Comparison of ferrous sulfate and ferrous glycinate chelate for the treatment of iron deficiency anemia in gastrectomized patients

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Abstract  
Objectives: Postgastrectomy iron deficiency anemia has a variable prevalence and occurs in 20–50% of patients. Food fortification reports examining ferrous glycinate chelate have shown that it can be 2.5–3.4 times more bioavailable than ferrous sulfate, with minimal gastrointestinal symptoms. The present study was designed as a controlled experimental study including 18 gastrectomized patients with iron deficiency anemia to compare the effects of ferrous sulfate and ferrous glycinate chelate in the treatment of anemia and to evaluate the presence of side effects.  
Methods: Patients were divided in two groups: group 1 received ferrous sulfate (200 mg twice a day, corresponding to 80 mg of elemental iron) and group 2 received ferrous glycinate chelate (250 mg/d, corresponding to 50 mg of elemental iron) for 4 mo. Laboratory measurements were performed at baseline and after 2 and 4 mo.  
Results: Group 1 showed an apparent recovery in laboratory parameters, with increases in medium corpuscular hemoglobin (P = 0.02), serum iron (P = 0.02), and ferritin (P = 0.04), and a decrease in transferrin (P = 0.002) after 4 mo. Individualized analysis showed that only one patient using ferrous sulfate had anemia at the end of the study in contrast to six patients using ferrous glycinate. In addition, ferritin levels increased above 20 μg/L at the end of the study in seven patients using ferrous sulfate in contrast to one patient using ferrous glycinate.  
Conclusion: Patients with iron deficiency anemia after gastrectomy treated with ferrous sulfate had better results in hematologic laboratory parameters than those who used ferrous glycinate chelate. © 2008 Elsevier Inc. All rights reserved.

Keywords: Ferrous glycinate chelate; Ferrous sulfate; Iron deficiency anemia; Gastrectomy

Introduction  
Anemia is a common complication in gastrectomized patients. It can be caused by iron or vitamin B12 deficiency, and its prevalence may reach up to 50% of patients [1]. Iron deficiency anemia is more common than vitamin B12 deficiency and can lead to hypochromic and microcytic anemia [2,3].

Iron deficiency anemia prevalence in gastrectomized patients varies from 15% to 54% in the literature [1,2,4–6], and its main causes are reduced gastric acid secretion, duodenal exclusion, inadequate intake, rapid food passage to the intestine, and alkaline gastritis [1,4,5,7].

The solubility of inorganic iron decreases when gastric acid secretion is reduced. Consequently, ferrous ions are less absorbed in gastrectomized patients. There are some investigators who believe that this decrease in absorption is as important as iron ingestion deficiency for the development of iron deficiency anemia [8].

Most luminal iron is present as Fe³⁺ and is reduced to Fe²⁺ by ferric reductase at the apical membrane of mucosal...
cells, but both forms of iron can form complexes with phytate, tannin, etc., preventing uptake into mucosal cells [9–12].

Classically, ferrous sulfate has been used for iron deficiency anemia since the beginning of the 19th century [13]. Nevertheless, it can cause many gastrointestinal side effects such as heartburn, abdominal pain, nausea, and diarrhea, leading to decreased treatment efficacy.

Since the 1980s, many studies have examined ferrous glycinate chelate fortification of different foods [9,10, 14–16]; these studies showed that ferrous glycinate chelate is 2.5- to 3.4-fold more bioavailable than ferrous sulfate [9,10,17], that its absorption is controlled by body iron storage [14], and that it causes fewer side effects than ferrous sulfate [9,15]. In addition, it has been hypothesized that iron amino acid chelates prevent iron from binding to inhibitors in food [11] and, in deprived areas of our country, food is composed basically of rice, beans, and vegetables, rich sources of phytates.

Thus, the goal of our study was to compare ferrous glycinate chelate with ferrous sulfate in relation to anemia and iron status in gastrectomized patients.

Materials and methods

Patients

The study sample was chosen from 190 gastric cancer patients, all of whom underwent gastrectomy at the Londrina Cancer Hospital from 1996 to 2004. Sixty-eight patients had already died; 43 patients did not come to the interview, refused to participate in the study, or presented some condition associated with iron deficiency anemia (gynecologic hemorrhage, gastrointestinal bleeding, blood transfusion or surgical procedure within the previous 6 mo, use of nonsteroidal anti-inflammatory drug), and 31 patients presented with recurrence or metastasis of the tumor or another malignant neoplasia. Clinical evaluation and biochemical tests (renal and thyroid function tests) to avoid the possibility of other causes of chronic anemia were performed.

Forty-eight patients underwent hematologic evaluation, and 18 patients fulfilled the criteria to enter the protocol: hemoglobin level <12 g/dL, transferrin saturation <16%, and serum ferritin level <20 µg/L. Before the beginning of the study, all patients underwent upper digestive endoscopy to exclude the possibility of recurrence or remnant gastric cancer and received medication (alendazole).

All patients gave informed consent, and the study protocol was fully approved by the ethical committee of the University of Londrina (Paraná, Brazil).

Clinical and laboratory evaluation

The following parameters were determined after a 12-h fasting period: hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration, which were measured using an automated counter (Pentra 120 Retic, ABX-HORIBA, Montpellier, France). Serum iron, serum transferrin, and transferrin saturation percentage (100 × serum iron/total iron binding capacity) were measured by the Ferrozine method using an automatic chemistry analyzer (Dimension AR, Dade-Behring, Deerfield, IL, USA). Serum ferritin was determined by the Microparticle Enzyme Immunoassay method using an automatic analyzer (AxSYM, Abbott, IL, USA). Anthropometric measurements of weight and height were performed, and body mass index was calculated as weight (kilograms) divided by height (meters) squared.

Study design

In this randomized, parallel design, 18 patients were assigned to one of two groups; the first group (G1) consisted of nine patients who received ferrous sulfate (ferrous sulfate EMS) at 400 mg/d (two capsules), corresponding to 80 mg of elemental iron, and the second group (G2) consisted of nine patients who received ferrous glycinate chelate (Neutrofer) at 250 mg/d (plastic vial with 5 mL), corresponding to 50 mg of elemental iron.

Clinical and laboratory evaluations of all patients were performed at the beginning of the study and after 2 and 4 mo. Compliance was monitored at each visit by questioning patients and counting pills.

Statistical analysis

Distribution of age, sex, time after gastrectomy, and type of surgery was analyzed by the Mann-Whitney and Fisher’s exact tests (SPSS 10.0 for Windows, SPSS, Inc., Chicago, IL, USA). Comparison of blood parameter values between the groups at the beginning of the study and after 2 and 4 mo were calculated using the Mann-Whitney test. P < 0.05 was considered statistically significant. Values are presented as median and range.

Results

Patient characteristics are presented in Table 1. There were no statistically significant differences between groups upon entry into the study.

In general, both groups of patients had no gastrointestinal complaints after using ferrous sulfate or ferrous glycinate chelate. There were no statistically significant differences with respect to side effects between groups.

At the beginning of the study, both groups were similar with regard to all parameters evaluated (Table 2).

After 2 mo of treatment, transferrin level was the only parameter that showed an improvement in iron status based on a statistically significant decrease (P < 0.02) in patients
receiving ferrous sulfate versus patients receiving ferrous glycinate (Table 3).

After 4 mo, there was a statistically significant increase in mean corpuscular hemoglobin (P < 0.02), serum iron levels (P < 0.02), and serum ferritin (P < 0.04) and a statistically significant decrease in transferrin levels (P < 0.002) in patients receiving ferrous sulfate versus patients receiving ferrous glycinate (Table 3). In addition, patients receiving ferrous sulfate demonstrated an increase in hemoglobin and mean corpuscular volume compared with patients receiving ferrous glycinate, although these results were not statistically significant (P < 0.09). Patients receiving ferrous sulfate demonstrated increased transferrin saturation and serum ferritin that were two and three times greater, respectively, than the levels observed at the beginning of the study, achieving normal results for these parameters at the end of the study (Table 3).

Individualized analysis showed that only one patient (patient no. 3) using ferrous sulfate had anemia at the end of the study (Fig. 1) in contrast to six patients (patient nos. 1, 2, 4, 5, 6, and 8) using ferrous glycinate (Fig. 2). A progressive increase in serum ferritin levels (>20 μg/L) at the end of the study was also verified in seven patients using ferrous sulfate at the end of the study in contrast to only one patient using ferrous glycinate. Moreover, seven patients using ferrous glycinate maintained serum ferritin levels below 10 μg/L at the end of the study.

In the present study, the prevalence of iron deficiency anemia in the 48 gastrectomized patients who participated in the blood evaluation was 37.5%. The prevalence of iron deficiency anemia in gastrectomized patients varies considerably and depends on many factors: patient selection, type of surgery, time after gastrectomy, the presence of anemia before surgery, use of iron supplementation, etc. Studies examining hematologic alterations in gastrectomized patients in greater detail were performed in the 1960s and 1970s [2,18,19]. In the 1990s, studies referred to anemia as being a common postgastrectomy complication, but without specific details on the hematologic alterations [1,4,5].

Iron deficiency anemia is defined as a hemoglobin level below 12g/dL, transferrin saturation below 16%, and serum ferritin level below 20μg/L. This rigorous definition of iron deficiency anemia can help to explain the smaller number of patients selected for the study because, of the 48 who participated in the blood analysis, only 18 fulfilled these criteria.

In the present study, the dose of elemental iron used for the treatment of iron deficiency anemia was not similar between groups, because many studies in the literature have suggested that ferrous amino acid chelate is two to four

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Table 1
Clinical features of patient groups*

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ferrous sulfate</th>
<th>Ferrous glycinate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>5/4</td>
<td>5/4</td>
<td>1.0</td>
</tr>
<tr>
<td>Age (y)</td>
<td>65 ± 11.74</td>
<td>52 ± 14.30</td>
<td>0.08</td>
</tr>
<tr>
<td>Time after gastrectomy (y)</td>
<td>3.0 ± 3.46</td>
<td>2.6 ± 9.70</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥18.5–≤24.9</td>
<td>7</td>
<td>7</td>
<td>0.73</td>
</tr>
<tr>
<td>≥25–&lt;30</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Billroth II partial gastrectomy</td>
<td>5</td>
<td>8</td>
<td>0.3</td>
</tr>
<tr>
<td>Roux-en-Y partial gastrectomy</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total gastrectomy</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Alkaline gastritis</td>
<td>2</td>
<td>6</td>
<td>0.15</td>
</tr>
</tbody>
</table>

BMI, body mass index
* Values are numbers of patients or means ± SDs.

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Discussion

In contrast to many studies showing favorable results with ferrous glycinate chelate, the present study demonstrated that patients using ferrous glycinate did not present decreased anemia when compared with patients using ferrous sulfate. Conversely, there was a marked improvement in laboratory parameters observed for patients using ferrous sulfate. This was shown by increases in hemoglobin, serum iron, transferrin saturation, and serum ferritin to normal levels at the end of the study. Analysis of individual patients confirmed the mean data, mainly through the following findings: only one patient using ferrous sulfate had anemia at the end of the study in contrast to six patients using ferrous glycinate. The same trend was found with regard to iron deficiency, for which a progressive increase in serum ferritin levels (serum ferritin >20 μg/L) was verified in seven patients using ferrous sulfate at the end of the study in contrast to only one patient using ferrous glycinate. Moreover, seven patients using ferrous glycinate maintained serum ferritin levels below 10 μg/L at the end of the study.

In the present study, the prevalence of iron deficiency anemia in the 48 gastrectomized patients who participated in the blood evaluation was 37.5%. The prevalence of iron deficiency anemia in gastrectomized patients varies considerably and depends on many factors: patient selection, type of surgery, time after gastrectomy, the presence of anemia before surgery, use of iron supplementation, etc. Studies examining hematologic alterations in gastrectomized patients in greater detail were performed in the 1960s and 1970s [2,18,19]. In the 1990s, studies referred to anemia as being a common postgastrectomy complication, but without specific details on the hematologic alterations [1,4,5].

Iron deficiency anemia is defined as a hemoglobin level below 12g/dL, transferrin saturation below 16%, and serum ferritin level below 20μg/L. This rigorous definition of iron deficiency anemia can help to explain the smaller number of patients selected for the study because, of the 48 who participated in the blood analysis, only 18 fulfilled these criteria.

In the present study, the dose of elemental iron used for the treatment of iron deficiency anemia was not similar between groups, because many studies in the literature have suggested that ferrous amino acid chelate is two to four

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Table 2
Blood parameter values* of gastrectomized patients at beginning of study

<table>
<thead>
<tr>
<th></th>
<th>Ferrous sulfate</th>
<th>Ferrous glycinate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.3 (9.1–11.6)</td>
<td>10.7 (9.3–11.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>MCV (IL)</td>
<td>82.5 (73.2–90.5)</td>
<td>86.0 (56.9–96.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>24.7 (23.3–30.1)</td>
<td>26.1 (19.3–29.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>MCHC (%)</td>
<td>30.3 (26.5–36.3)</td>
<td>30.6 (27.9–34.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Iron (μg/dL)</td>
<td>39 (23–69)</td>
<td>42 (23–76)</td>
<td>0.9</td>
</tr>
<tr>
<td>Transferrin (μg/L)</td>
<td>425 (250–531)</td>
<td>425 (250–528)</td>
<td>0.8</td>
</tr>
<tr>
<td>TS (%)</td>
<td>9.0 (5.8–13.8)</td>
<td>9.0 (5.5–14.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td>8.5 (3.9–19)</td>
<td>6.2 (2.3–12.3)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; TS, transferrin saturation
* Values are medians (ranges).
times more efficiently absorbed than ferrous sulfate [9–11,17]. Thus, ferrous glycinate was administered at a 37.5\% lower daily dose than ferrous sulfate (50 and 80 mg, respectively).

Other advantages that have been described in favor of ferrous glycinate in comparison with ferrous sulfate are fewer side effects [11], fewer alterations of organoleptic properties [15], and greater bioavailability [17]. In the present study, none of these favorable effects was observed, or could be suggested to occur, with ferrous glycinate compared with ferrous sulfate.

At the end of the study, when patients using ferrous sulfate were compared with patients using ferrous glycinate, statistically significant differences in many parameters associated with iron status were observed, demonstrating a clinical response in favor of ferrous sulfate. Meanwhile, if we were to consider serum ferritin levels as the best available way of measuring iron storage [20], ferrous glycinate was not sufficient to replenish these levels at the present dosage.

In general, ferrous glycinate chelate has been used with favorable results for food fortification with iron [15,16]. Other studies have compared fortification of food with ferrous glycinate with ferrous sulfate in heterogeneous populations (anemic and non-anemic) in terms of iron absorption and found higher absorption associated with ferrous glycinate [9,10].

Table 3
Comparison of blood parameter values* at baseline, M1, and M2 in G1 and G2

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group</th>
<th>Baseline</th>
<th>M1</th>
<th>M2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>G1</td>
<td>10.3 (9.1–11.6)</td>
<td>12.1 (10.4–13.2)</td>
<td>12.9 (10.6–15.1)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>10.7 (9.3–11.2)</td>
<td>11.8 (9.7–14.3)</td>
<td>11.2 (9.6–14.4)</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>G1</td>
<td>82.5 (73.2–90.5)</td>
<td>84.7 (77.2–96.1)</td>
<td>88.0 (72.3–90)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>86.0 (56.0–96.8)</td>
<td>84.0 (65.0–91.4)</td>
<td>79.1 (65.0–96.6)</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>G1</td>
<td>24.7 (23.3–30.1)</td>
<td>27.5 (24.1–31.4)</td>
<td>29.0 (27.7–32.3)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>26.1 (19.3–29.5)</td>
<td>25.9 (19.4–31.3)</td>
<td>24.6 (21.0–32.6)</td>
</tr>
<tr>
<td>MCHC (%)</td>
<td>G1</td>
<td>30.3 (26.5–36.3)</td>
<td>31.7 (29.3–37.6)</td>
<td>34.7 (31.2–38.2)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>30.6 (27.9–34.4)</td>
<td>31.4 (28.6–37.0)</td>
<td>33.0 (28.2–36.0)</td>
</tr>
<tr>
<td>Iron (µg/dL)</td>
<td>G1</td>
<td>39 (23–69)</td>
<td>52 (31–88)</td>
<td>80 (72–93)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>42 (22–76)</td>
<td>40 (24–90)</td>
<td>52 (20–152)</td>
</tr>
<tr>
<td>Transferrin (µg/DL)</td>
<td>G1</td>
<td>425 (250–531)</td>
<td>387 (244–607)</td>
<td>353 (301–957)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>425 (250–528)</td>
<td>460 (292–935)</td>
<td>373 (306–482)</td>
</tr>
<tr>
<td>TS (%)</td>
<td>G1</td>
<td>9.0 (5.8–13.8)</td>
<td>13.2 (4.9–26.5)</td>
<td>18.3 (4.0–31.0)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>9.0 (5.5–14.9)</td>
<td>8.2 (6.6–16.4)</td>
<td>11.6 (4.0–25.2)</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>G1</td>
<td>8.5 (3.9–19)</td>
<td>12.3 (7.7–38.6)</td>
<td>26.9 (11.6–60.6)</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>6.2 (2.3–12.3)</td>
<td>7.4 (5.3–88.1)</td>
<td>6.4 (4.3–38.6)</td>
</tr>
</tbody>
</table>

G1, group receiving ferrous sulfate; G2, group receiving ferrous glycinate; M1, 2 mo after treatment; M2, 4 mo after treatment; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; TS, transferrin saturation

* Values are medians (ranges).

† \( P < 0.02 \), M1 (G1) versus M1 (G2).

‡ \( P < 0.02 \), M2 (G1) versus M2 (G2).

§ \( P < 0.002 \), M2 (G1) versus M2 (G2).

Fig. 1. Hemoglobin values in the nine patients who used ferrous sulfate at the beginning of the study (white bars) and after 2 mo (hatched bars) and 4 mo (black bars).

Fig. 2. Hemoglobin values in the nine patients who used ferrous chelate glycinate at the beginning of the study (white bars) and after 2 mo (hatched bars) and 4 mo (black bars).
By comparing the effects of ferrous glycinate with those of ferrous sulfate in 40 anemic infants and young children, Pineda and Ashmead [17] found a hemoglobin increase in both groups, but serum ferritin levels increased only in patients receiving ferrous glycinate. In contrast, Silva et al. [21] performed a double-blind crossover study comparing the absorption of 60 mg of elemental iron from ferrous sulfate, ferrous glycinate, and iron ethylene-diaminetetraacetate in 12 non-anemic volunteers, and the results obtained with ferrous sulfate showed a statistically significant increase in serum iron when compared with ferrous glycinate chelate and iron ethylene-diaminetetraacetate.

In the present study, the increase in gastric pH due to alkaline gastritis found in some patients could partly explain the unfavorable results obtained with ferrous glycinate [12]; alkaline gastritis was verified in six patients using ferrous glycinate and two patients using ferrous sulfate. Even though they presented alkaline gastritis, three patients using ferrous glycinate and one patient using ferrous sulfate demonstrated increased serum ferritin levels.

Some studies have suggested a relation between *Helicobacter pylori* infection and iron deficiency anemia. Although multifactorial in its nature, this connection has been partly attributed to the development of alkaline gastritis due to *H. pylori* infection [22,23], resulting, as a consequence, in an iron absorption disorder.

The presence of *H. pylori* infection in the gastric remnants of gastrectomized patients has a high prevalence, varying from 65.1% [24] to 80.3% [25]. Roviello et al. [26] found a decrease in serum iron levels in gastrectomized patients with *H. pylori* infection in the gastric remnant.

When considering the results of the present study, the following limitations must be considered. First, *H. pylori* infection, which can interfere with iron absorption, was not verified. Thus, we cannot exclude the possibility that infection influenced the results. Second, only a few patients (18 of 190) who underwent gastrectomy met the criteria to be included in the comparison between the two preparations.

Nevertheless, the present study also has several strengths. First, to our knowledge, this is the first study to directly compare the effects of ferrous glycinate chelate and ferrous sulfate in gastrectomized patients with iron deficiency anemia. Second, we tried rigorously to ensure that the patients did not present any other conditions associated with anemia, and excluded even those patients with doubtful data from the study. Thus, we were confident that these patients had the unique diagnosis of iron deficiency anemia secondary to gastrectomy. The rigorous definition of iron deficiency anemia used in the present study also helped to reinforce this diagnosis. Third, in this controlled, randomized parallel design, both groups were similar with regard to all parameters evaluated at the beginning of the study. Fourth, in developing, and even in developed countries, costs make an important difference in treatment compliance. Therefore, ferrous sulfate, besides its low cost, can be considered a very efficient treatment for supplementation of gastrectomized patients with iron deficiency anemia.

In conclusion, in the present study, ferrous sulfate showed better results than ferrous glycinate chelate for the treatment of iron deficiency anemia in gastrectomized patients.

In future studies comparing different kinds of ferrous supplementation in gastrectomized patients, in addition to alkaline gastritis, it will be important to consider other factors such as *H. pylori* infection. Further investigation using similar doses of the products is necessary to confirm the superior results obtained in the present study with ferrous sulfate compared with ferrous glycinate chelate in gastrectomized patients.

References


