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CLINICAL TRIAL STUDY

Iron Bisglycinate Chelate and Polymaltose Iron for the Treatment of Iron Deficiency Anemia: A Pilot Randomized Trial

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Abstract: ***Background*:** Iron Deficiency Anemia (IDA) is a major public health problem worldwide. Iron Bisglycinate Chelate (FeBC) and polymaltose iron (FeP) are used for the treatment of IDA and exhibit good tolerability with a low incidence of adverse effects. However, these compounds have important differences in their structures and bioavailability.

***Objective*:** To compare the efficacy of oral supplementation with FeBC and FeP in anemic children.

***Methods*:** In this double-blind study, children aged 1 to 13 years who were diagnosed with IDA were randomly divided into two groups: i) FeBC, supplemented with iron bisglycinate chelate, and ii) FeP, supplemented with polymaltose iron (3.0 mg iron/kg body weight/day for 45 days for both groups).

***Results*:** Both treatments resulted in significant increases in hemoglobin levels, Mean Corpuscular Volume (MCV) and Cell Distribution Width (RDW) and in a reduction of transferrin levels, relative to initial values. However, only FeBC treatment significantly increased ferritin and Mean Corpuscular Hemoglobin (MCH) levels. A significant negative correlation was observed between the increase in ferritin and initial hemoglobin levels in the FeBC group, indicating that the absorption of FeBC is regulated by the body iron demand.

***Conclusion*:** These results provide preliminary evidence to suggest a greater efficacy of FeBC than FeP in increasing iron stores.

Keywords: Iron deficiency anemia, iron supplementation, iron bisglycinate chelate, polymaltose iron, bioavailability, ferritin.

1. INTRODUCTION

Iron deficiency results from the progressive long-term reduction of the body iron reserves in the form of ferritin, eventually becoming insufficient to meet the basal needs of the organism. This depletion of iron stores leads to changes that are detected in laboratory tests, including hemoglobin content, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), transferrin saturation, and zinc-erythrocyte protoporphyrin [1].

Iron Deficiency, Anemia (IDA) represents approximately 50% of all anemia cases [2]. This disease may be caused by low bioavailability of iron sources, making the metal less available for erythropoiesis and leaving insufficient stores to compensate for the demands of the organism. Additionally, certain physiological conditions lead to an increased need for iron, as in growing children and women of childbearing age or pregnant [3].

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An estimate by the World Health Organization (WHO) in 2011 showed that IDA affects approximately 800 million children (6-59 months of age) and women, the highest prevalence being in children (42.6%) [4]. This same analysis showed a significant prevalence of IDA in Brazil, affecting 24% of the country's children [4]. Iron deficiency in children may result in changes in growth, motor skills and behavioral and cognitive development, which can be observed even several years after deficiency correction [5, 6].

Among current IDA treatment options, supplementation with ferrous sulfate is one of the most common clinical practices. However, this compound has the disadvantage of low patient compliance due to adverse gastrointestinal effects, which may compromise therapy, especially during the recovery of iron stores after the reestablishment of hemoglobin levels [1].

Iron Bisglycinate Chelate (FeBC) and polymaltose iron (FeP) are the iron compounds used in clinical practice that exhibit greater tolerability and lower incidence of adverse effects compared to iron salts, which represent important advantages for treating IDA [7-10]. FeBC is composed of

two glycine molecules chelated to ferrous iron (Fe^{2+}) ion by covalent bonds [11], while FeP is a stable complex of ferric iron (Fe^{3+}) and partially hydrolyzed dextrin (polymaltose) [12]. These structural differences between FeBC and FeP elicit different responses to these treatments.

Studies reported an increased bioavailability and efficacy of FeBC in increasing the levels hemoglobin and ferritin levels compared to ferrous sulfate [8, 13-15], while these parameters of FeP has been described as similar [7, 10, 12, 16, 17] or less than that of ferrous sulfate, ascorbate or fumarate [18-21]. Although several studies have separately compared the efficacy of FeBC or FeP with ferrous sulfate, there is a lack of studies directly comparing the FeBC and FeP efficacies. Thus, given the high prevalence of IDA in children, the present pilot study aimed to compare the effects of FeBC and FeP supplementation for 45 days on the hematological parameters of anemic children aged 1 to 13 years.

2. METHODS

2.1. Study Participants

The study was conducted from July 2016 to December 2016 in Reino da Garotada, a non-profit institution in the city of Poá, São Paulo state, Brazil. This institution serves families living in precarious social and economic conditions. Twenty anemic children aged 1-13 years completed the study. Those treated with drugs that interfered with iron absorption or supplemented with iron 60 days before the start of treatment were excluded from the study. None of the participants had any signs of infection (fever, vomiting or diarrhea) on blood collection days. Children weighing over 30 kg were also excluded, as they received a standard dose of 90 mg iron, which was not proportional to their weight.

2.2. Iron Supplementation

Supplements consisted of identical-looking syrups, named A and B, with the same elemental iron concentration (10 mg Fe/mL), in the form of FeBC (Ferrochel, Albion Laboratories Inc., Clearfield, UT, USA) or FeP (Noripurum, Takeda Pharma Ltda., Jaguariúna, SP, Brazil). Syrups were prepared by Sensitiva Pharmacy (Farmácia Sensitiva, São Paulo, SP, Brazil), following the Good Pharmaceutical Practices established by the Agência Nacional de Vigilância Sanitária (ANVISA). The supplements were produced every 10 days to avoid oxidation or deterioration. Children were supplemented once daily for 45 days with 3.0 mg of elemental iron per kg of body weight. Syrup dosage was measured using a 20 mL standard graded measuring syringe made of clear plastic for best volume accuracy. Syrups were given with meals, as is common in the IDA treatment [22]. Anemic children not included in the study received the same treatment as those included, and non-anemic children participated in an iron fortification program.

2.3. Experimental Design

The study was characterized as randomized and double-blind, with groups normalized by age. Children with hemoglobin levels, measured by portable hemoglobin analyzer (HemoCue Hb301, Ängelholm, Sweden), below the WHO stipulated IDA criteria (children aged 6-59 months, <11.0 g/dL; 5-11 years, <11.5 g/dL; 12 years or older, <12.0 g/dL) [23] were referred for complete blood count, ferritin, and transferrin tests in a specialized laboratory. Only those children who had confirmed hemoglobin levels below the WHO criterion by means of complete blood count and who presented alterations in at least one of the other parameters related to iron metabolism (MCV, MCH, ferritin or transferrin levels according to Table **1**) were included in the study [1, 23, 24]. None of the patients had low hemoglobin and MCV and normal transferrin and ferritin, consistent with thalassemia trait [25].

Table 1. Age-dependent limits of normal for hemoglobin and iron status parameters (MCV, MCH, ferritin and transferrin) for children adopted in the present study as the eligibility criteria (MCH, Mean Corpuscular Hemoglobin; MCV, Mean Corpuscular Volume).

Parameter	Age	Value
Hemoglobin	6-59 mo	< 11.0 g/dL
	5-11 yo	< 11.5 g/dL
	12-14 yo	< 12.0 g/dL
MCV	1-23 mo	< 67 fL
	24-59 mo	< 73 fL
	5-7 yo	< 74 fL
	8-12 yo	< 76 fL
MCH	1-23 mo	< 22 pg
	2-7 yo	< 25 pg
	8-12 yo	< 26 pg
Ferritin	6-59 mo	< 12 ng/mL
	5+ yo	< 15 ng/mL
Transferrin	1-14 yo	> 365 mg/dL

Children diagnosed with IDA were randomized using computer generated random numbers, by an independent statistician, who was not an investigator, into 2 groups: i) FeBC group, supplemented with iron bisglycinate chelate (n=9) or ii) FeP group, supplemented with polymaltose iron (n=11). A trained nurse technician administered the treatments to each child after the main meal as a single daily dose for 45 days. Participating children, care providers and investigators who accessed outcomes were blind to the exact intervention administered. Unblinding was performed only after completion of the study. Data regarding side effects were collected systematically for each child every treatment day by the nursing technician.

2.4. Statistical Analysis

Statistical analyses were performed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL, USA) and included only the data from patients who completed this trial. Statistical analyses were conducted on the Least Square Means (LSM) of each component of the treatments with FeBC and FeP. An analysis of covariance was performed on hemoglobin levels. The 95% Confidence Intervals (CIs) for the difference of the Least-Squares (LS) means between FeBC and FeP groups were calculated. Pearson correlation tests were performed to assess the relationship between initial hemoglobin status and the increase in ferritin levels. The data are presented as mean±SEM or mean difference [95% CI]. For all analyses, a P value <0.05 was considered statistically significant.

2.5. Hematologic and Anthropometric Assessments

A portable hemoglobin analyzer, HemoCue Hb301 (HemoCue AB, Ängelholm, Sweden), was used to measure hemoglobin levels. Blood samples were collected by digital puncture. Transferrin levels were measured by immunoturbidimetry, and ferritin was measured by chemiluminescence (Siemens Healthcare Diagnostics, Deerfield, IL, USA). MCV, MCH and RDW were measured by standard clinical laboratory methods (XE 2000, Roche Diagnostics, Mannheim, Germany). Blood samples were collected prior to treatment with iron and after completion of the study. Therefore, each child served as their own control.

Children were weighed using an electronic scale (EB9013, Camry, São Paulo, Brazil), and those under 2 years of age were weighed along with a guardian, whose weight was then subtracted from the total weight to obtain the child's weight. The heights of the children were measured with an anthropometer (Balmak, São Paulo, Brazil), and children under 2 years of age were measured horizontally using an infantometer (INF100, Balmak). All children were weighed without shoes and wearing light clothing. The weight and height were measured twice, and the mean values were used. Measurements were repeated when the two initial measurements had differences above 100 g for weight, and 1 cm for height.

2.6. Ethical Considerations

The study protocol was approved by the Research Ethics Committee of the School of Medical and Health Sciences of the Pontifícia Universidade Católica de São Paulo (No 1.412.059, CAAE 52679615.4.0000.5373) and is registered with the WHO under Universal Trial Number U1111-1216-2727. The study, its objectives and methodology were explained in detail to participants and guardians of the children before the study began. All children and guardians agreed to participate in the study and gave written informed consent.

3. RESULTS

3.1. Research Subjects

Initially, all 395 children of the institution of both genders, from 1 to 14 years old, were invited to participate in the study, all of whom underwent hemoglobin measurement using the HemoCue device. A total of 67 children had hemoglobin levels below the criteria for IDA stipulated by the WHO (children aged 6-59 months, <11.0 g/dL; 5-11 years, <11.5 g/dL; 12 years or older, <12.0 g/dL) [23] and were referred for complete blood count, ferritin and transferrin tests in a specialized laboratory. In total, 26 children were confirmed to have IDA. One child presented divergent results compared to the others and was referred for medical follow-up for more detailed evaluation. Five children weighed over 30 kg and were excluded from the study, as previously mentioned. One child from FeBC group did not complete the study. Thus, a total of 20 children, aged 1-13 years, participated in the study. The initial characteristics of the children are summarized in Table **2**. There were no variations regarding their initial descriptive measures, demonstrating homogeneity between groups. During the intervention, no adverse effects were reported.

3.2. Iron Parameters Evaluated

The effects of FeBC or FeP treatments for 45 days on hemoglobin, MCV, MCH, RDW, transferrin, and ferritin

Table 2. Summary of the initial characteristics of the two groups (FeBC, iron bisglycinate chelate; FeP, polymaltose iron).

Group	FeBC	FeP
Type of treatment	Iron bisglycinate chelate	Polymaltose iron
Number of participants	9	11
Age (years)	3.9±1.2	3.9±0.7
Gender (Males)	6	7
Body weight (kg)	16.1±1.8	17.3±1.5

levels are shown in Table **3**. There were no significant differences between the two groups compared to baseline levels. Both treatments resulted in significant increases in hemoglobin, MCV and RDW levels and reduction in transferrin level compared to baseline. However, only the FeBC group showed a significant increase in MCH and ferritin levels compared to baseline. No significant differences were observed between the initial and final levels of MCH and ferritin in FeP group. Fig. (**1**) shows the initial and final ferritin levels in both groups.

3.3. Correlation Between Initial Hemoglobin and Increased Ferritin

To evaluate the possible relationship between initial hemoglobin levels and the increase in ferritin levels, a correlation analysis was performed (Fig. **2**). A significant negative correlation was observed in the FeBC group (r=-0.667, p=0.025). This result indicates that the lower the initial hemoglobin level is, the higher the ferritin increase in this group, suggesting that the increase in iron stores was regulated by the need of the subjects. No significant correlation was found in the FeP group (r=-0.429, p=0.094).

4. DISCUSSION

In this work, we observed that both FeBC and FeP treatments led to increased hemoglobin, MCV, RDW, and decreased transferrin levels. However, only the FeBC group showed a significant increase in ferritin and MCH. These results provide preliminary evidences to suggest a greater efficacy of FeBC for treating IDA, which is notable considering that the treatment duration was limited to 45 days and a low dose was administered, with iron supplementation at the lower limit of the recommended therapeutic dose for children (3-6 mg/kg of elemental iron/day) [26].

Hemoglobin and ferritin are considered the most efficient indicators of response to iron treatment. The measurement of hemoglobin content is more commonly used, largely because of its low cost and fast results. However, in most circumstances, serum ferritin is the most sensitive and specific method among the various tests to diagnose IDA, and is superior to tests such as transferrin saturation, mean cell volume, and quantification of zinc protoporphyrin levels [27]. This method is recommended by the WHO to determine the stored iron concentration, since the ferritin levels correlate with the bodily iron stores [1]. Ferritin polymers form box-

Table 3. Results of hemoglobin, MCV, MCH, RDW, transferrin and ferritin in anemic children before and after treatment with iron (FeBC, Iron Bisglycinate Chelate; FeP, Polymaltose Iron, MCH, Mean Corpuscular Hemoglobin; MCV, Mean Corpuscular Volume; RDW, Cell Distribution Width).

Parameter	FeBC			FeP		
	Initial	Final	95% CI	Initial	Final	95% CI
Hemoglobin (g/dL)	10.7±0.2	12.2±0.3*	[0.925; 2.053]	10.7±0.2	12.2±0.2*	[1.074; 2.108]
MCV (fL)	72.5±2.4	74.2±2.3*	[0.290; 2.933]	73.8±1.2	76.1±1.3*	[0.695; 3.850]
MCH (pg)	24.4±1.0	24.9±0.9*	[0.038; 0.940]	24.9±0.5	25.5±0.5	[-0.071; 1.235]
RDW (%)	14.4±0.5	15.0±0.4*	[0.061; 0.961]	14.3±0.4	14.9±0.5*	[0.012; 1.260]
Transferrin (mg/dL)	302±15.6	276±12.4*	[-48.480; -5.075]	301±9.1	276±2.7*	[-42.477; -8.432]
Ferritin (ng/mL)	21±3.9	37±5.0*	[9.337; 22.219]	25±5.2	34±3.9	[-0.221; 18.039]

Note: Values are expressed as the mean±standard error of the mean (SEM), [95% CI]. *Significant difference compared to baseline values (p<0.05).

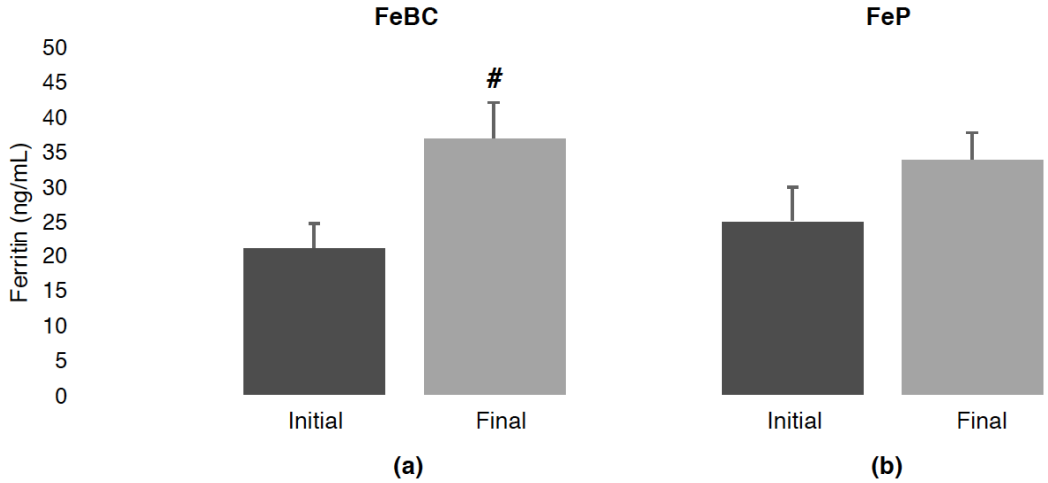

Fig. (1). Initial and final levels of ferritin in the groups treated with **(a)** iron bisglycinate chelate and (**b**) polymaltose iron. #p<0.05. Values are expressed as the mean±SEM (FeBC, iron bisglycinate chelate; FeP, polymaltose iron).

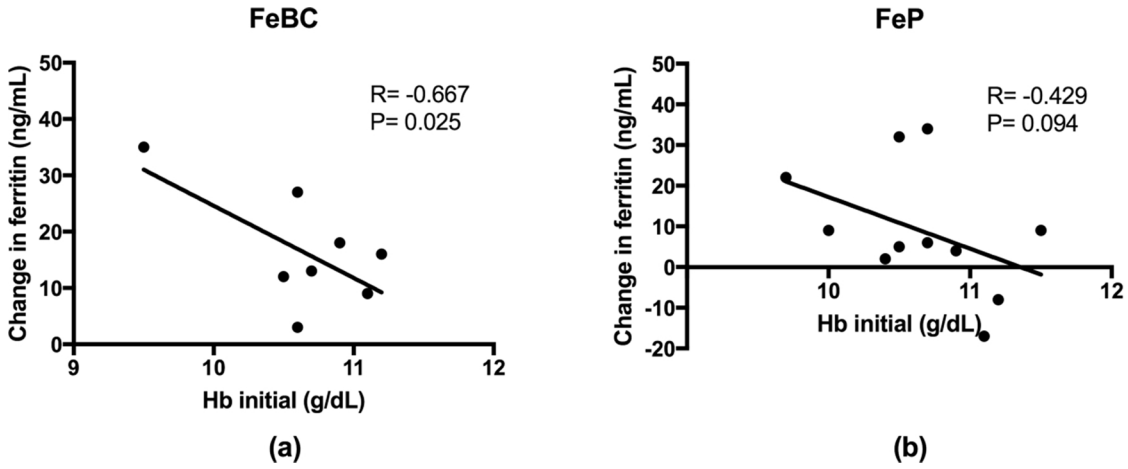

Fig. (2). Correlation analysis between initial hemoglobin levels and the change in ferritin levels after treatment. A significant negative correlation was observed in the group treated with iron bisglycinate chelate (FeBC) (**a**), while no correlation was observed in the group treated with polymaltose iron (FeP) (**b**). Two children treated with FeBC presented the same values of initial hemoglobin (11.1 g/dL) and change in ferritin (9.0 ng/mL), resulting in two overlapping points in (a).

like structures, each with a central cavity for storing iron. This protein guarantees the iron homeostasis while avoiding the harmful effects of its free ionic form [28].

Treatment of IDA with iron supplements can be divided into two phases: first the hemoglobin levels are restored and then the iron stores are replenished. However, to fully restore this mineral reserve, supplementation should continue for approximately 3 months after the normalization of hemoglobin levels [29]. Unfortunately, this strategy generally does not achieve the expected outcome due to patients' lack of adherence to treatment [30], mainly due to adverse effects such as epigastric discomfort, nausea, diarrhea or constipation [1]. Although both FeBC and FeP show good tolerability, exhibiting a lower incidence of adverse events when compared to ferrous sulfate [7, 8], FeBC appears to be more effective in replenishing iron stores, favoring a reduction in required supplementation time. This represents an important advantage for treating IDA by reducing incomplete treatments that frequently occur for varied reasons.

Literature data demonstrated that FeBC is effective in increasing iron stores and is superior to ferrous sulfate [8, 13-15]. In one such study, 40 children (6-36 months) with IDA received a daily dose of folic acid (250 mg) and iron (5 mg/kg body weight) as FeBC or ferrous sulfate. After 28 days, hemoglobin concentrations increased in both groups; however, only the FeBC group showed increased ferritin levels [13]. Moreover, compared to ferrous sulfate, FeBC supplementation has been shown to elicit a more sustained ferritin increase [14]. Another study showed that supplementation with FeBC or ferrous sulfate (30 mg elemental iron/day) for 90 days in 200 children (5-13 years old) with low ferritin levels resulted in an increase in ferritin. However, six months latter, this increase was significantly higher in the FeBC group [14].

In contrast, studies have indicated that FeP is less effective than ferrous sulfate in increasing iron stores [7, 31, 32]. One study compared the effects of supplementation with FeP (100 or 200 mg elemental iron) or ferrous sulfate (120 mg elemental iron) for 12 weeks in iron-deficient adults [33]. Only ferrous sulfate significantly increased ferritin, indicating that supplementation with FeP did not increase the iron stores of the subjects even at a dose almost twice that of ferrous sulfate. Moreover, supplementation with 200 mg of FeP presented similar efficacy to 120 mg of ferrous sulfate, reestablishing normal hemoglobin levels in 80% of patients, whereas 100 mg of FeP led to the reestablishment of hemoglobin in 50%. Similar results were observed for other erythrocyte markers, including MCH [33]. Another recent study with 59 anemic children aged 9-48 months compared iron supplementation with ferrous sulfate or FeP at the same dose of the present study (3 mg/kg body weight) for 12 weeks [34]. Ferrous sulfate treatment resulted in a 1.0 g/dL greater increase in hemoglobin levels and in higher ferritin increase and proportion of children with complete resolution of IDA compared to FeP treatment. Interestingly, FeP treatment resulted in a significantly higher incidence of diarrhea [34].

In the present study, we observed a significant increase of MCH in the FeBC group, but not in FeP group. MCH is derived from the red blood cell count and hemoglobin concentration and, as a measure of the entire circulating mass of red blood cells, it changes slowly. These changes are detected only after several weeks or months of storage of iron by the body [35]. This result reinforces preliminary evidence of greater effectiveness of FeBC in restoring bodily iron stores compared to FeP.

The structural and absorption characteristics of FeBC and FeP may contribute to the differences in their bioavailability and efficacy when compared to other compounds. Several studies showed that FeBC has high bioavailability, better absorption, higher efficacy in increasing hemoglobin and ferritin levels, and greater performance in treating IDA compared to ferrous sulfate [8, 13, 36-41]. The bioavailability of FeP, in turn, was described as similar to that of ferrous sulfate [7, 12, 16, 17]. However, studies indicate lower bioavailability of this compound compared to ferrous sulfate or fumarate [18-21].

Iron bisglycinate chelate has a stable structure, with a molecular weight of approximately 204 daltons (Da),

whereas FeP are complexes with molecular weights between 50,000 and 452,000 Da [42]. High molecular weight compounds may be more difficult for the body to absorb. For example, amino acid-chelated minerals should have a maximum molecular weight of 1,000-1,500 Da to be properly absorbed [43, 44]. Likewise, a dramatic reduction in bioavailability was observed for macromolecules above 600 Da [45, 46]. Therefore, these differences in their structures and size may contribute to different absorption rates.

The mechanisms of iron absorption differ between FeBC and FeP. FeP has a slow rate of iron transfer from the intestinal lumen to the portal circulation. One study in rats showed that this transfer rate peaked at 30 minutes with ferrous ascorbate, in contrast to 24 hours required for FeP [47], whereas the absorption of FeBC was higher than that of ferrous sulfate (8.68% *vs*. 1.34%, $p<0.0001$) in a study using a dual-radioisotope method. FeBC was consistently 5.3 times more absorbed than ferrous sulfate, and this ratio was not altered by the simultaneous consumption of both compounds, indicating no exchange between the two iron sources in the intestinal pool or before entering the mucosa – if there were such an exchange, equal proportions of the two compounds would be absorbed. This result indicates that FeBC enters the cellular mucosa in a chelated form [44], which reinforces the importance of structure and size of the compound in determining its absorption.

The regulation of iron absorption according to the need of the organism is important to avoid metal-induced oxidative damage and the negative consequences of iron overload, which include diabetes, osteoporosis, joint pain and neurodegeneration [48]. Our results indicated a significant inverse correlation between the initial hemoglobin levels and the increase in iron reserves provided by FeBC supplementation (r=-0.667, p=0.025), *i.e*., FeBC increased ferritin levels in individuals with low initial hemoglobin levels. This result suggests that the absorption of FeBC is regulated by the iron demand of the organism, corroborating previous results that showed the same correlation between the absorption of FeBC and basal hemoglobin [13, 49] and ferritin [50-53] levels. This characteristic suggests that this compound is safe as a therapeutic agent for treating iron deficiencies and for long-term supplementation or food fortification, even after normalization of hemoglobin levels.

On the other hand, the absence of significant correlation between increases in ferritin and initial hemoglobin levels in the FeP group corroborates previous data by Devaki *et al*. [54]. In that study, adolescents with different initial iron status (healthy, iron-deficient, or IDA) were supplemented with 100 mg/day of FeP. The highest increases in ferritin (91.5 ng/mL after 4 months of treatment) were observed in healthy adolescents, who had higher initial hemoglobin levels (13.5±0.2 g/dL), than iron-deficient adolescents (12.5±0.2 g/dL) or anemic adolescents (10.0±0.2 ng/dL). To the best of our knowledge, no studies have found that iron absorption from FeP is regulated by the initial iron status of the organism, which may suggest a greater propensity of this compound to lead to iron overload.

The present work is a pilot study because of limitations imposed by the small number of participating children and the short treatment duration, which underscores the importance of an expanded future study to further explore this important safety issue of treating IDA in children.

CONCLUSION

The present work provides preliminary evidence to suggest that FeBC is more effective than FeP in increasing iron stores in the body. Moreover, the results suggest that, in contrast to FeP, FeBC absorption is proportional to iron demand, showing it to be a safe compound for treating IDA.

LIST OF ABBREVIATIONS

ANCOVA	=	Analysis of Covariance
ANVISA	=	Agência Nacional de Vigilância Sanitária
CI	=	Confidence Interval
Da	=	Daltons
FeBC	=	Iron Bisglycinate Chelate
FeP	=	Polymaltose Iron
IDA	=	Iron Deficiency Anemia
LSM	=	Least Square Mean
MCH	=	Mean Corpuscular Hemoglobin
MCV	=	Mean Corpuscular Volume
RDW	=	Cell Distribution Width
WHO	=	World Health Organization

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Research Ethics Committee of the School of Medical and Health Sciences of the Pontifícia Universidade Católica de São Paulo (No 1.412.059, CAAE 52679615.4.0000.5373) and is registered with the WHO under Universal Trial Number U1111-1216-2727.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/).

CONSENT FOR PUBLICATION

All children and guardians agreed to participate in the study and gave written informed consent.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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J.J.N. and C.V.R.M conceived the experimental design of the study. C.V.R.M. and A.R.V. conducted the study experiments. All authors analyzed the results, wrote the article

and approved the final submitted manuscript. We thank the staff of the Reino da Garotada and Dr. Marcia Gutierrez of the Sensitiva Compounding Pharmacy who kindly prepared the iron supplements.

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