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Comparison of a Combination Ferrous Fumarate Product and a Polysaccharide Iron Complex as Oral Treatments of Iron Deficiency Anemia: A Taiwanese Study

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Abstract

Despite efforts to improve iron supplements for iron deficiency anemia, there is no consensus on products that balance efficacy, safety and tolerability, and cost. Ferrous products are effective, but they are associated with more gastrointestinal side effects than ferric products. Ferric products tend to have lower absorption. We present results from a 12-week study that randomized 72 people with uncomplicated iron deficiency anemia to receive a ferrous iron supplement (Ferall, a combination of ferrous fumarate with ascorbic acid, folic acid, and cyanocobalamin) or a ferric iron polysaccharide complex (Niferex, ferroglycine sulfate) plus ascorbic acid. The ferrous product was significantly more effective, the primary and secondary endpoints including changes in levels of hemoglobin and serum ferritin. There was a slightly higher frequency of gastrointestinal side effects in patients taking the ferrous product, but both supplements were well tolerated. No participant withdrew from the study because of side effects. We concluded that the ferrous product is safe and effective for use in uncomplicated iron deficiency anemia. The lack of direct comparison between single-agent ferrous fumarate and the combination ferrous product limited interpretation of results in terms of possible effects due to other components, such as ascorbic acid.
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Key words: Ferrous; Ferric; Iron deficiency anemia; Iron supplementation

1. Introduction

Iron is essential for all body cells and is a key component of hemoglobin. In vivo, iron readily and reversibly moves between the ferrous (Fe^{2+}) and ferric (Fe^{3+}) oxidation states. Because iron is carried in the blood and stored in tissues as a variety of iron compounds, cell damage due to participation by unbound cations in reactions producing free radical species is minimized. Iron deficiency is the most common cause of anemia worldwide [1].

Ferrous salt preparations historically have been effective treatments of iron deficiency anemia. However, these agents also have been associated with more side effects than ferric preparations, probably owing to production of hydroxyl free radicals and resultant inflammation in the gastrointestinal (GI) tract [1]. On the other hand, iron is absorbed far less efficiently from ferric salts owing to duodenal formation of iron hydroxide polymers with a high affinity for intestinal mucus.

Coingestion of ascorbic acid can increase the absorbance of iron (either ferrous or ferric in source) from the GI tract, but recent results of research with white subjects who were not iron deficient indicated that cosupplementation of iron and ascorbic acid can increase the level of oxidative reactions in the GI tract, causing frank ulcerations in healthy adults and exacerbation of inflammation in people with chronic GI inflammatory disease [2]. Additional research may reveal whether vulnerability to such oxidative stress is confined to 1 or more ethnic or racial groups or is universal.

Pharmaceutical firms have continued to develop and evaluate different types of iron supplements as therapy for iron deficiency anemia, attempting to balance efficacy, safety and tolerability, and cost. One class of formulations consists of an iron complex including a low molecular weight polysaccharide. Niferex (ferroglycine sulfate) is an example of such an oral preparation. One study showed that Niferex had an absorption comparable with that of a ferrous salt (ferrous fumarate) but had significantly fewer GI side

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effects [3]. Among the ferrous salts, which remain the standard in many parts of the world [1], ferrous fumarate is the least toxic. It has an oral median lethal dose (LD_{50}) of 630 mg/kg in comparison with ferrous gluconate and ferrous sulfate (LD_{50} values of 320 mg/kg and 230 mg/kg, respectively). The combination supplement Ferall contains 460 mg ferrous fumarate, 60 mg ascorbic acid, 1 mg folic acid, and 10 μg cyanocobalamin.

The ferric supplement Niferex has been one of the most common supplements used for patients with iron deficiency anemia in Taiwan. Our history with Niferex suggested that patients achieve insufficient response with this ferric polysaccharide complex. Hemoglobin level typically does not rise enough to reach the lower limit of the normal range. Consequently, we have a direct clinical interest in finding a supplement with greater efficacy and acceptable tolerability.

For the current study, we compared a combination ferrous iron product (Ferall) with a ferric polysaccharide complex product (Niferex) as oral treatment of iron deficiency anemia in our patient population.

2. Methods

2.1. Study Design

Informed participants were randomized to receive open-label Ferall, 1 capsule daily (ferrous fumarate equivalent of 151 mg elemental iron, 60 mg ascorbic acid, 1 mg folic acid, 10 μg cyanocobalamin) or Niferex, 1 capsule daily (ferroglycine equivalent of 150 mg elemental iron), plus 50 mg ascorbic acid for a duration of 12 weeks (84 consecutive days). Standardization of dosing (oral capsule) and scheduling (once daily timing before breakfast) was intended to minimize any extraneous factors that could contribute to a significant difference in absorption and thus efficacy, safety, or both. Subjects were randomized for the open treatment period with sequential enumeration in a defined block size. Randomization was performed by Lotus Pharmaceutical (Taipei, Taiwan). The number of subjects per block was unknown to the investigators.

2.2. Patient Selection and Enrollment

Adults with the diagnosis of iron deficiency anemia according to World Health Organization criteria (hemoglobin concentration <13 g/dL in men and <12 g/dL in women) at 1 Taiwanese medical center were eligible for the study. Exclusion criteria by history were drug or alcohol abuse, allergy or side effects with iron therapy, and use of any other investigational drug within a month of enrollment. In addition, people who had any type of cancer, renal dysfunction, or major organ disease were excluded, as were people with any other type of coexisting anemia. Trial ethics complied with recommendations adopted by the 18th World Medical Assembly, 1964, with later revisions. Patients were free to withdraw at any time.

2.3. Efficacy Endpoints

The primary endpoint for efficacy was change in blood hemoglobin level from baseline to the end of the 12-week study period. Secondary measures included serum ferritin, total iron binding capacity (TIBC), percentage saturation of TIBC, and mean corpuscular volume (MCV).

2.4. Safety Endpoints

GI safety was measured individually through evaluation of the following 6 adverse GI events: abdominal pain, heartburn, nausea, vomiting, constipation, and diarrhea. The clinical measurement was the proportion of subjects who reported any adverse event (GI or otherwise). The scale used for the study rated the presence and severity of each GI event on a scale of 0 to 3, 0 representing the absence of the problem, and 1, 2, and 3 individually defined to represent mild, moderate, and severe symptoms (case report form available on request).

2.5. Assessment of Endpoint Measures

Laboratory testing for primary and secondary endpoint measures was conducted at baseline and weeks 4, 8, and 12. Safety evaluations (assessment of GI symptoms) also were conducted at baseline and weeks 4, 8, and 12.

2.6. Statistical Methods

Changes in hemoglobin level for the 2 groups were compared by analysis of covariance with baseline value as covariate. For each of the secondary efficacy endpoints, analysis of variance was used to detect any statistically significant differences between groups. For the qualitative safety endpoints, Fisher exact test was used to compare results for the 2 study groups. Statistical significance was defined as $P < .05$.

3. Results

3.1. Patients and Implementation of Study Design

A total of 80 people were enrolled. Thirty-nine subjects were randomized to the ferrous product Ferall, and 41 subjects were randomized to the ferric product Niferex. A total of 60 people (31, ferrous product; 29, ferric product) completed the full 12-week period of medication use and participated in all follow-up evaluations. Criteria for inclusion in data analysis were use of at least 1 dose of study medication and completion of at least 1 follow-up evaluation. Thus our findings on efficacy and safety were based on the 72 participants (36, ferrous product Ferall; 36, ferric product Niferex) who met these 2 criteria by beginning medication, being evaluated at week 4, and being evaluated after the end of the study period. Of the 8 patients not included in data analysis, 4 were lost to follow-up after the study period, and 4 did not continue from entrance into the study to week 4 (all 4 randomized to the ferric product Niferex). The demographic and baseline information on the 72 participants on whose data results were based is summarized in Table 1. There were no statistical differences between the 2 groups of participants (36 people each) or between either drug group and the analyzed population as a whole (72 people).

Table 1.
Summary of Participants' Demographic and Baseline Information

Characteristic	Combined (N = 72)	Ferrous/Ferall (n = 36)	Ferric/Niferex (n = 36)	*P**
Sex				.674
Male	6 (8.3%)	2 (5.6%)	4 (11.1%)	
Female	66 (91.7%)	34 (94.4%)	32 (88.9%)	
Mean age (SD), y	38.8 (12.48)	37.8 (10.39)	39.7 (14.35)	.525
Mean body mass index (SD)	21.5 (2.88)	21.1 (3.16)	22.0 (2.53)	.166
Mean pulse rate, beats/min, (SD)	74.3 (6.80)	74.1 (6.44)	74.6 (7.23)	.771
Mean hemoglobin concentration (SD), g/dL				
Women	9.3 (1.69)	9.4 (1.72)	9.3 (1.68)	.837
Men	9.2 (1.68)	9.5 (2.40)	9.1 (1.63)	.793

*Fisher exact test for categorical data; analysis of variance for continuous data.

Among the 72 patients, causes of iron deficiency anemia in men were hemorrhoids (4 patients) and peptic ulcer disease (2 patients). By far the most common cause in women was menorrhagia (50 patients), followed by hemorrhoids (5 patients), menorrhagia complicated by hemorrhoids (4 patients), restrictive vegetarianism (4 patients), and peptic ulcer disease (3 patients).

3.2. Efficacy Endpoints

3.2.1. Baseline Hemoglobin

Table 1 presents information on baseline hemoglobin status by sex and by study arm. The mean baseline hemoglobin concentration for women in the ferrous product group was 9.4 g/dL, statistically the same as the value for women in the ferric product group, 9.3 g/dL. Mean levels also were statistically the same for men in the ferrous and ferric product groups (9.5 g/dL and 9.1 g/dL, respectively). Finally, there was no statistical difference between either group and the analyzed population as a whole.

3.2.2. Changes in Hemoglobin over Course of Study

The primary efficacy endpoint, change in hemoglobin level over the course of the study, is presented in Table 2. At randomization, mean hemoglobin concentration was 9.38 g/dL for ferrous product subjects and 9.26 g/dL for ferric product subjects. At the end of the study, mean hemoglobin level had risen to 12.19 g/dL for the 36 people in the ferrous product group and 9.88 g/dL for the 36 people in the ferric product group, improvements of 2.84 g/dL and 0.6 g/dL, respectively. Improvement in hemoglobin level for the ferrous product compared with the ferric product was statistically significant ($P < .0001$). Analysis of data within each study arm showed that there was statistically significant improvement from time point to time point for each medication with 1 exception. There was no significant improvement between baseline and week 4 for patients taking the ferric product.

3.2.3. Serum Ferritin and Other Secondary Iron Measures

The pattern for serum ferritin change over the course of the study was similar to that for hemoglobin (Table 3). Baseline levels were 6.32 ng/mL for patients randomized to the ferrous product and 5.14 ng/mL for patients randomized to the ferric product (no statistical difference). By week 4, however, there was a significant difference in improvement in ferritin level between the 2 study arms (an increase of 8.68 ng/mL to 15.00 ng/mL for the ferrous product and an increase of 0.87 ng/mL to 6.21 ng/mL for the ferric product, a difference of 7.81 ng/mL, $P < .0001$). The mean increase in serum ferritin level from baseline to the end of the study was 12.47 ng/mL for the ferrous product and 2.61 ng/mL for the ferric product, a significant difference (9.86 ng/mL between groups, $P = .0002$). The lower level of improvement in serum ferritin level over time with the ferric product also was demonstrated in a lack of significance in improvement between individual time points compared with the pattern for the ferrous product, in which there was a statistical difference between ferritin levels between time points.

The pattern over time for changes in TIBC paralleled that for serum ferritin (data not shown). Baseline values were comparable for the 2 study arms. Improvement from

Table 2.
Hemoglobin Levels over the Course of the Study

Time Point	Mean Ferrous/Ferall (SE) (n = 36)	Mean Ferric/Niferex (SE) (n = 36)	Ferrous-Ferric Product Difference	*P* for Difference
Baseline	9.38 (0.28)	9.26 (0.28)	0.12	.7645
Week 4	11.20 (0.25)	9.44 (0.25)	1.76	<.0001
Week 8	12.18 (0.24)	9.85 (0.25)	2.33	<.0001
Week 12	12.30 (0.26)	10.19 (0.27)	2.11	<.0001
Study end	12.19 (0.27)	9.88 (0.27)	2.31	<.0001
Change from baseline to study end	2.84 (0.22)	0.60 (0.22)	2.24	<.0001

Table 3.
Serum Ferritin Levels over the Course of the Study

Time Point	Mean Ferrous/Ferall (SE) (n = 36)	Mean Ferric/Niferex (SE) (n = 36)	Ferrous-Ferric Product Difference	*P* for Difference
Baseline	6.32 (0.70)	5.14 (0.69)	1.18	.2346
Week 4	15.00 (1.20)	6.21 (1.22)	8.79	<.0001
Week 8	14.29 (0.81)	5.39 (0.85)	8.91	<.0001
Week 12	19.26 (2.13)	8.38 (2.20)	10.88	.0008
Study end	18.60 (1.87)	7.58 (1.84)	11.02	.0001
Change from baseline to study end	12.47 (1.80)	2.61 (1.74)	9.86	.0002

time point to time point (ie, decrease in mean TIBC level) was statistically significant for the ferrous product group but not the ferric product group. At the end of the study, mean TIBC level had decreased significantly for patients taking the ferrous product (from 412.72 μg/dL to 332.97 μg/dL) but only slightly for patients taking the ferric product (from 410.41 μg/dL to 400.19 μg/dL). Transferrin saturation showed the same general pattern over time (data not shown). Baseline values were comparable. The difference between study arms in improvement of saturation by week 4 was statistically significant (14.02% for the ferrous product, 1.44% for the ferric product, $P < .0001$), as was the difference between arms in improvement between baseline and end of study (17.33% for the ferrous product, 0.95% for the ferric product, $P < .0001$).

3.2.4. Mean Corpuscular Volume

Improvement in the size of circulating erythrocytes (MCV) is an important sign of remediation of iron deficiency anemia. Our data are shown in Table 4. Patients in both study arms moved from a comparable baseline MCV to a significantly better MCV at the end of the study. However, the baseline to end of study increase in MCV was dramatically higher for the ferrous product than for the ferric product (11.3 fL and 2.1 fL, respectively, $P < .0001$).

3.3. Safety Endpoints: GI Symptoms

Information on the 6 symptoms for which we collected information—abdominal pain, heartburn, nausea, vomiting, constipation, and diarrhea—is presented in Table 5. Although more participants in the ferrous product group reported abdominal pain, heartburn, vomiting, and constipation than did participants in the ferric product group, the differences were not significant. In contrast, more than 30% of patients taking the ferrous product reported mild-to-moderate nausea compared with 2.8% of patients taking the ferric product, and this difference was significant ($P = .003$). There was a marginally significant difference in the incidence of diarrhea, more patients in the ferrous product group reporting the problem than patients in the ferric product group (13.9% and 0.0%, respectively, $P = .054$).

4. Discussion

Both iron supplements, a ferrous-based combination product (Ferall) and a ferric polysaccharide complex (Niferex), raised mean hemoglobin level over the course of the 12-week study. Improvement in hemoglobin level was significantly better with the ferrous product than with the ferric product. In addition, statistically significant improvement over baseline was noted earlier (week 4) for the ferrous product than for the ferric product (week 8). Superior efficacy of the ferrous product also was found for the secondary endpoints: serum ferritin, TIBC, transferrin saturation, and MCV. The results for patients in this study who took Niferex, the ferric polysaccharide complex, were comparable with those we have seen historically with the same general patient population, Taiwanese adults. Hemoglobin concentration did not rise enough to reach the lower limit of the normal range. In contrast, both hemoglobin concentration and MCV rose into the normal range for patients in the current study who took the ferrous supplement.

Both iron supplements were well tolerated, no patients withdrawing from the study for a GI reason or for any other type of self-reported adverse event. Among the 6 GI symptoms we monitored—abdominal pain, heartburn, nausea, vomiting, constipation, and diarrhea—only mild-to-moderate nausea and diarrhea were significantly more common for the ferrous product than for the ferric polysaccharide product.

Table 4.
Changes in Mean Corpuscular Volume over the Course of the Study

Time Point	Mean Ferrous/Ferall (SE) (n = 36)	Mean Ferric/Niferex (SE) (n = 36)	Ferrous-Ferric Product Difference	*P* for Difference
Baseline	72.47 (1.60)	71.00 (1.60)	1.47	.5183
Week 4	78.04 (1.43)	71.86 (1.43)	6.18	.0032
Week 8	81.49 (1.41)	73.55 (1.46)	7.94	.0002
Week 12	84.58 (1.55)	74.80 (1.61)	9.78	.0001
Study end	83.56 (1.49)	73.30 (1.49)	10.26	<.0001
Change from baseline to study end	11.30 (0.96)	2.10 (0.96)	9.20	<.0001

Table 5.
Summary of Safety Information (Gastrointestinal Symptoms)

Symptom	Combined (N = 72)	Ferrous/Ferall (n = 36)	Ferric/Niferex (n = 36)	*P*
Abdominal pain				.493
Mild	1 (1.4%)	1 (2.8%)	0	
Moderate	1 (1.4%)	1 (2.8%)	0	
Heartburn				.614
Mild	4 (5.6%)	3 (8.3%)	1 (2.8%)	
Nausea				.003
Mild	10 (13.9%)	9 (25.0%)	1 (2.8%)	
Moderate	2 (2.8%)	2 (5.6%)	0	
Vomiting				.421
Mild	2 (2.8%)	2 (5.6%)	0	
Moderate	3 (4.2%)	2 (5.6%)	1 (2.8%)	
Constipation				.674
Mild	5 (6.9%)	2 (5.6%)	3 (8.3%)	
Moderate	1 (1.4%)	0	1 (2.8%)	
Diarrhea				.054
Mild	4 (5.6%)	4 (11.1%)	0	
Moderate	1 (1.4%)	1 (2.8%)	0	

At the broadest level of comparison for ferrous-based versus ferric-based iron supplementation, the findings were within expectations. The ferrous product was more effective but had a higher level of reported GI side effects. The ferrous product was significantly more effective, producing earlier and greater improvement in primary and secondary efficacy endpoints. Although we did not evaluate baseline and incremental quality-of-life measures such as fatigue at rest or exercise tolerance, it may be beneficial to do so in future studies as an adjunct to quantitative efficacy measures. We found only a marginal difference in GI side effects in our study, mild-to-moderate nausea and diarrhea being the problems more common among patients taking ferrous-based supplementation. In an indirect measure of quality-of-life impact of side effects, we monitored reasons for withdrawal from the study and found no individual withdrew because of perceived drug side effects.

We concluded that the ferrous-based combination product Ferall is superior to the ferric polysaccharide product Niferex as treatment of uncomplicated iron deficiency anemia in our patient population. Our findings appeared to be significantly different from those obtained in an earlier study that showed Niferex had absorption comparable with that of ferrous fumarate but with significantly fewer GI side effects [3]. However, the earlier study involved dialysis patients, a population different from ours, and this difference may have had a significant impact on the findings. Such an impact was strongly suggested in a report from Tinawi and colleagues [4]. Those investigators found that healthy persons serving as controls had a significant rise in serum iron level with a single dose of ferrous sulfate but not with Niferex. Patients undergoing continuous ambulatory peritoneal dialysis did not have a significant rise in response to either iron supplement.

Our study design differed from others in the use of a ferrous-based combination product (Ferall, consisting of 460 mg ferrous fumarate, 60 mg ascorbic acid, 1 mg folic acid, and 10 μg cyanocobalamin) rather than single-agent ferrous sulfate or ferrous fumarate. We excluded people with anything other than simple iron deficiency anemia from this study, so no participants were unintentionally treated for anemia related to vitamin deficiency. Absorption of iron may well have been increased, however, by the presence of a considerable amount of ascorbic acid (100% recommended daily allowance in the United States) in Ferall and cosupplementation with ascorbic acid (50 mg) for patients receiving Niferex. A study directly comparing single-agent ferrous fumarate (a standard treatment in the United States) with the ferrous combination product Ferall in people without vitamin deficiency and without other vitamin supplementation may clarify the question.

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