Ferrous Sulfate Versus Ferrous Fumarate Plus Zinc Sulfate and Vitamin C for Treatment of Iron Deficiency Anemia in Children

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Abstract: During childhood, different oral iron preparations are widely used in iron deficiency anemia (IDA) and prophylaxis. The purpose of this study was to compare the efficacy of different oral iron preparations in children with IDA. Eighty-nine children (age range, 1 to 17 years) with IDA were randomized to receive therapy orally in two divided doses of either 5 mg Fe^{2+}/kg/day ferrous sulfate (FS group, *n* = 45) or ferrous fumarate plus zinc and vitamin C (FZ group, *n* = 44). Hematological profile and iron status were evaluated at the beginning and on days 15 and 45 of treatment. Mean Hb, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), red cell distribution weight (RDW), and iron and ferritin levels were significantly higher in both groups on days 15 and 45 of treatment. Mean changes in Hb were 2.5 ± 1.2 g/dL and 2.1 ± 0.7 g/dL on day 15 (*P* = 0.295), and 3.9 ± 1.8 g/dL and 3.5 ± 1.2 g/dL on day 45 (*P* = 0.331) in the FS and FZ groups, respectively. Our study suggests that ferrous sulfate and ferrous fumarate plus zinc and vitamin C were well tolerated and were highly effective in correcting IDA in children. Ferrous fumarate plus zinc and vitamin C did not influence hematologic recovery compared with ferrous sulfate in this group.

Keywords: Anemia, Iron deficiency, Ferrous sulfate, Ferrous fumarate, Children, Zinc, Vitamin C.

INTRODUCTION

Iron deficiency is the most frequent and widespread micronutrient deficiency worldwide because it is common in developing and developed countries alike [1]. Anemia is the most common clinical manifestation of iron deficiency. The current treatment strategy for iron deficiency anemia (IDA) involves the oral use of ferrous sulfate (Fe^{2+}) and ferric iron polymaltose complex (Fe^{3+}) [2, 3]. However, in clinical practice bivalent iron salts are preferred over ferric iron preparations [4].

Experimental studies showed that high amounts of zinc reduced iron absorption [5]. It is also reported that supplementation of zinc together with iron reduced its bioavailability in infants, while supplementation with only zinc reduced plasma iron levels in adolescents [6, 7]. However, in another study, if the Fe:Zn ratio was 2:1, there was no change in the level of iron [8]. On the basis of the literature, zinc supplementation alone does not appear to have a clinically important negative effect on iron status. However, when zinc is given with iron, iron indicators do not improve as greatly as when iron is given alone [9].

Vitamin C supplementation enhances iron absorption, although it has a relatively minor effect in individuals ingesting normal, balanced diets [10]. Ferrous ascorbate provides a significantly higher rise in hemoglobin levels in comparison to colloidal iron in children [11]. However, studies investigating the effect of vitamin C on ferrous sulfate absorption far outnumber those on other iron fortificants, especially in meals containing inhibitors of iron absorption [12].

Because there are some concerns about their interactions in absorption from the intestines [5, 8, 9, 12, 13], in the present study we aimed to compare the effects of zinc sulfate (Zn-S) and vitamin C on hematological parameters when ferrous sulfate alone and ferrous fumarate, zinc, and vitamin C in combination are administered in children with IDA.

PATIENTS AND METHODS

A total of 89 consecutive patients who attended the Pediatric Hematology/Oncology Outpatient Clinic at Eskisehir State Hospital, Turkey, between August 2013 and January 2014 were enrolled in this open-label randomized trial. The study was approved by the Ethical Committee of Eskisehir State Hospital. IDA was defined as hemoglobin (Hb) below 10.6 g/dL for children at or below the age of 2 years, and below 11 g/dL for children older than 2 years and with a serum ferritin value below 12 ng/mL [14, 15]. The children with IDA, aged between 1 and 17 years, using simple randomization with no restrictions or matching, were allocated into the ferrous sulfate (Ferro-Sanol® susp. or capsule/Adeka) group or ferrous fumarate/zinc/vitamin C (Ferrozinc® susp. or capsule/Berko) group. Iron was given at a dose of 5 mg/kg/day Fe^{+2} by oral route on an empty stomach [15]. Children weighing 45 kg or more received two capsules a day. The FZ group received zinc monohydrate 1.6 mg/kg/day and vitamin C 6.3

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mg/kg/day via iron capsule or syrup. All patients were seen at the Outpatient Clinic on days 15 ± 2 and 45 ± 5 of treatment. At each visit, all patients were examined and side effects and all data were recorded. Adherence was defined as high if the parents reported drug use on 6 to 7 days during the week before assessment.

Children were excluded if they had acute infection, had a history of chronic disease [except neurologic disease] or parasites, suffered blood loss for any reason, or had occult blood in their stools. There was no control group of children with IDA followed without active treatment as that would have been unethical and an infringement of basic human rights.

Analytical Methods

Blood samples were collected from a peripheral vein into vacutainers containing ethylenediaminetetraacetic acid and jelled serum tubes. A hemogram was obtained, and ferritin, iron, and total iron binding capacity levels were determined using commercial kits (Abbott) on the same day. Whole blood count was measured by an automated analyzer (Celldyn 3700, Abbott, IL, USA). All analyses were performed at a single laboratory.

Statistical Analysis

Normal distribution of variables was tested using the Kolmogorov-Smirnov test. A chi-square test was used to assess relationships between categorical independent variables. Differences between groups were tested by Student's *t*-test, while differences between pairs of observations were analyzed by paired *t*-test. The data were expressed as mean ± standard deviation (SD) and differences were considered statistically significant at $P < 0.05$. Statistical analyses were performed using SPSS for Windows Release 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

The FS group included 45 patients (male/female: 23/22) and the FZ group included 44 patients (male/female: 24/20); the sex ratio was not significantly different between the groups ($P = 0.746$). The mean age of the FS group was 7.8 ± 5.5 years, while that of the FZ group was 6.3 ± 6.1 years. Forty-five (51%) of them were 1-4 years old.

The drugs were generally well tolerated but in 6 patients treatment was ceased due to side effects (3 patients in the FS group and 3 patients in the FZ group were excluded from the study). Adherence to treatment was generally good. The adherence rate was 83% in the subjects receiving ferrous sulfate, compared with 84% in those receiving ferrous fumarate plus zinc and vitamin C ($P > 0.05$). No significant differences were observed between the groups with respect to the mean age, sex, or side effect ratios ($P > 0.05$) (Table **1**).

The hematologic parameters were similar between the two study groups at the beginning of the study. The patients' mean Hb (Figure **1**), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), red cell distribution weight (RDW), and iron and ferritin levels were significantly higher in both groups on days 15 and 45 of treatment (Table **2**).

Table 1: Comparison of Side Effects due to Iron Treatment in the Sulfate and Fumarate Groups

	Baseline		Day 15		Day 45	
	FS	**FZ**	**FS**	**FZ**	**FS**	**FZ**
Rbc (million/mm3)*	4.5 ± 0.8	4.6 ± 0.8	4.6 ± 0.6	4.9 ± 0.5	5 ± 0.5	4.9 ± 0.7
Hemoglobin (g/dL)*	8.1 ± 1.5	8.2 ± 1.7	10.6 ± 1.1	10.1 ± 1.4	12 ± 1.4	11.6 ± 1.9
MCH (pg)*	20 ± 4	18 ± 3	21 ± 1	20 ± 2	23 ± 2	23 ± 3
MCHC (g/dL)*	30 ± 2	30 ± 2	31 ± 1	30 ± 2	31 ± 1.6	32 ± 1.9
MCV (fL)*	61 ± 5	61 ± 7	69 ± 4	67 ± 7	73 ± 3	73 ± 5
RDW (%)*	21 ± 5	21 ± 3	27 ± 11	26 ± 8	21 ± 2	23 ± 5
Iron (mg/dL)*	13 ± 5	12 ± 5	-	-	38 ± 19	31 ± 15
IBC (mg/dL)*	457 ± 70	453 ± 54	-	-	340 ± 68	378 ± 58
Ferritin (ng/mL)*	3.5 ± 2.7	2.4 ± 2.3	-	-	31 ± 18	22 ± 23

FS, Ferrous sulfate group; FZ, ferrous fumarate plus zinc and vitamin C group.
*Student's *t* test between FS and FZ groups, baseline and on days 15 and 45 ($P > 0.05$).
*Paired *t* test between baseline and on days 15 and 45 ($P \leq 0.001$).

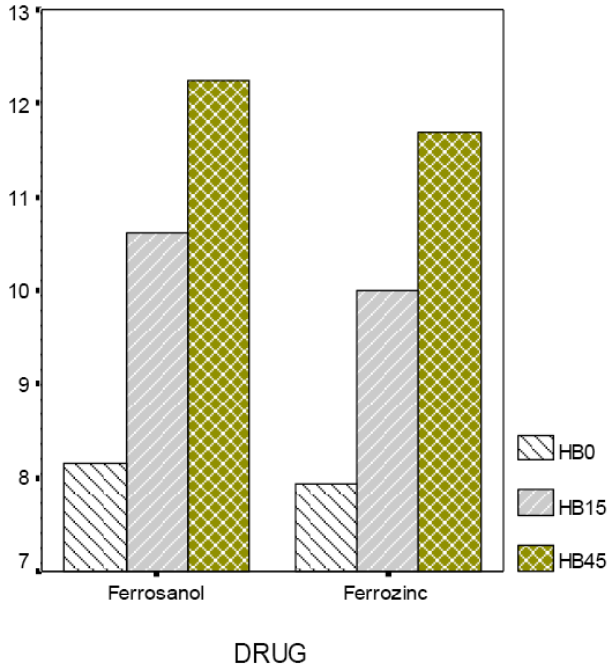

Figure 1: Hemoglobin levels of groups on baseline and on days 15 and 45 of therapy.

Mean red blood cell (RBC) count and mean hemoglobin concentration (MCHC) were not significantly different ($P > 0.05$). Mean changes in Hb were 2.5 ± 1.2 g/dL and 2.1 ± 0.7 g/dL on day 15 ($P = 0.295$) and 3.9 ± 1.8 g/dL and 3.5 ± 1.2 g/dL on day 45 in the FS and FZ groups, respectively ($P = 0.331$). No patient showed a decrease in Hb in either group.

The cost of ferrous fumarate plus zinc and vitamin C is twice as high as those of ferrous sulfate.

DISCUSSION

Current treatment of IDA is successfully performed orally with either Fe^{2+} or Fe^{3+} preparations. Moreover, it is reported that ferric polymaltose was not as effective as ferrous sulfate, although it increased hemoglobin and serum iron [16, 17]. The dose of 3-5 mg/kg or 60 to 120 mg of elemental iron of ferrous sulfate per day for a minimum duration of 3 months in adolescents and adults, including pregnant women, is recommended [18, 19]. Among ferrous preparations, FS remains the established and the standard treatment for iron deficiency given its acceptable tolerability, high effectiveness, and low cost [3]. The absorptive capacity of the normal duodenum for iron is essentially saturated with about 25 mg of elemental iron in ionic form.

Deficiencies of other trace elements, especially zinc, are frequently seen in children with IDA [19, 20]. Therefore, in the treatment of patients with IDA, zinc, in addition to iron, may be considered [21, 22]. A study from Indonesia compared prophylactic treatment regimens of 10 mg/d of iron, 10 mg/d of zinc, or both in babies starting at 4 months of age and continuing for 6 months [6]. In that study, the percentage of babies who had anemia (Hb<11 g/dL) was higher in those taking iron and zinc compared to those taking only iron (46% vs. 28%; P<0.05). The authors suggested that supplementation of zinc together with iron reduced its bioavailability. Another study found that only supplemental zinc during 12 weeks in adolescent athletes reduced plasma iron levels [7]. In addition, experimental studies showed that high amounts of zinc reduced iron absorption [5]. However, if the Fe: Zn ratio was 2:1, there was no change in the level of iron in another study [8]. In order to reduce the possible interaction of iron and zinc based on these findings, iron and zinc may be used at different times. Because there were no differences between the hematological data of our 2 groups during treatment, it is seen that

Table 2: Therapeutic Efficacy of Ferrous sulfate (FS) and Ferrous Fumarate Plus Zinc and Vitamin C (FZ). Data are Mean ± SD

	FS group* (*n* = 35)	FZ group* (*n* = 37)
Difficulty in drinking (*n*)	2	1
Stomachache (*n*)	1	1
Constipation (*n*)	3	4
Diarrhea (*n*)	0	0
Nausea and vomiting (*n*)	1	2
Stopped receiving treatment due to side effects (*n*)	3	3

FS, Ferrous sulfate group; FZ, ferrous fumarate plus zinc and vitamin C group.
*Differences were not significant.

the iron absorption was not affected if iron and zinc were given at the same time.

Vitamin C supplementation enhances iron absorption, although it has a relatively minor effect in individuals ingesting normal, balanced diets [10]. Furthermore, it is reported that ferrous ascorbate provides a significantly higher rise in hemoglobin levels in comparison to colloidal iron in children such that each child received elemental iron 3 mg/kg/day for 12 wk [11]. Our results showed that ferrous fumarate plus ascorbic acid supplementation on an empty stomach did not have any positive effect on hematologic recovery. However, studies investigating the effect of vitamin C on ferrous sulfate absorption far outnumber those on other iron fortificants, especially in meals containing inhibitors of iron absorption [12, 13].

Among ferrous preparations, FS remains the established and the standard treatment for iron deficiency given its acceptable tolerability, high effectiveness, and low cost [2]. Our study showed that ferrous fumarate plus zinc and vitamin C drugs were significantly more expensive [average 50%] than ferrous sulfate. However, this drug did not contribute to hematologic recovery and had similar side effects compared with ferrous sulfate in children with IDA. This form of replacement may not produce fewer problems than ferrous sulfate and is not ideal as the initial treatment for iron deficiency.

It was reported that an Hb increase of more than 1 g per dL (10 g per L) after iron therapy has been started confirms the diagnosis of iron deficiency [22]. Our patients' mean hemoglobin levels increased 2 g/dL with both drugs after 15 days. The increase in hemoglobin 15 days after the beginning of the treatment was not significantly higher in the group of children that received FS (10.6 ± 1.1 g/dL) compared to the group of patients treated with FZ (10.1 ± 1.4 g/dL]. In addition, no patient had decreased hemoglobin levels after treatment compared to baseline values.

Anemia affects all population groups, but the most susceptible groups are pregnant women and young children [18]. Low birth weight infants, young children, and women of childbearing age are particularly at risk of IDA. Adolescents participating in strenuous training are another pediatric subpopulation at risk for iron deficiency [14]. The most susceptible groups of our child population are young children and adolescents who participate in senior high school and national higher education entrance examinations in addition to participating in strenuous training.

Although ferrous sulfate is most often recommended, patients frequently complain of gastrointestinal discomfort, constipation, and bloating, as well as stool discoloration, thus making its use unacceptable to many. Interestingly, in a randomized, controlled trial comparing 3 mg/kg/day of ferrous sulfate drops with a placebo in infants, there was no significant difference in the frequency of vomiting, diarrhea, or fussiness in iron-treated infants compared with placebo-treated infants [24]. Our study showed that the two drugs had similar types and ratios of side effects (totally 19%); in 6% of children treatment was ceased due to side effects.

The limitations of this research were the short duration of follow-up and the fact that it was not a double-blind trial. In general, if researchers describe a trial as double-blind, readers can assume that they have avoided bias [25]. The comparison of the drugs is most readily accepted if the results are from randomized controlled trials [26]. Open-label studies are frequently incorporated in the design of randomized controlled trials. However, we compared the two different oral iron preparations and did not have a control group, the results of the patients procured during the treatment were compared to their baseline and post-treatment values, and each patient was assessed with his/her own control in both groups.

In conclusion, our study suggests that ferrous sulfate and ferrous fumarate plus zinc and vitamin C are well tolerated and highly effective in correcting IDA in children. Ferrous fumarate plus zinc and vitamin C did not impact on hematologic recovery compared with ferrous sulfate in this group.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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