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Original Article

The efficacy of divalent iron preparations with and without zinc in the treatment of iron deficiency anemia

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Abstract

Aim: Iron deficiency anemia (IDA) is the most frequently detected cause of anemia in Turkey and worldwide. In this study, we investigated the efficacy of the iron preparations of ferrous sulfate (group FeS, Fe^{2+}) and ferrous fumarate combined with Zn (group Fe^{2+}-Zn) in the treatment of IDA.

Materials and Methods: Seventy children receiving FeS and 24 children receiving Fe^{2+}-Zn due to IDA between June 2018 and January 2019 were included in the study. The Hb, MCV, MCH, RBC, transferrin saturation, ferritin levels before treatment and in the 1st and 3rd months after treatment, period of drug use, and the frequency of gastrointestinal adverse effects in the two groups were investigated.

Results: There was no difference between the two groups regarding age and sex. The mean drug dose in FeS group was 4.01±0.98 mg/kg/day and 4.12±0.06 mg/kg/day in the Fe^{2+}-Zn group ($p>0.05$). The Hb, MCV, MCH, RBC, transferrin saturation, and ferritin levels in both groups in the 1st and 3rd months after treatment were found significantly higher compared with the levels before treatment. No difference was detected between the two groups for the same parameters before treatment, and in the 1st and 3rd months after treatment ($p>0.05$, for all). The period of drug use in Fe^{2+}-Zn group (median:4.5 months) was longer than in the FeS group (median:4 months) ($p<0.05$). No difference was detected in the frequency of adverse effects ($p>0.05$).

Conclusion: We found that FeS and Fe^{2+}-Zn preparations had similar effects on hematologic parameters and iron status in IDA; however, the treatment period in patients who received Fe^{2+}-Zn was longer.

Keywords: Iron deficiency anemia; divalent iron; zinco

INTRODUCTION

Iron (Fe), and zinc (Zn) are the most frequently detected micronutrient deficiencies in developing countries, and are mostly detected in individuals who live in lower income regions (1). Deficiencies of these elements result in growth retardation, decreased cognitive functions, perinatal complications, and increased risk of morbidity and mortality (1). These results show the importance of the treatment of the micronutrient deficiencies.

Iron deficiency anemia (IDA) is the most frequently detected cause of anemia in Turkey and worldwide (2,3). The World Health Organization (WHO) estimated that approximately 293 million children and 468 million non-pregnant women were affected by anemia worldwide, 50% of which were due to iron deficiency (4). Similarly, nutritional Zn deficiency is detected in a high ratio of 15.7% worldwide, and in Turkey (5-7). The deficiency of other trace elements, particularly Zn, is frequently associated with IDA in developing countries such as Turkey (8,9). There is a close association between Zn and Fe, and this association is possibly associated with the effect of Zn on the functions of proteins that have a role in Fe homeostasis and transport (10). For this reason, Zn may be considered as an adjunct to iron in the treatment of patients with IDA (11). However, there are concerns about the combined use of the two elements. The results of studies investigating the effects of adding zinc to oral iron preparations on hematologic parameters and serum Fe and Zn levels are controversial.

We investigated the effects of ferrous sulfate (FeS) and Zn combined with ferrous fumarate (Fe^{2+}-Zn) on hematologic parameters and iron status in children with IDA.

MATERIALS and METHODS

One hundred and twenty-four children who were being treated for IDA between June 2018 and January 2019 were included in this retrospective study. Hemoglobin

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levels of <11 g/dL in children aged between 6-59 months were accepted as anemia (12), and transferrin saturation <16% and ferritin level of <12 ng/mL were accepted as iron deficiency (13). The drugs were recommended to be taken one hour before meals, or two hours after meals. Patients who required a daily dose of FeS (20 mg ferrous sulfate/ 5mL), 20 mL/day and above were prescribed Fe^{2+}-Zn preparation (39.77 mg ferrous iron fumarate, 15 mg zinc sulfate, 200 µg folic acid, 50 mg vitamin C/ 5mL). The patients' files were retrospectively evaluated. The hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red blood cell count (RBC), transferrin saturation, ferritin levels at presentation to hospital, and in the first and third months were recorded. Also, period of drug use, drug doses and gastrointestinal adverse effects were recorded. The criteria for drug discontinuation was accepted as Hb level of >11 g/dL, and a ferritin level of >12 ng/mL.

This study was approved by the ethics committee (ethic approval no:17/2018) and was conducted in accordance with principles of Helsinki. A written informed consent was obtained from the legal guardians of children.

Exclusion criteria

A total of 30 patients with acute, and chronic infectious conditions (n=4), malabsorption syndrome (n=2), parasitosis (n=4), a history of iron use in the last three months (n=5), discontinuation of drug due to gastrointestinal adverse events (n=8), and patients who could not be followed up (n=15) were excluded from the study. The flow diagram for the study group is shown in Figure 1.

Statistical analyses

Statistical analyses were performed using SPSS for Windows version 15.0 software (SPSS, Inc., Chicago, IL, US). Categorical data were compared using a Chi-square test, while the normality of distributions was evaluated using a Kolmogorov–Smirnov test. Descriptive statistics were reported as median and interquartile distribution (Q1–Q3) range. Group comparisons with non-normal distribution were analyzed using the Mann–Whitney U-test, and otherwise, an independent sample t-test. Repeated-measures ANOVA and Friedman test were used to analyze the parameters over time in the groups. A value of P < 0.05 was considered statistically significant.

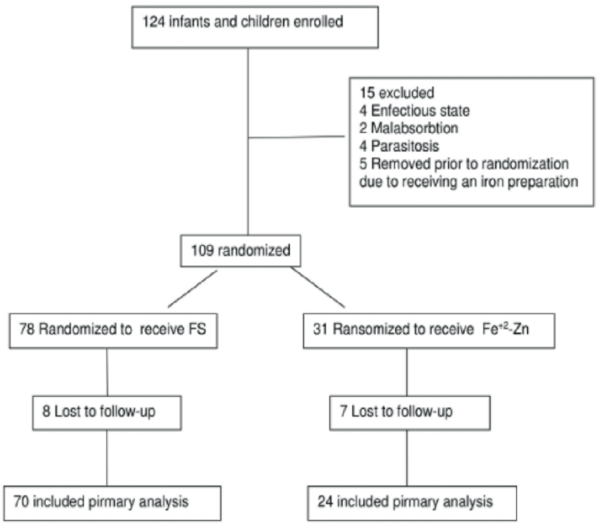

Figure 1. Flow diagram of the study group

RESULTS

Ninety-four patients were included in the study. Seventy patients were given FeS and 24 patients were given Fe^{2+}-Zn preparations. The median age of the FeS group was 26 months (16 to 41 months), and the female/male ratio was 28/42. The median age of the Fe^{2+}-Zn group was 29 months (18 to 62 months), and the female/male ratio was 8/16. There was no difference between the groups regarding age and sex (p>0.05). The mean drug dosage in FeS group was 4.01±0.98 mg/kg/day (min-max; 3-6mg/kg/day), and 4.12±0.06 mg/kg/day (min-max; 4-5mg/kg/day) in Fe^{2+}-Zn group. There was no difference regarding the drug dosages between the groups (p>0.05).

In the FeS group; Hb, MCV, MCH values at the 1st month after treatment were higher than the values before treatment; and the Hb, MCV and MCH values at the 3rd month after treatment were higher than both the values before treatment and the values at the 1st month after treatment. RBC, transferrin saturation, ferritin values at the 1st and 3rd months after treatment were higher than

Table 1. Comparison of laboratory parameters of the FeS group before treatment, and in the first and third months after treatment

	Before treatment	1st month	3rd month	P
Hb (g/dl)	9.90 (8.60-10.45)	10.9 (10.10-11.95)	11.70 (11.30-12.70)	$<0.01^{1-2}$, $<0.001^{1-3,2-3}$
MCV (fl)	63.50 (57.10-67.20)	66.10 (62.60-72.50)	72.10 (67.95-73.95)	$<0.01^{1-2}$, $<0.001^{1-3,2-3}$
MCH (pg)	20.30 (17.95-22.60)	21.40 (19.80-23.45)	23.80 (22.35-25.45)	$<0.01^{1-2}$, $<0.001^{1-3,2-3}$
RBC (x10^6fl)	4.95 (4.44-5.26)	5.05 (4.75-5.52)	5.03 (4.76-5.28)	$<0.01^{1-2,1-3}$
Saturation (%)	6.25 (4.30-9.46)	12.50 (6.64-22.68)	17.12 (9.60-21.95)	$<0.001^{1-2,1-3}$
Ferritin(ng/ml)	7.61 (4.69-19.75)	19.61 (8.88-32.21)	21.90 (10.49-51.65)	$<0.05^{1-2}$, $<0.001^{1-3}$

Hb: Hemoglobin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, RBC: Red blood cell count 1: Before treatment, 2: 1st month after treatment, 3:3rd month after treatment

those before treatment. There was no difference between RBC, transferrin saturation, ferritin values at the 1st and 3rd months after treatment. (Table 1).

Hb, MCV, MCH, transferrin saturation and ferritin values at the 1st and 3rd months after treatment were higher than the values before treatment in the Fe^{2+}-Zn group. There was no difference between the values at the 1st and 3rd months. RBC value at the 3rd month after treatment was found to be higher than the value before treatment. There was no difference in this value between the 1st and 3rd months after treatment (Table 2).

No differences were detected regarding the Hb, MCV, MCH, RBC, transferrin saturation, and ferritin levels between the two groups before treatment, and in the 1st and 3rd months after treatment (p>0.05, for all).

Adverse effects and period of drug use

Tolerable gastrointestinal adverse effects were detected in 6 (8.5%) patients in the FeS group, and in 2 (8.5%) patients in the Fe^{2+}-Zn group. No difference was found between the groups regarding the frequency of adverse effects (p>0.05). The treatment period was longer than 3 months in 23 patients (32.8%) in the FeS group, and in 5 patients (20.8%) in the Fe^{2+}-Zn group. The period of drug use in the FeS group (4 months; range, 3-4.25 months) was found statistically shorter compared with the Fe^{2+}-Zn group (4.5 months; range, 2.25-5 months) (p=0.036) (Figure 2).

Table 2. Comparison of the laboratory parameters of the Fe^{2+}-Zn group before treatment, and in the first and third months after treatment

	Before treatment	1st month	3rd month	P
Hb (g/dl)	10.10 (8.55-10.20)	11.65 (10.32-12.32)	11.80 (10.85-12.72)	$<0.05^{1-2}$, $<0.001^{1-3}$
MCV (fl)	61.35 (56.90-65.35)	68.85 (58.05-70.80)	69.10 (61.72-72.32)	$<0.01^{1-2}$, $<0.001^{1-3}$
MCH (pg)	19.60 (17.24-21.05)	22.85 (18.72-23.50)	23.0 (19.85-24.70)	$<0.05^{1-2}$, $<0.001^{1-3}$
RBC (x10^6fl)	5.10 (4.61-5.38)	5.16 (4.98-5.20)	5.19 (5.16-5.44)	$<0.05^{1-3}$
Saturation (%)	5.89 (4.05-6.67)	8.90 (6.60-24.90)	11.12 (5.29-31.90)	$<0.01^{1-2}$, $<0.001^{1-3}$
Ferritin(ng/ml)	7.18 (4.29-20.53)	17.35 (7.58-29.18)	23.34 (13.30-30.70)	$<0.01^{1-2}$, $<0.001^{1-3}$

Hb: Hemoglobin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, RBC: Red blood cell count 1: Before treatment, 2: 1st month after treatment, 3:3rd month after treatment

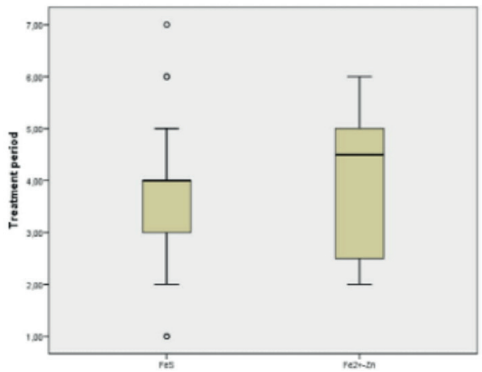

Figure 2. Box plots of treatment period in the two treatment groups

DISCUSSION

The successful treatment of IDA requires the normalization of hemoglobin concentrations with iron replacement, to fill iron stores, and recognition and correction of the underlying etiology (14). The recommended standard dosage for the treatment of IDA in infants and children is 2 to 6 mg/kg/day of elementary iron (daily 1-3 doses) for 3 to 6 months (14). FeS is used as standard for treatment with its acceptable tolerability, high efficacy, and low cost. In our study, we found that the mean Hb levels increased to 10.73 g/dL in the first month, and 11.70 g/dL in the third month from 9.59 g/dL, with the administration of FeS with a mean 4 mg/kg/day twice daily (Table 1). Our results showed that a 4 mg/kg/day twice daily dosage of FeS was efficient in the treatment of IDA.

Researchers investigating Turkish populations reported that Zn deficiency might accompany in patients with Fe deficiency (15-18). Arcagok et al. (17) reported the rate of Zn deficiency as 9.2% in children with Fe deficiency, and Ergül et al. (18) in their study with 560 children aged 6 months-16 years, demonstrated that iron deficiency and IDA were more frequent in children with low Zn levels in hair compared with children with no Zn deficiency.

The results were different in studies that investigated the effects of Zn in combination with Fe on hematologic parameters and serum iron status. Alarcon et al. (19) demonstrated that the addition of Zn to Fe supplementation had positive effects on iron parameters, and on the duration of diarrhea. Researchers showed that 3-month FeS supplementation (30mg) in healthy infants did not change Zn levels (20), Fe supplementation had no significant effect on Zn absorption in breastfed infants (21), and Fe supplementation in baby formula had no significant negative effect on Zn absorption (22). Researchers in a study from Turkey demonstrated that there was no difference in hematologic parameters in the beginning of treatment, and in the first and third month of treatment, and in ferritin levels in the third month between children who were given FeS only and children who were given FeS and Zn;Zn levels were higher in children who were given FeS and Zn compared with children who were

given FeS only (23). Schultink et al. (24) compared the laboratory parameters of anemic children (Hb<11 g/dL) who were administered FeS and an FeS-Zn combination for 8 weeks, and showed that greater improvement in iron was detected in patients receiving FeS only; however, there was no statistically significant decrease in Zn levels.

Our results show that the ferrous fumarate preparation combined with Zn in two doses of 4 mg/kg daily was also effective in the treatment of IDA. We also found that there was no difference in the first and third months after treatment regarding Hb levels, transferrin saturation, and ferritin levels in patients receiving two different preparations. These results demonstrate that the positive changes on laboratory parameters of the combined Zn and ferrous fumarate preparations were similar to those of FeS. The only difference between the two preparations was the period of treatment. Although there was no difference in laboratory parameters, the period of drug use in children who were administered combined Zn with ferrous fumarate was longer (Figure 2).

Both in vivo and in vitro studies have shown that the mechanisms mediating in the interaction of Fe and Zn were strongly associated with the levels and ratios of metals (10). Olivares et al. (25) demonstrated that Fe administration with Zn in combination in an aqueous solution inhibited the dose-dependent Fe bioavailability. The authors observed that iron absorption was not affected when the Zn/Fe molar ratio was 2:1; however, 28% iron absorption inhibition was detected when the Zn/Fe molar ratio was 5:1, and 40% iron absorption inhibition was detected when the ratio was 20:1. In the majority of reviews that investigated the interactions between Fe and serum Zn levels, researchers reported that Fe had no effect on Zn levels in young children who were administered iron supplementation only. The addition of Fe to Zn supplementation was reported to have no negative effect on Zn levels in these studies (23). The ratio of Fe/Zn was 2.64 in the Fe^{2+}-Zn preparation in our study, and no difference was detected regarding iron levels, transferrin saturation, and ferritin levels with the FeS receiving group.

CONCLUSION

Iron preparations including Zn and Fe had a similar effect to the FeS preparation in correcting the anemia, and iron parameters in the treatment of IDA. The possibility of using lower volumes of drug with Fe^{2+}-Zn could be an advantage; however, the longer period for treatment compared with FeS was a disadvantage. It may be suggested as an alternative in the treatment of IDA in children, particularly those who live in low income regions, who are anticipated to have micronutrient deficiency.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: It was approved by Eskisehir Osmangazi University clinical research ethics committee (2018/17).

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