Evaluation of efficacy and tolerability of ferrous bisglycinate tablets in comparison with ferrous sulphate tablets in patients with iron deficiency anemia

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ABSTRACT

Background: Iron deficiency anemia is the most common nutritional deficiency disorder in the world, especially in India and other developing countries. Surveys in different parts of the country reveal that 87% of pregnant women suffer from anemia and about 10% have severe anemia. Aim: The present study was carried out to evaluate the efficacy and tolerability of ferrous bisglycinate tablets in comparison with ferrous sulphate tablets in patients with iron deficiency anemia.

Methods: Adult patients with iron deficiency anemia received either ferrous bisglycinate or ferrous sulphate tablet twice daily for six weeks. Clinical and laboratory evaluations were performed at the baseline, on 21st day and at the end of treatment on day 42. Patients were also evaluated for any adverse effects occurring during the course of the study.

Results: The 42-day daily treatment with ferrous bisglycinate or ferrous sulphate resulted in significant increase in haemoglobin (Hb) levels. The increase in Hb in ferrous bisglycinate group was 22.72%, which was significantly higher than the ferrous sulphate group (18.66%).

The overall efficacy of the treatment assessed by both the patient and the physician was similar in both groups. At the end of the study, percentage of patients who suffered from side effects was significantly higher in ferrous sulphate group (14.6%-constipation, 14.1%-nausea) compared to ferrous bisglycinate (7.8%-constipation, 8.9%-nausea).

Conclusion: Ferrous bisglycinate is a potentially valuable therapeutic agent for the treatment of iron deficiency anemia with significant Hb rise and lack of unwanted side effects when compared to ferrous sulphate.

Key words: Iron, Anemia, Ferrous Bisglycinate.

INTRODUCTION

Iron is found in abundance on our planet and, relative to the nutritive amount required by man, is theoretically plentiful. In spite of this natural abundance, iron deficiency anemia is the most common nutritional deficiency disorder in the world, especially in India and other developing countries1. Prevalence of anemia in all the groups is higher in India as compared to other developing countries. Young children and women in the reproductive age group, especially during pregnancy are the most vulnerable to iron deficiency anemia. This is due to increased physiologic requirements, combined with increased losses and poor dietary intakes2.

WHO has estimated that prevalence of anemia in developing and developing countries in pregnant women is 14% and 51% respectively and 65-75% in India2. Surveys in different parts of the country reveal that 87% of pregnant women suffer from anemia and about 10% have severe anemia (Hb < 8 g/dL).3. About half of the global maternal deaths due to anemia occur in South Asian countries; India contributes to about 80 per cent of the maternal deaths due to anemia in South Asia2.

Ferrous sulphate is the most widely used form of iron supplement to treat iron deficiency anemia. It is inexpensive, but many individuals experience unpleasant side effects, particularly gastrointestinal (GI) intolerance with this form of iron. The observed side effects vary from 5-60% and appears to be dose related4. In addition, the bioavailability of ferrous sulphate is low, requiring large therapeutic doses (150 to 300 mg iron daily).

For the treatment of iron deficient population, the ideal source of supplemental iron should be absorbed efficiently, be bioavailable after absorption, and not produce gastric side effects5.

Ferrous bisglycinate chelate is composed of two molecules of glycine that are chelated to one ferrous atom by covalent and coordinate covalent bonds. The advantage of ferrous bisglycinate over other sources of supplemental iron is that it’s greater bioavailability into the mucosal cells results in more iron being quickly and safely delivered to target tissues of the body in times of need. This potentially allows for smaller doses of supplemental iron, which can result in fewer gastric complaints and reduced risk of iron overload. The efficacy of ferrous bisglycinate in iron deficiency anemia has been reported in adults, adolescents and young children6,7.

Hence, the present study was undertaken to evaluate the efficacy and tolerability of ferrous bis-glycinate + Folic acid + Vitamin B12 tablets in comparison with ferrous sulphate for the treatment of iron deficiency anemia in Indian women.

MATERIALS AND METHODS:

Study design: This randomized, comparative study was conducted in seven centers across the country. Adult female patients over 18 years of age with a Hb level between 8-10 g/dL were included in the study. Written informed consent was obtained from each of the participant before the study initiation. Patients were enrolled from the outpatient clinics of each of the participating physician. Complete history was taken, general and systemic examination was done to satisfy inclusion and exclusion criteria.

Patients with associated conditions like megaloblastic anemia or pernicious anemia, thalassemia, sickle cell or aplastic anemia, bleeding peptic ulcer, piles, esophageal varices, helminthiasis were excluded from the study. Also excluded were patients suffering from severe or uncontrolled systemic and metabolic diseases and who were on treatment with other haematinic agents within 24 hours before the start of the study.
Treatment:
On day 0 (day of therapy initiation), patients who fulfilled the inclusion and exclusion criteria were subjected to complete clinical examination. The severity of clinical symptoms present at the time of admission was recorded on the CRF.

Each patient was then assigned to one of the two treatment groups: Group I: Ferrous bisglycinate tablet containing 30 mg elemental iron, 11 mg of elemental zinc, 0.5 mg of folic acid and 7.5 µg of vitamin B12. Group II: Ferrous sulphate tablet containing 30 mg elemental iron. Patients were instructed to receive one tablet of either ferrous bisglycinate or ferrous sulphate twice daily after meals for 6 weeks.

Efficacy assessment:
Efficacy was compared on the basis of improvement in:
1. Clinical parameters
2. Laboratory parameters

Clinical evaluation: Clinical evaluation was done on the basis of improvement of the following parameters:
1. Pallor
2. Breathlessness
3. Weakness
4. Palpitations

The severity of the symptoms present were recorded independently in respect to each patient on a four-point scale with qualifying norms.
0 = Absent  Symptom absent
1 = Mild  Symptom present but no interference with daily activities
2 = Moderate  Symptom present & some interference with daily activities
3 = Severe  Symptom present with incapacitation

Labatory parameters:
Laboratory evaluation was done on the basis of Hb estimation. Clinical and laboratory evaluations were performed by the investigator at outpatient visits at the baseline, on day 21 and on day 42.

Safety and tolerability analysis:
Patients were monitored for any adverse effects at each visit. All adverse effects or unexpected events were recorded in the case report form. Patients were queried by the investigators for any adverse effects between study visits. The nature, date of onset, and duration of adverse effects were recorded. All investigator-reported clinical adverse effects were recorded at each study visit and evaluated by the investigators for seriousness, intensity and relationship to the study medication.

Global clinical evaluation:
At the end of the study, global assessment of the efficacy and tolerability of the treatment by both the investigator and patient were recorded on four-point scale as: Excellent, Good, Satisfactory or Poor

Statistical Analysis:
All values are expressed as mean ± S.D. Haemoglobin analysis was performed by one-way analysis of variance (ANOVA) followed by Bonferroni’s post test. Efficacy variables (changes in score for pallor, breathlessness, weakness and palpitations) and adverse effects were analyzed using the Kruskal-Wallis test. The results were considered to be statistically significant if P < 0.05

RESULTS:
A total of 420 patients satisfied the inclusion and exclusion criteria and were enrolled in seven centers for the study. 45 patients were lost to follow up during the study: 19 in ferrous bisglycinate group and 26 in ferrous sulphate group. Statistical analysis was performed on 375 patients (191 patients in the ferrous bisglycinate group and 184 in the ferrous sulphate group) who completed the study. The patients were well balanced with respect to baseline demographic characteristics (Table 1).

Table 1: A summary of the demographic characteristics of the two groups

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>191</td>
<td>184</td>
</tr>
<tr>
<td>Age (ys)</td>
<td>25.4±5.16</td>
<td>24.4±4.05</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>50.1±7.82</td>
<td>48.4±7.74</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± S.D.

Evaluation of haemoglobin:
Table 2 reveals the effect of ferrous bisglycinate and ferrous sulphate on haemoglobin levels.

Table 2: Effect of ferrous bisglycinate and ferrous sulphate treatment on haemoglobin levels

<table>
<thead>
<tr>
<th>Group</th>
<th>Haemoglobin (g/dL)</th>
<th>Day 0</th>
<th>Day 21</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8.8±0.78</td>
<td>9.8±0.74</td>
<td>10.8±0.78</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>8.8±0.75</td>
<td>9.7±0.64</td>
<td>10.4±0.66</td>
<td></td>
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</tbody>
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By one way ANOVA
* P<0.05 when compared to the corresponding values on day 0 of same group
1 P<0.05 when compared to the corresponding day 42 values of ferrous sulphate group

In the ferrous bisglycinate group, the Hb rise was 1.09 g/dL on day 21 and 2.00 g/dL on day 42 which was significantly higher (P < 0.05) compared to the baseline values. In the ferrous sulphate group, the Hb rise was 0.92 g/dL on day 21 and 1.65 g/dL on day 42 which was significantly lower (P < 0.05) compared to the baseline values.

On day 42, the mean increase in Hb of the group receiving ferrous bisglycinate (22.72 %) was significantly higher (P < 0.05) than that of the group receiving ferrous sulphate (18.66%). On day 21, the haemoglobin rise was not statistically different in both the groups (Fig. 1).

Safety and tolerability analysis:
Patients were monitored for any adverse effects at each visit. All adverse effects or unexpected events were recorded in the case report form. Patients were queried by the investigators for any adverse effects between study visits. The nature, date of onset, and duration of adverse effects were recorded. All investigator-reported clinical adverse effects were recorded at each study visit and evaluated by the investigators for seriousness, intensity and relationship to the study medication.

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Evaluation of clinical efficacy:
Pallor score: Table 3 shows the effect of ferrous bisglycinate and ferrous sulphate treatment on pallor score.

Table 3: Effect of ferrous bisglycinate and ferrous sulphate treatment on pallor score

<table>
<thead>
<tr>
<th>Group</th>
<th>Pallor score (Mean ± SD)</th>
<th>Day 0</th>
<th>Day 21</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.14±0.61</td>
<td>0.49±0.53 (57.02)</td>
<td>0.21±0.41 (81.57)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1.24±0.66</td>
<td>0.62±0.67 (50.79)</td>
<td>0.49±0.72 (61.11)</td>
<td></td>
</tr>
</tbody>
</table>

By Kruskal-Wallis test
* P<0.05 when compared to day 0 values of same group
1 P<0.05 when compared to the corresponding day 42 values of ferrous sulphate group

In the ferrous bisglycinate group, pallor score reduced by 57.02% on day 21 and 81.57% on day 42 which was significantly lower (P< 0.05) compared to the baseline values. Reduction in ferrous bisglycinate group was statistically significant (P< 0.05) compared to the baseline values. In the ferrous sulphate group, the reduction was 50.79% on day 21 and 61.11% on day 42 which was significantly lower (P< 0.05) compared to the baseline values.

Breathlessness score:
Table 4 shows the effect of ferrous bisglycinate and ferrous sulphate treatment on breathlessness score.
Iron deficiency anemia is the single largest nutrient disease affecting the world today. The prevalence of iron deficiency anemia is more pronounced among infants, adolescents, women of child bearing age, pregnant women and athletes. This worldwide deficiency is, in part, a result of diet. Iron deficiency is usually the result of low bioavailability of dietary iron. The availability of iron from many foods is low. Common food ingredients like phytates, phosphates and fiber reduce iron absorption. Besides diet, an individual’s iron status is also related to his or her needs. Additionally, certain cations may compete with the iron for intestinal absorption sites and reduce its absorption.

Effect of treatment on safety and tolerability:
The number of patients experiencing side effects is shown in Fig. 2. After 6 weeks of the study, ferrous sulphate treatment resulted in significantly higher gastrointestinal adverse effects compared to ferrous bisglycinate. In the ferrous sulphate group, 14.6% of patients complained of constipation compared to 7.8% in ferrous bisglycinate group, which was significantly higher (P<0.05). In addition, 14.1% patients in ferrous sulphate group experienced nausea which was significantly higher (P<0.05) compared to ferrous bisglycinate (8.9%). All the adverse effects experienced in the both the groups were mild in nature.

DISCUSSION:
Iron deficiency anemia is the single largest nutrient disease affecting the world today. The prevalence of iron deficiency anemia is more pronounced among infants, adolescents, women of child bearing age, pregnant women and athletes. Ferrous sulphate is a widely used iron supplement in iron deficiency anemia. But other compounds present in the diet such as phytates, phensols or fibers. The compliance of the patients to the treatment is also usually low due to the gastrointestinal upsets induced by this form of iron.

Ferrous bisglycinate chelate was developed to provide a safer product with improved bioavailability. Iron chelated with glycine is not as reactive with food ingredients, which leaves more of the iron potentially available for absorption. High levels of phytates or fibers in the diet do not interfere with the superior absorption of ferrous bisglycinate. Besides being less affected by dietary inhibitors, the absorption of ferrous bisglycinate is not inhibited by presence of other minerals in the diet. Ferrous bisglycinate has been used and successfully
evaluated in terms of efficacy and tolerability in infants, adolescents and pregnant women.\textsuperscript{7}

Research has demonstrated that ferrous bisglycinate is not hydrolyzed in the intestine and is efficiently absorbed intact. Once absorbed into the mucosal tissue, the chelate is hydrolyzed, and the release of the iron into the plasma and the rest of the body tissues and organs is regulated similarly to that of any other source of iron. The iron released from the chelate is effectively utilized by the haematopoietic tissues and the amino acid portion of the molecule is metabolized through the normal amino acid metabolic pathways.\textsuperscript{5}

The present study was carried out to compare the efficacy and tolerability of ferrous sulphate and ferrous bisglycinate in a population who widely suffers from iron deficiency anemia and frequently ingests iron supplements.

After 42 days of treatment, there was significant increase in haemoglobin level in the ferrous bisglycinate group compared to ferrous sulphate (22.72\% vs 18.66\% respectively). The results indicate that more of the iron from the chelate than from ferrous sulphate was absorbed, which suggests a higher bioavailability for the ferrous bisglycinate chelate. Ferrous bisglycinate is absorbed into the mucosal cells in greater quantities, due, in part, to entering into fewer absorptive inhibiting reactions in the gut. The greater amount of absorbed iron is of great importance when iron deficiency or anaemia exists.\textsuperscript{1}

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The greater bioavailability of the ferrous bisglycinate chelate has been confirmed in other studies. In a study of infants with iron deficiency anemia, ferrous bisglycinate chelate was absorbed 3.4 times greater than ferrous sulphate. Bioavailability of ferrous bisglycinate and ferrous sulphate were 90.9\% and 27.6\% respectively. A dose study of adolescents reported that 30 mg of iron from ferrous bisglycinate chelate was as effective in treating iron deficiency anaemia as 120 mg of iron from ferrous sulphate.\textsuperscript{7}

At the end of the study, treatment with ferrous bisglycinate resulted in significant reduction in the clinical signs and symptoms of iron deficiency like pallor and breathlessness compared to ferrous sulphate. The results indicate that clinical improvement of iron deficiency anemia is better with ferrous bisglycinate than ferrous sulphate.

After the six-week study period, twice as many patients taking ferrous sulphate complained of gastric problems like constipation and nausea as compared with ferrous bisglycinate. The potential for gastric irritability is reduced in ferrous bisglycinate because this form of iron is shielded by the amino acid ligands of the chelate. It does not form an insoluble precipitate with the dietary phytic acid, bran, etc., which leads to fewer chemical reactions that can potentially interfere with iron absorption and cause gastrointestinal side effects.

In conclusion, ferrous bisglycinate appears as a potentially valuable therapeutic agent in the treatment of iron deficiency anemia due to its higher bioavailability and absence of unwanted side effects.

REFERENCES:
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