal (19 mg Fe/day), this intervention did not increase hemoglobin levels nor reduce anemia in children aged 5 to 10 years, but iron stores were improved when compared to control [11].

Other studies using extruded rice grains fortified with MFP have achieved positive outcomes. Moreti et al. [7] obtained a 50% reduction in IDA (30% from 15%) in a 7-month RCT with preschoolers, which fortified a rice meal with 20 mg Fe daily. Angeles et al. [8] compared different rice fortifications (ferrous sulfate and MFP) compared to a control group with non-fortified rice, in a six-month intervention on schooldays with anemic schoolchildren. There was significant reduction in anemia prevalence, from 100 to 38 and 33% in the intervention groups compared to 63% in the control. However, in a study by Bagni et al. [19] there was apparently no impact on hemoglobin levels in preschoolers (when compared to control), in a 16-week intervention with rice fortified with iron chelate once weekly.

Food fortification, in recent years, has drawn the attention of care professionals and health authorities around the world; in the Global Report, published in 2009 [20], food fortification was defended as an approach that has shown great success, whether in packets for in-home use or delivered through mass fortification programs, this kind of intervention warrants urgent and wide expansion. Additionally, in May 2008 the Copenhagen Consensus Panel [21] in analyzing 30 options for the world's best investment for development, considered the provision of micronutrients as the best alternative.

Limitations of this study

Some limitations need to be acknowledged and addressed regarding the present study. The study was limited with respect to measurement of iron status; IDA was estimated and not measured. This study was conducted as a quasi-experimental study, not randomized; therefore, it was not possible to control anemia levels at baseline between the different schools. We acknowledge that with non-encapsulated ferric pyrophosphate is of low availability and that other food components consumed with the rice may have inhibited or enhanced iron bioavailability. However, these differences are inherent to studies that measure the effectiveness of interventions in real environments, without changing the daily routine of the schools. Nevertheless, at baseline, the variables assessed did not justify the difference in anemia levels. Additionally, individual consumption was not measured due to the nature of the study, conducted in the customary school ambit, with the intention to treat.

What this study adds

Although the reduction in hemoglobin was not statistically significant in the control group, there was a significant increase in anemia prevalence. This may have been caused by the fact that several children (12 children) in the study were on the borderline between anemia and non-anemia, (for example hemoglobin measurements approximately 11.0 or 11.1 g/dL before intervention, and 10.9 g/dL after intervention) thus, the non-anemic children in the control group were classified as anemic after the intervention.

Nevertheless, as there was no change in hemoglobin values or anemia rates in the intervention group we may assume this intervention prevented preschoolers from becoming anemic. Furthermore as this intervention was conducted once weekly, it may constitute a useful strategy to reduce operational costs and intervention follow-ups in poor communities. As far as our review shows this study is singular as it is the first to fortify rice with ferric pyrophosphate in preschoolers with weekly iron dosages. This intention-to-treat intervention was conducted in public schools with anemic and non-anemic participants. For traditionally highly anemic populations, which have rice as a staple in their diet, this could provide an alternative method to prevent anemia.

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