Effectiveness of Treatment of Iron-Deficiency Anemia in Infants and Young Children With Ferrous Bis-glycinate Chelate

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Forty infants, 6 to 36 mo old, with iron-deficiency anemia (hemoglobin < 11 g/dL) were matched and assigned to two groups. One group received $FeS0_4$ and the other received ferrous bis-glycinate chelate at a dose of 5 mg of Fe daily per kilogram of body weight for 28 d. Both groups had significant hemoglobin increases ($P < 0.001$), but only the group treated with ferrous bis-glycinate chelate had significant increases ($P < 0.005$) in plasma ferritin. Apparent iron bioavailabilities were calculated at 26.7% for $FeS0_4$ and 90.9% for ferrous bis-glycinate chelate. Regression analysis indicated that absorption of both sources of iron were similarly regulated by the body according to changes in hemoglobin. We concluded that ferrous bis-glycinate chelate is the iron of choice for the treatment of infants with iron-deficiency anemia because of its high bioavailability and good regulation. *Nutrition* 2001;17:381–384. ©Elsevier Science Inc. 2001

KEY WORDS: anemia, infants, ferrous bis-glycinate chelate, $FeS0_4$, hemoglobin, ferritin, iron

INTRODUCTION

Iron deficiency is the single most common nutrient deficiency in the world today and affects affluent societies and developing countries.[1] The World Health Organization estimated that more than 1.3 billion people have iron deficiency or iron-deficiency anemia and that about 1.2 billion of these people are located in developing countries.[2,3] Most of the affected individuals are young children who are particularly susceptible because of their rapid growth rates and small, if any, iron reserves. This results in exogenous iron needs that are inadequately met by traditional diets.[4]

In healthy, full-term infants, born from well-nourished mothers, the first 3 to 4 mo of life are characterized by a relative abundance of iron, with 50 mg of the 75 mg Fe/kg of body weight present in their erythrocytes and the remainder in their tissues. The hemoglobin level of a newborn usually declines to about 10 g/dL by postnatal weeks 6 to 8. As rapid growth is established, the iron stores of the infant are mobilized for the production of supporting hemoglobin, myoglobin, and iron enzymes. By 4 mo of age, infant iron stores are generally depleted.[5–7]

During early infancy, the infant is maintained exclusively by breast-feeding. The quantity of iron in breast milk ranges from approximately 0.05 mg/L to approximately 1.5 mg/L, with the median being 0.47 mg/L, depending on the stage of lactation.[8] The usual daily intake of the baby is approximately 600 mL of milk.[9] Up to 1 y of age, the daily iron requirement of most infants is approximately 0.96 mg/d. By 4 mo of age, the infant's iron stores have been depleted, and the contribution of iron in breast milk is approximately 0.28 mg/d. Thus, the need for exogenous iron becomes a priority. This need is even more critical in infants with low birth weights or from mothers with lower amounts of iron in their breast milk. When supplemental iron is unavailable, a high prevalence of iron-deficiency anemia occurs in infants 6 to 36 mo old.[6]

Iron-deficiency anemia in infants, if not corrected rapidly, can interfere in normal maturation and development. Children who were anemic as infants may demonstrate measurably lower motor skills and, in some instances, irreversible mental alterations when entering school at about age 7 y.[10–12] There also is decreased resistance to infections and increased morbidity associated with iron-deficiency anemia.[4] Thus, the need to prevent and/or treat iron-deficiency anemia as rapidly as possible is of great importance in preserving the health and maintaining normal growth and development of the child.

Because the iron requirements of rapidly growing infants ($\geq$4 mo) are generally greater than can be met solely by the limited quantity of iron in breast milk, their diets must be augmented with additional food. One widely used method is supplementing the breast milk with iron-fortified cow's milk or specially fortified baby formulations. Bioavailability studies have clearly shown that the source of the iron that fortifies this supplemental food is as important as the total amount.[7] Because of their low solubility, some iron salts are poorly absorbed from the intestine. To enhance their bioavailability, ascorbic acid may be included. In the case of more soluble iron salts, once ionized, the Fe^{+2} ion still may not be absorbed because of potential reactions with a number of naturally occurring dietary constituents such as other metals, fibers, fats, and/or phenols.[13–16]

The present study compared the efficiency of using soluble ferrous sulfate or ferrous bis-glycine chelate to treat iron-deficiency anemia. Ferrous bis-glycinate chelate (CAS Registry No. 2015034–9) is composed of two molecules of glycine that are chelated to an atom of ferrous iron by covalent and coordinate covalent bonds. This particular form of chelated iron was reported to be effective in reversing iron-deficiency anemia in adults, adolescents, and young children.[17–20]

MATERIALS AND METHODS

Forty infants aged 6 to 36 mo participated in the study. These children were admitted to the Nutritional Recovery Unit of the Pediatric Department of the San Juan de Dios General Hospital in

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TABLE I.

A SUMMARY OF THE CHARACTERISTICS OF THE TWO GROUPS

Group	A	B
Type of treatment	Ferrous Sulfate	Fe Bis-glycinate Chelate
Number of participants	20	20
Age (mo)	19.5 ± 7.43	20.15 ± 8.24
Sex ratio (M:F)	1:1	1.5:1
Body weight (kg)	7.96 ± 2.18	6.16 ± 1.56
Initial hemoglobin (g/dL)	8.72 ± 1.638	8.04 ± 1.493
Initial ferritin (μg/L)	43.9 ± 23.2	53.6 ± 36.18
Weight/height	69.6 ± 5.27	67.05 ± 12.6

Guatemala City. The hospital is located at an altitude of 5000 ft (1500 m) above sea level. Besides being anemic, all infants had protein-energy malnutrition, with or without edema. Each infant had a weight/height index no greater than 75% of normal. For inclusion in the study, the hemoglobin levels of each infant had to be below 11 g/dL. Any child who had chronic inflammation, renal insufficiency, or active infections or had been treated with chloramphenicol or other drugs that interfered with iron absorption was excluded from the study. Before participating in the study, written authorization was obtained from the parents of each child. All the infants completed the study. Before commencing this study, the protocol was reviewed and approved by the hospital's Internal Human Rights Committee.

The study was a double-blind design, and the treatments were identified only at the conclusion of the study, after statistical analysis of the data had been completed. The treatments consisted of identically appearing syrups labeled A and B that contained equal amounts of iron per milliliter (30 mg Fe/mL) as ferrous sulfate or ferrous bis-glycinate chelate (Ferrochel, Albion Laboratories Inc., Clearfield, UT, USA). The syrups were prepared by Unipharm Pharmaceutical Company in Guatemala City. The standard treatment protocol of the hospital called for a daily dosage of 5 mg of iron per kilogram of body weight and 250 μg/d of folic acid. These treatments were administered to each child as a single dose of the required amount of iron based on body weight plus folic acid. The study lasted 28 d.

At the beginning of the study, each participant was assigned to one of two treatment groups, A or B. During the study, all children were closely evaluated to detect any type of intolerance to either iron treatment; none was detected. Each child in group A was matched as closely as possible to a child in group B in terms of malnutrition type, age (±5 mo), and hemoglobin level. To that end, the infants were initially grouped according to hemoglobin ranges before being assigned to group A or B. The hemoglobin-level ranges selected were 5 to 7, 8 to 9, and 10 to 11 g/dL.

The mean plasma ferritin level was higher than the value normally accepted as an indicator of depleted iron stores (10 μg/L). However, increased ferritin levels are common findings in severely malnourished children or those just recovering from malnutrition. This finding might be due to undetected mild infections that result in transient increased values for ferritin. We believe that the children in this study likely were malnourished, but we did not verify it. (At the conclusion of the study, after treatment with iron, the plasma ferritin levels increased significantly, which was interpreted as indicative of replenished iron stores despite the rather high initial values. To emphasize this point, actual values rather than geometric means are reported.)

The characteristics of the children in the study are summarized in Table I.

Two heparinized blood samples were taken from a dorsal vein in the hand of each child for the determination of hemoglobin and ferritin, one sample before iron treatment and another 28 d later, at the conclusion of the study. Thus, each child served as its own control. Hemoglobin was determined with the procedure recommended by the International Committee for Standardization in Hematology.[21] Ferritin was measured by a commercial radioimmunoassay procedure (Fer-Iron II, Ramco Laboratories, Inc., Houston, TX, USA).

For statistical analysis, software from Statgraphs and Statistical Analysis for the Sciences (SAS) was used. Distribution analysis, notched box and whisker plots, paired *t* tests, least-significant difference error intervals, and analysis of variance were done. The apparent iron bioavailability of each iron source in the formulas was measured according to the methods of Gordeuk et al.[22] and Forbes et al.[23]

TABLE II.

EFFECT OF 28 D OF TREATMENT WITH FERROUS BIS-GLYCINATE CHELATE OR FERROUS SULFATE ON HEMOGLOBIN LEVELS*

Group	*n*	Mean ± SD (g/dL)		
		Basal	Posttreatment	Change†
A (ferrous sulfate)	20	8.7 ± 1.64	10.5 ± 0.81	1.8 ± 1.59
B (ferrous bis-glycinate chelate)	20	8.0 ± 1.49	10.5 ± 0.22	2.5 ± 1.31

* Analysis of variance showed no difference within basal or treatment groups but significant differences between basal and treatment values ($P < 0.001$).

† Posttreatment minus basal values.

RESULTS

The 28-d effect of the daily treatment with 5 mg of iron/kg of body weight from ferrous sulfate or ferrous bis-glycinate chelate on the hemoglobin levels is shown in Table II. Analysis of variance showed no statistical difference between the hemoglobin levels of the two groups at the beginning of the study. Both treatments resulted in significant increases in hemoglobin levels ($P < 0.001$). The mean increase in the hemoglobin of the group receiving ferrous bis-glycinate chelate was greater than that of the group receiving ferrous sulfate, but the difference between the two treatments was not significant.

When active infections are absent, iron stores within the body can be estimated by measuring the increase in ferritin.[24] In this study, both treatments resulted in increased levels of plasma ferritin. However, only the treatment with ferrous bis-glycinate chelate resulted in significant ferritin increases ($P < 0.005$), as seen in Table III. Analysis of variance showed no significant difference in mean plasma ferritin levels between groups A and B at the beginning of the study but did show a significant difference at the end ($P < 0.05$).

Regression analysis of the data confirmed that absorption of ferrous bis-glycinate chelate or ferrous sulfate was regulated by the iron requirements of the participating individuals. As shown in Figure 1, the change in hemoglobin was inversely proportional to the basal hemoglobin level, regardless of the source of iron used in the treatment. The magnitude of the slope regression was similar for both iron compounds, even though ferrous bis-glycinate chelate absorption was greater than ferrous sulfate. Both ferrous bis-glycinate chelate and ferrous sulfate were strongly correlated (−0.66 and −0.86, respectively).

TABLE III.

EFFECT OF 28 D OF TREATMENT WITH FERROUS BIS-GLYCINATE CHELATE OR FERROUS SULFATE ON PLASMA FERRITIN LEVELS*

Group	*n*	Mean ± SD (μg/L)		
		Basal	Treatment	Change
A (ferrous sulfate)	20	43.9 ± 23.20	70.4 ± 45.71	26.5 ± 53.98
B (ferrous bis-glycinate chelate)	20	53.6 ± 36.18	128.2 ± 86.94	74.6 ± 75.90

* Analysis of variance showed no difference within basal groups. There was a significant treatment effect for iron bis-glycinate chelate ($P < 0.005$) but not for $FeSO_4$. There was also a significant difference ($P < 0.05$) between groups after 28 d.

DISCUSSION

After 28 d of treatment, there were significant increases in hemoglobin levels and body iron reserves as measured by plasma ferritin levels after treatment with ferrous bis-glycinate chelate. The results clearly indicate that more of the iron from the chelate than from ferrous sulfate was absorbed, which suggests a higher bioavailability for the ferrous bis-glycinate chelate.

With the data presented in Tables II and III, which summarize the changes in hemoglobin and ferritin, the apparent bioavailability of each source of iron was calculated. Total blood volume was estimated at 75 mL/kg of body weight.[25] The total iron ingested during the 28 d of treatment was known, based on the daily intake of 5 mg Fe/kg of body weight. Because of differences in the body weights of the children participating in the study and the prescribed hospital protocol of daily administration of 5 mg Fe/kg of body weight, total iron intakes were 1120 mg for the group receiving ferrous sulfate and 868 mg for the group receiving ferrous bis-glycinate chelate. One gram of hemoglobin contains 3.44 mg of iron, and 1 μg/L of ferritin is estimated to represent 10 mg of deposited iron.[22,23] These figures can thus be incorporated into the following formula to estimate apparent iron bioavailability (AB; H, hemoglobin, Hb).

$$\%AB = \left(\frac{[body\ weight\ \{kg\} \times 0.075][\Delta Hb\ \{g/L\} \times 3.44 + [\Delta ferritin\ \{\mu g/L\} \times 10]}{total\ Fe\ intake\ [mg]} \right) \times 100$$

The apparent bioavailabilities of the ferrous bis-glycinate chelate and ferrous sulfate were 90.9% and 26.7%, respectively, in participating infants. The ratio of apparent bioavailabilities showed that the ferrous bis-glycinate chelate was absorbed 3.4 times better than ferrous sulfate.

The greater bioavailability of the ferrous bis-glycinate chelate has been confirmed in other studies. A dose–response study of adolescents reported that 30 mg of iron from the ferrous bis-glycinate chelate were as effective in treating iron-deficiency anemia as 120 mg of iron from ferrous sulfate. In this same study, treatments with 60 or 120 mg of iron from the ferrous bis-glycinate chelate resulted in higher plasma ferritin levels than did 120 mg of iron from ferrous sulfate.[18]

In a study of college-age students, iron absorptions from $^{59}FeS0_4$ and ^{55}Fe bis-glycinate chelate were compared when the two iron sources were mixed and consumed together in a breakfast meal of cornmeal porridge. The iron from the ferrous bis-glycinate chelate was consistently absorbed approximately 4.7 times more than the ferrous sulfate, and the difference was significant ($P < 0.05$).[20]

In a study of marginally iron-deficient adult women, the absorptions of ^{55}Fe bis-glycinate chelate and ^{59}Fe-labeled ferrous ascorbate were compared. Not only was the ferrous bis-glycinate chelate better absorbed than ferrous ascorbate (52% versus 40%), but the absorption of this chelate was regulated by the body iron reserves in a manner similar to that of ferrous ascorbate or ferrous sulfate.[26]

The regression analysis data shown in Figure 1 also suggest

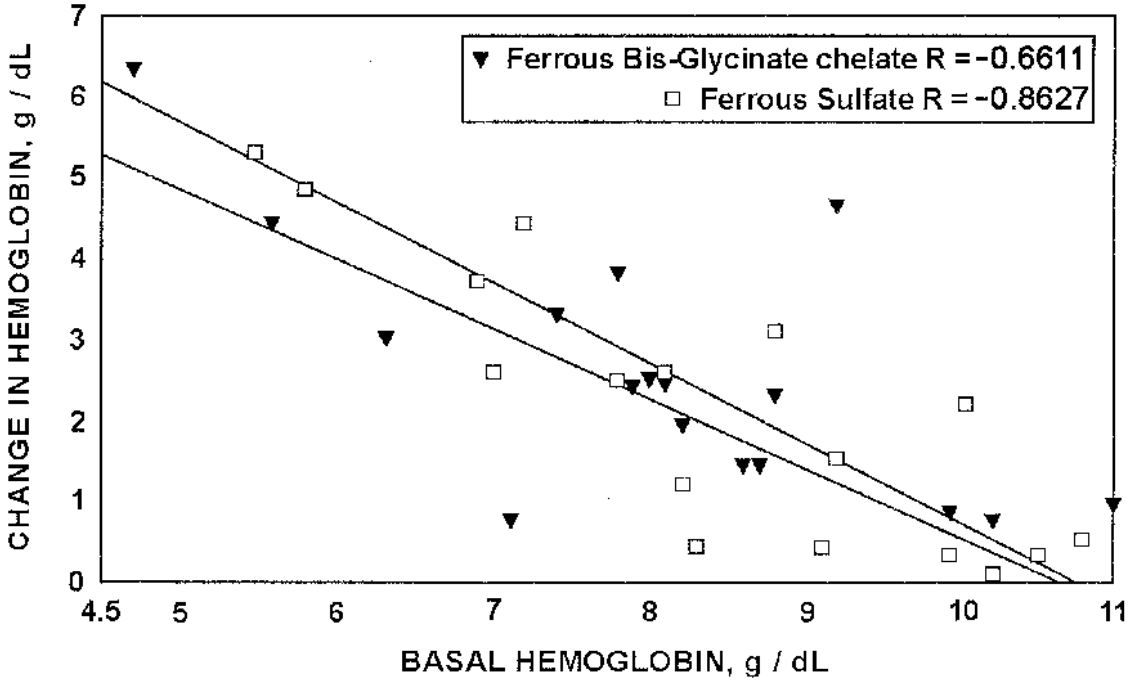

FIG. 1. Regression analysis shows that iron-absorption values were inversely proportional to hemoglobin levels, regardless of the iron source.

that the mechanisms regulating the absorption of the two forms of iron in this study are also similar. Bovell-Benjamin et al. found a similar regulation in their regression analysis of ferrous bis-glycinate chelate and ferrous sulfate.[20] Iost et al. also reported the regulation of iron absorption after a 7.3 mo study in anemic children in Brazil.[19] The study by Fox et al.[27] on weaned infants, which was elaborated upon by Ashmead,[28] found apparent regulation of the absorption of iron from ferrous sulfate and ferrous bis-glycinate chelate. The exact mechanism regulating ferrous bis-glycinate chelate requires further elucidation.

CONCLUSION

In a study of infants with iron-deficiency anemia, ferrous bis-glycinate chelate was absorbed or retained 3.4 times greater than ferrous sulfate, making it the iron of choice for treatment. Regression analysis showed that absorption of the bis-glycinate chelated form of iron was regulated by the iron status of the body similarly to ferrous sulfate.

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