Original Article

PREVENTING ANEMIA IN PRESCHOOLERS: A COMPARATIVE ANALYSIS OF SUGAR CANE HONEY AND IRON SUPPLEMENTS

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Abstract: Iron deficiency (ID) and anemia remain pressing public health concerns, affecting populations across both developed and developing nations. According to the World Health Organization, approximately 40% of preschool children are estimated to suffer from anemia, with this age group being particularly vulnerable due to their high iron requirements driven by rapid growth.

Various risk factors contribute to iron deficiency anemia (IDA), including low birth weight, excessive cow's milk consumption, insufficient dietary iron intake, low socioeconomic status, and frequent infections, all of which can deplete iron stores and increase the likelihood of ID. Importantly, ID can lead to adverse consequences such as impaired cognitive performance, reduced physical endurance, and a heightened risk of infant mortality due to compromised immune function.

In 2011, it was estimated that a staggering 273.2 million preschool-age children globally (42.6%) suffered from anemia, with 17.1 million (22.3%) in the Americas alone. A national study in Brazil further revealed that around one-fifth of children under five years of age grapple with anemia.

This abstract underscore the persistence and far-reaching impact of ID and anemia, shedding light on the significance of addressing these health challenges on a global scale.

Keywords: Iron Deficiency, Anemia, Preschool Children, Global Health, Risk Factors

1. Introduction

Iron deficiency (ID) and anemia are still major public health problems in both industrialized and developing countries (McLean *et al*, 2009; World Health Organization, 2020). According to the World Health Organization (2020), 40% of preschool children are estimated to be anemic, they are a special risk group due to their high iron requirements because of their rapid growth (Domellöf *et al*, 2014). Risk factors for iron deficiency anemia (IDA) include low birth weight, excessive cow's milk consumption, inadequate dietary iron, low socioeconomic status and frequent infections, which may result in diminished iron stores and increased probability of ID (UNICEF, 1998; Dary &Hurrell, 2006; Domellöf *et al*, 2014). In turn, ID may lead to a reduction in cognitive performance, decreased physical endurance, and increased risk of infant mortality due to depletion of the immune system

(Lozoff *et al*, 2000; Gera *et al*, 2007; World Health Organization, 2016; Global Burden of Disease Child and Adolescent Health Collaboration *et al*, 2017).

For the year 2011, it was estimated that 273.2 million (42.6%) preschool-age children (6-59 months) worldwide were anemic, with 17.1 million (22.3%) in the Americas (World Health Organization, 2015; World Health Organization, 2016). According to a national study conducted in Brazil, researchers reported that approximately one-fifth of children under the age of five years were anemic (Brazil, 2009).

In Brazil, in order to address IDA prevalence, the National Food and Nutrition Policy was created in order to guarantee the quality of foodstuffs, as well as promoting health eating practices and preventing and controlling nutritional disorders (Brazil, 2012). However, in spite of these measures, high IDA prevalence rates still persist in the Brazilian population, justifying the search for innovative, sustainable, and low-cost strategies capable of reducing IDA prevalence.

Hence, this study seeks to analyze the effects of sugar cane honey for the prevention and/or treatment of IDA. In this investigation, we compared the effect of sugar cane honey given once daily versus ferrous sulfate oral solution given once weekly versus control, on Hb concentrations, and anemia prevalence rates in preschoolers aged 24-36 months.

2. Methods

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 2016.

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 and the third Group C. Group A received 18.6 g sugar cane honey once daily (intervention); Group B was allocated to 6 mg/kg *elemental iron* once weekly (intervention); and Group C was designated as control.

All preschoolers aged 24 to 36 months from the three 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

In this study, the preschoolers in Group A received a disposable cup containing 18.6 g of sugar cane honey once daily (Monday through Friday) (Table 1). The preschoolers in Group B 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 16 weeks, beginning and ending on the same date for all groups.

2.3. Sugar cane honey production

After undergoing a cleaning process, the sugar cane is milled, the juice obtained in the milling passes through decanters and sieves, for removal of impurities, and remains in rest for 24 hours. In this period acidification of the juice occurs, in which the sucrose is transformed into glucose and fructose, which prevents crystallization. The juice is then heated, when there is the evaporation of water, until the ideal point is obtained. Once this point is reached, the sugar cane honey is cooled enough to be packed in the pots or bottles.

Sugar cane honey can be used as a natural sweetener, a nutritious substitute for sugar because it is rich in calcium, iron, magnesium, selenium and other important nutrients (United States Department of Agriculture, 2016) (Table 1).

Table 1. Main vitamin and mineral composition of sugar cane honey (18.6 g portion)

Vitamins and minerals	**Dose (18.6 g portion)**
Niacin	0.173 mg
Vitamin B6	0.125 mg
Calcium	38 mg
Iron	0.88 mg
Magnesium	45 mg
Phosphorus	6 mg
Potassium	272 mg
Sodium	7 mg
Zinc	0.05 mg

Source: United States Department of Agriculture, 2016.

2.4. 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 (World Health Organization, 2001).

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.

2.5. Sample size

According to previous studies conducted in this region anemia prevalence in the study population was estimated at 40-50% (Arcanjo *et al*, 2009; Carvalho *et al*, 2010; Matos *et al*, 2016). 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 (Lwanga, & Lemesshow, 1991).

2.6. 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.

2.7. 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). One-way analysis of variance (ANOVA) was used to test differences among the three groups, and significant differences were evaluated with the Fisher and Bonferroni tests for multiple comparisons. 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 Federal University of 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, 20 preschoolers were excluded before blood analysis, six from group A (1 refused and 5 already using iron supplementation), nine from group B (3 refused and 6 already using iron supplementation), and five from group C (3 refused and 2 already using iron supplementation) (Figure 1).

Before the second biochemical evaluation (at the end of the intervention), there were 6 dropouts from Group A (5 left Infant Education Center, 1 absentee); in Group B there were 10 dropouts (5 left Infant Education Center, 2 absentee, 3 non-compliant); and in Group C there were 11 dropouts (7 left Infant Education Center, 2 absentee, 2 non-compliant) (Figure 1).

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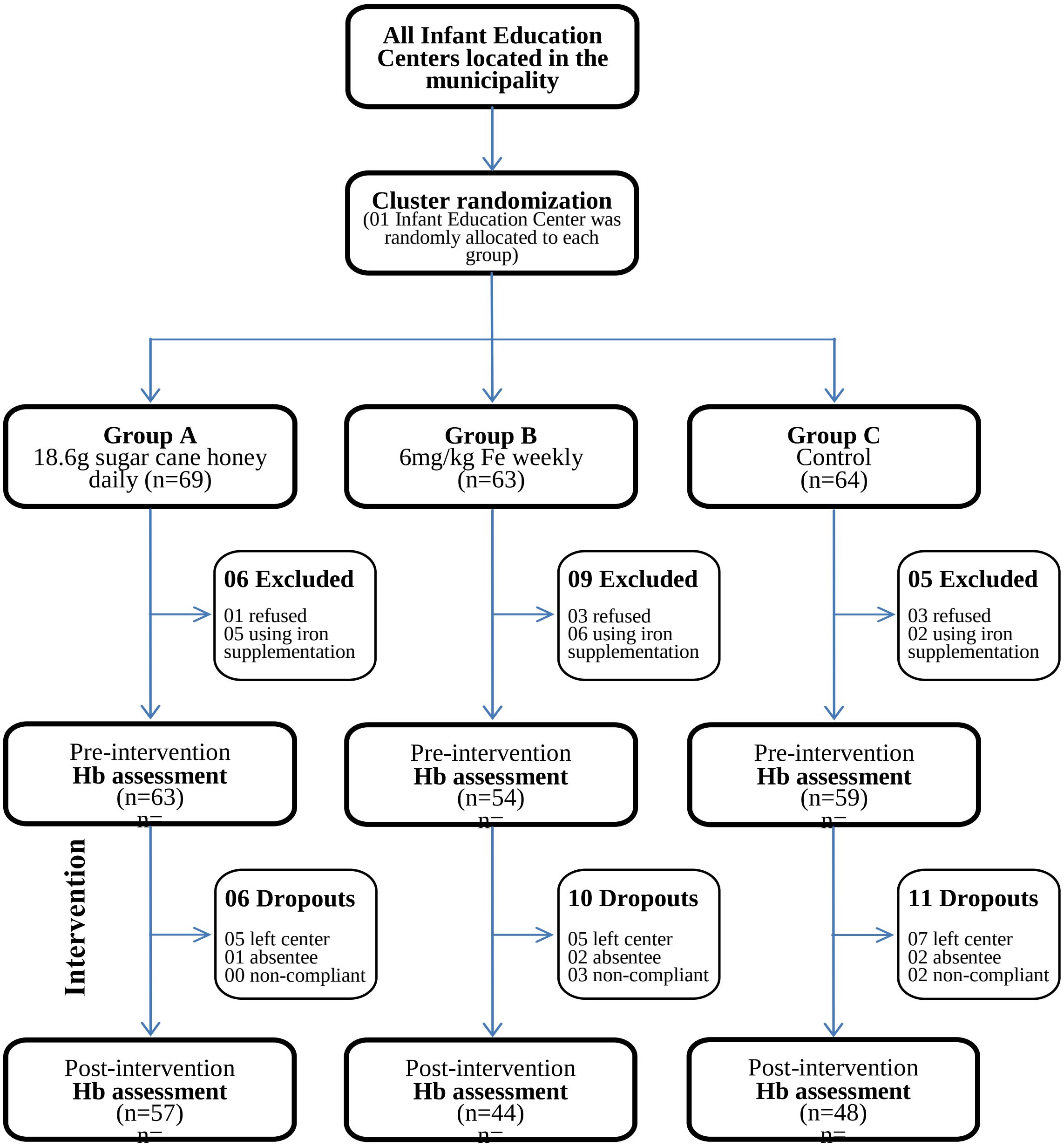

Figure 1. Study design.

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 29.4±3.29, 29.9±3.51for group B, and 30.4±3.36 for group C, p= .30; in group A, 31 participants were male and 32 were female, in group B 27 were male and 27 were female, and in group C 28 were male and 31 were female, p= .96. The p-values between groups for EBF, mother's schooling and family income were .46, .96, and .90, respectively.

However, there was a significant difference between the groups for mean Hb values; mean Hb for group A was 11.18±1.25 g/dL, 11.34±1.31 for group B, and 11.88±0.78 g/dL for group C, p= .003 (Table 2).

Table 2. Baseline characteristics of study participants, by intervention group and control

Variables	**Group A** *Sugar cane honey* (n=63)	**Group B** *Weekly iron* (n=54)	**Group C** *Control* (n=59)	*p* [a]
Age (months) *Mean±SD*	29.4±3.29	29.9±3.51	30.4±3.36	.30
Hemoglobin (g/dL)	11.18±1.25	11.34±1.31	11.88±0.78	**.003**
Gender M:F	31:32	27:27	28:31	.96
EBF	22	25	24	.46
Mother with ≥9y schooling	24	22	23	.96
Family income ≥300USD	29	23	25	.90

All numbers are absolute; SD standard deviation; M:F male:female; EBF exclusively breastfed up to 6 months of age; [a] Based on 1-way analysis of variance.

In Group A, mean Hb concentration before intervention was 11.10±1.29 g/dL, increasing to 11.60±0.72 g/dL after intervention, p= .002; anemia prevalence was 21 out of 57 (36.8%) at baseline, and 9 (15.8%) at the end of the intervention, p= .018. In Group B, 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 C), 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. In the comparison between intervention Groups A and B, there was no statistical difference, p= .449; however, when these are compared to the control group, both intervention groups presented statistically significant results (Group A versus C, and Group B versus C), p< .0001 (Table 3).

When considering alterations in mean Hb concentrations, there was an increase in mean Hb values for Group A (0.50±1.17), and Group B (0.85±1.42); however, Group C registered a reduction in mean Hb concentration (-0.74±0.96), p< .0001 (Table 3).

Table 3. Effects of sugar cane honey, weekly iron supplementation and control on hemoglobin levels, and anemia prevalence before and after intervention

	Group A (n=57) *Sugar cane honey*			**Group B** (n=44) *Weekly iron*			**Group C** (n=48) *Control*		
Variables	Before	After	*p*	Before	After	*p*	Before	After	*p*
Hb (g/dL) *Mean±SD*	11.10±1.29	11.60±0.72	**.002** [a]	11.19±1.42	12.04±0.96	**.0003**[a]	11.85±0.86	11.11±0.87	**<.0001**[a]
CI	10.75, 11.44	11.40, 11.79		10.76, 11.62	11.75, 12.33		11.60, 12.10	10.85, 11.36	
Mean increase in Hb *Mean±SD*		0.50±1.17			0.85±1.42			-0.74±0.96	**<.0001** [b]
CI		0.19, 0.81			0.41, 1.28			-1.02, -0.46	
Anemia[c]	21 (36.8)	9 (15.8)	**.018**[d]	20 (45.5)	4 (9.1)	**.0002**[d]	8 (16.7)	12 (25.0)	.452[d]

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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] Based on 1-way analysis of variance; [c] Anemia defined as Hb concentration <11.0 g/dL; [d] Based on Fisher's exact test (2-tailed); *P*-value between groups based on Fisher and Bonferroni tests: Group A x Group B = .449, Group A x Group C **< .0001**,Group B x Group C **< .0001.**

When considering only the anemic participants, in Group A (n=21), mean Hb concentration was 9.89±1.21 g/dL at baseline and 11.37±0.97 after intervention, p< .0001. From the twenty-one participants who were anemic at baseline, only 6 remained anemic after intervention (Hb <11.0 g/dL), p< .0001.

In the weekly supplementation group (Group B), 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 C), 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. Both intervention groups (A and B) presented an increase in mean Hb concentration, 1.49±0.99 and 1.76±0.85 g/dL, while the control group (Group C) presented a slight decrease in mean Hb concentration, p= .677. In the comparison between intervention Groups A and B, there was no statistical difference, p> .99; however, when compared to the control group, both intervention groups presented statistically significant results, p= .0004 and < .0001 (Table 4).

Table 4. Effects of sugar cane honey, weekly iron supplementation and control on hemoglobin levels, and anemia prevalence for anemic preschoolers, before and after intervention

	Group A (n=21) *Sugar cane honey*			**Group B** (n=20) *Weekly iron*			**Group C** (n=8) *Control*		
Variables	Before	After	*p*	Before	After	*P*	Before	After	*p*
Hb (g/dL) *Mean±SD*	9.89±1.21	11.37±0.97	**<.0001**[a]	9.82±0.60	11.58±0.45	**<.0001**[a]	10.78±0.14	10.60±1.27	.677[a]
CI	9.34, 10.44	10.93, 11.81		9.58, 10.06	11.34, 11.82		10.09, 11.46	9.91, 11.29	
Mean increase in Hb *Mean±SD*		1.49±0.99			1.76±0.85			-0.18±1.14	**<.0001**[b]
CI		1.03, 1.94			1.36, 2.16			-1.13, 0.78	
Anemia[c]	21	6	**<.0001**[d]	20	4	**<.0001**[d]	8	4	.077[d]

All numbers are absolute; Hb Hemoglobin; SD standard deviation; CI 95% Confidence interval; [a] Based on paired Student's *t*-tests; [b] Based on 1-way analysis of variance; [c] Anemia defined as Hb concentration <11.0 g/dL; [d] Based on Fisher's exact test (2-tailed); *P*-value between groups based on Fisher and Bonferroni tests: Group A x Group B = > .99, Group A x Group C **= .0004**,Group B x Group C **< .0001**

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 43% (group A) and 20% (group B) of experimental subjects. The difference, the Reduction of Absolute Risk (RAR), was 57% for group A and 80% for group B. The 95% confidence interval for this difference ranged from 36.0 to 78.3% (group A) and 62.5 to 97.5% (group B). Relative Risk (RR) was 0.63 and 0.36 for the sugar cane and weekly supplementation groups, respectively. The Number Needed to Treat (NNT) was 2 for group A and B. This means that one in every 2 preschoolers in the intervention groups benefited from the intervention. The 95 % confidence interval for the NNT ranged from 1.3 to 2.8 (group A) and 1.0 to 1.6 (group B).

4. Discussion

The objective of this study was to compare the effect of sugar cane honey given once daily versus once weekly iron supplementation given once weekly versus control on mean Hb concentration and anemia prevalence in preschoolers aged 2-3 years. At baseline, there were no statistically significant differences between the groups for age, gender, EBF during the first 6 months of life, mother's schooling, and family income.

At the end of the intervention, in the intergroup and intragroup comparisons, the following were observed:

a) In the sugar cane honey group -

- there was a significant increase in mean Hb concentration (0.50 g/dL);
- there was a significant reduction in anemia prevalence, from 36.8 to 15.8%;
- for the anemic preschoolers, mean increase in Hb concentration was 1.49 g/dL;
- 15 out of 21 participants who were anemic at baseline had normal hemoglobin levels after intervention;
- there was a significant NNT of 2.

b) In the weekly iron supplementation group -

- there was a significant increase in mean Hb concentration (0.85 g/dL);
- there was a significant reduction in anemia prevalence, from 45.5 to 9.1%;
- for the anemic preschoolers, mean increase in Hb concentration was 1.76 g/dL;
- 16 out of 20 participants who were anemic at baseline had normal hemoglobin levels after intervention;
- there was a significant NNT of 2.

c) In the control group –

- there was a significant decrease in mean Hb concentration (-0.74 g/dL);
- there was a significant increase in anemia prevalence, from 16.7 to 25.0%;
- for the anemic preschoolers, mean decrease in Hb concentration was -0.18 g/dL;
- the number of anemic participants increased from 8 to 12 after intervention.

As far as our review of the literature showed, no randomized controlled trials have been conducted with sugar cane honey. Nevertheless, Arcanjo *et al* (2009), in a randomized, controlled double-blind trial to measure the effect of consumption of a beverage fortified with evaporated sugarcane juice on hemoglobin levels in preschool children, observed significant increase in hemoglobin levels, and decrease in IDA. A review conducted by Jain & Venkatasubramanian (2017) has identified sugar cane honey (sugarcane molasses) as a potential dietary supplement for the management of IDA, due to its iron and its absorption enhancers, such as sulfur, fructose, and copper. Another study by Waheed & Ahmad (2008) witnessed that white sugar is a poor source of essential elements, recommending the introduction of molasses to the diet to achieve nutritional adequacy. 'Panela', which is another non-centrifugal sugar, is produced in a similar manner to that of sugarcane honey (by means of boiling and drying sugarcane juice); since panela is not subjected to a centrifugal process it retains all the natural nutrients of sugarcane (calcium, chloride, potassium, phosphorus, sodium, magnesium, iron, manganese, copper, zinc, chromium, cobalt, vitamin A, beta carotene, thiamin, riboflavin, niacin, pantothenic acid and vitamin C) (De Maria, 2013). In view of this, the consumption of both panela and sugarcane honey may provide beneficial effects through the ready absorption of the iron they contain in considerably high levels.

Weekly iron supplementation has already been the object of different interventions with varying results. In a randomized clinical trial performed by Hawamdeh *et al* (2013) to analyze three regimens of oral iron therapy, daily, once weekly, and twice weekly, in 148 anemic children, aged between 6 and 60 months. The researchers witnessed that the three groups of intervention resolved their anemia in similar proportions at 3 and 12 weeks. Another study conducted in India, a community-based cluster randomized control trial to compare the hemoglobin response with three different regimes: 1) 20 mg iron and 100 mg folic acid – once daily for 100 days, 2) 40 mg iron and 200 mg folic acid – once daily for 100 days, and 3) 40 mg iron and 200 mg folic acid - once a week for 15 weeks, in children aged 3 to 5 years with mild or moderate anemia. After 50 days of intervention, there was no difference between the groups. However, since baseline Hb values were not collected, and due to the fact that this study did not compare the results with a control group, it is difficult to quantify the effect of each intervention (Kapil *et al*, 2013).

A cluster-randomized study by Nogueira Arcanjo *et al* (2013) compared the effect of daily and weekly iron supplementation with control, on hemoglobin values and anemia prevalence in both anemic and non-anemic infants, aged 12 to 24 months. The authors concluded that both weekly and daily iron supplementation were effective in increasing hemoglobin levels and reducing anemia in infants. Another randomized controlled trial was conducted to compare the effects of weekly doses of 30 mg elemental iron (40 doses) and two cycles of 20 daily doses of 30 mg elemental iron separated by a four-month period (40 doses), in children under the age of 5 years; the researchers concluded that both supplementation regimens significantly reduced the prevalence of anemia (Coutinho *et al*, 2013).

De-Regil *et al* (2011) performed a systematic review to assess the effects of intermittent iron supplementation, alone or in combination with other vitamins and minerals, on nutritional and developmental outcomes in children from birth to 12 years of age compared with a placebo, no intervention or daily supplementation. The authors concluded that intermittent iron supplementation is efficacious to improve hemoglobin concentrations and reduce the risk of having anemia or ID when compared with a placebo or no intervention. However, since it is less effective than daily supplementation, its use is recommended in settings where daily supplementation has failed or has not been implemented.

Another review conducted by Lannotti *et al* (2006), to assess the health benefits and risks of iron supplementation in early childhood, found that even though hemoglobin concentrations were improved with iron supplementation among iron-deficient or anemic children, problems of compliance had been identified, hindering the implementation of effective iron-supplementation programs. As a result, the authors suggested the use of diet based approaches for anemia prevention and control.

Some limitations need to be acknowledged and addressed regarding the present study. Many confounding factors affect the outcome of Hb concentrations and anemia prevalence, such as illness, inconsistent eating habits, periods of rapid growth, etc. Another important fact, the period of intervention was short (limited by the school semester), a longer period of time may have presented more conclusive results; also, the intervention was limited to school days (excluding weekends and holidays), in other words the intervention suffered constant interruptions.

Another possible limitation is that this study depended exclusively on Hb concentrations to measure outcomes, without serum ferritin levels or soluble transferrin receptors, which measure iron stores in the organism. However, the inclusion of these measurements would have implied operational difficulties and possibly a lower number of participants in the study. However, despite these limitations our study was able to identify differences between the groups.

Both interventions significantly increased mean Hb concentration in a moderately anemic population of infants in the northeast of Brazil (where anemia prevalence is usually high) compared to control, with a significant decrease in anemia prevalence; most importantly, most of the participants who were anemic at baseline were cured after intervention. However, since sugar cane honey is definitely a more pleasurable and tasty experience (especially for young children) it may be an easier intervention to implement, with greater adherence than traditional supplementation regimes. Furthermore, it would be interesting to better investigate the other nutrients present in sugar cane honey, to identify possible iron absorption enhancers, since this intervention achieved a significant increase in Hb levels with a relatively low iron intake, 0.88 mg/day. This study provides an innovative low-cost strategy to treat and prevent IDA, especially in sugarcane growing countries (Brazil, India, China, Thailand, Pakistan, Mexico, Cuba, Columbia, Australia, USA, Philippines, South Africa, Argentina, Myanmar, Bangladesh, etc.).

For several decades, different iron supplementation and fortification regimes have been implemented to reduce ID, and despite these different strategies in developing low- and middle-income countries, it is still the most common cause of anemia worldwide; furthermore, untreated IDA may cause irreversible sequels especially in young children. In view of this, there is an important and urgent need to find effective and innovative low-cost strategies for the prevention and treatment of IDA. In our study, both sugar cane honey and weekly iron supplementation provided a beneficial effect on Hb values, reducing the prevalence of anemia when compared to control. Moreover, further studies are necessary to confirm the effectiveness of sugar cane honey interventions in different populations on a larger scale.

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