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Original Article

Low Dose, Short-Term Iron Supplementation in Female Blood Donors of Childbearing Age: a Randomized, Double-Masked, Placebo-Controlled Study

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Abstract

Background: Iron supplementation for blood donors is a controversial concept. However, to maintain regular blood donors, as a source of blood supply, the present paradigm is not appropriate and dose not prevent harms to blood donors.

Methods: A randomized, double-masked, placebo-controlled study, was conducted by enrolling 95 female regular blood donors of childbearing age (18-49 years). The participants were selected randomly (systematic random sampling) from 300 donors who donated one unit of whole blood. These individuals were randomly assigned to receive 50 mg elemental iron or placebo once daily. Each donor was scheduled for serum ferritin determination at the beginning of the study, and 28th and 56th days after donation. Adverse effects of the treatment were evaluated on 7th, 28th and 56th days.

Results: After one blood donation, mean serum ferritin concentration remained largely constant in the iron group on 28th day of the treatment, (P= 0.064) whereas it was lower in the placebo group (P= 0.001). There was no significant difference between the placebo and iron group in terms of the incidence of gastrointestinal adverse effects.

Conclusion: The results of the present study indicate that short-term, low dose iron supplementation replace iron loss caused by phlebotomy, protect the female regular blood donors from iron deficiency, and assist retaining this group of donors for future donation.

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Keywords ● Blood donors ● female ● ferritin

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Introduction

Iron deficiency is a concern for all blood donors.[1-5] Blood donation-induced iron deficiency is not significant in males even with donation of 2-3 units per year.[6] Postmenopausal women can donate blood without becoming iron deficient if they have initially had adequate iron stores.[7] However, women of childbearing age are at increased risk of iron deficiency if they donate blood more than one unit a year.[8,9]

Each time donation of 425-475 ml blood is associated with a substantial (213 mg) iron loss in female blood donors.[6] A healthy individual receiving an adequate diet might not be able to compensate such a loss in a period of less than 6 months.[10-12]

Iron deficiency is associated with various complications including decreased cognitive and work abilities, increased predisposition to infection, adverse psychological effects, and certain socioeconomic consequences.[13-16] Moreover, the deficiency results in low hemoglobin levels, reportedly causing 40-75% deferrals, that 95% of which occurs in women.[12]

A number of approaches have been proposed to tackle the blood donation-induced iron deficiency in blood donors, including limitation of the frequency of blood donation associated with reduction in the source of blood supply,[17] and improving the methods of screening for iron deficiency in blood donors. However, these approaches are not always practical because of the difficulty and expenses. Many authors recommend iron supplementation for blood donors after blood donation, that is quick and effective.[4,10,12,17] Iron treatments for repeated blood donors is controversial. Many authors do not recommend iron supplementation for blood donors because it may lead to aggravation of undiagnosed hemochromatosis and interfering with colon cancer screening programs. However, others recommend iron supplementation for female blood donors and a few studies recommend it for female regular blood donors.[4,12]

Iron supplementation programs have few limitations: 1) iron supplementation should compensate iron losses due to blood donation and provide positive iron balance; 2) iron supplementation should be given in a short-term period due to the masking of underlying diseases with iron supplementation. Therefore, low-dose and short-term iron supplementation should compensate iron losses due to blood donation and prevent over treatment (without changes in serum ferritin concentration before and after the blood donation).

The present randomized double-masked trial was conducted to determine the effects of short-term, low-dose iron supplementation in women of childbearing age who donate blood regularly.

Subjects and Methods

Participants

The study was conducted at Ghasre-E-Dasht and Zand blood donation centers in Shiraz city (south of Iran) from January to April 2007. Ninety-five out of 300 female blood donors were randomly selected by systematic random sampling. Included participants were female blood donors who were 18-49 years old, had more than one time blood donation in the last year (regular donors), had a hemoglobin concentration ≥12 g/dl, and were in a healthy status based on Iranian blood donation guidelines.[18] The participants who were using iron supplementation were excluded. The study was approved by the Ethics Committee of Shiraz University of Medical Science, and written informed consents were obtained from the participants. Based on the serum ferritin concentration, the sample size was calculated to be 30 donors per group, assuming a power of 0.9, a significance level of 0.05, a smallest meaningful difference of ferritin 10µg/l between the groups, standard deviation (SD) of 10 µg/l, and plus 30% attrition calculation.

Methods

One blood unit (450±45 ml) was collected from each participant using blood bags with 63 ml citrate phosphate dextrose. A sample of 5 ml was also withdrawn and used for the measurement of serum ferritin levels. The samples were kept frozen at -18°C until performing the laboratory tests on a weekly basis.

After blood donation, the participants were informed about the study aims and protocol. They were asked to respond to a brief oral questionnaire, including information about name, address, telephone number, age, last blood donation, total lifetime donation, number of pregnancies, date of the last pregnancy, and prior iron supplements. These participants were then assigned randomly (random block design) to receive ferrous sulfate equivalent to 50 mg elemental iron or placebo, at a double-masked basis. Drug-free iron tablets that were similar to ferrous sulfate tablets were used as placebo. The participants were instructed to take the pills at bedtime. After one week of receiving the drug or placebo, the participants were called in order to follow the complications of the treatment. They were also scheduled for two visits on the 28th and 56th days to test the blood for determination of serum ferritin and examination of the treatment complications. The serum ferritin concentrations were stratified as adequate iron stores (>30 µg/l), small iron stores (12-30 µg/l), and depletion iron stores (<12 µg/l).

Compliance was defined as ingestion of at least 90% of the prescribed tablets, which checked on the 28th and 56th days.[19]

Laboratory Analysis

Serum ferritin level was determined using ELISA by a Dynex ELISA reader and Monobind

kit (Accubined ELISA Microwells, USA).

Statistical Analysis

The data were analyzed using analysis of variance (ANOVA) with repeated measurement for intra-group comparisons and expressed as mean ± SD. Whenever a significant difference was found with repeated ANOVA, its sources were located using pair *t* test, with an adjusted alpha value using Bonferroni procedure. Between groups comparisons were made using unpaired *t* test. The Fisher's exact test was used to compare between the groups. Analysis was performed using SPSS software version (11.5). A P value less than 0.05 was considered significant.

Results

Ninety-five female donors (34.0±8.5 years old) who previously had donated blood 6.1±1.8 times were enrolled in the study. The participants' demographic information is shown in table 1.

Of the 95 participants, 70 (74%) completed the study. The reasons for withdrawal among the remaining 25 subjects included: 17 experienced adverse events (9 assigned to iron group and 8 to placebo group), six individuals withdrew voluntarily (one from iron group and five from the placebo group) and two who missed the follow-up in the placebo group. The total number of withdrawals was similar for the two groups (20.4% in the iron-treated group *v* 28.3% in the placebo group). However, voluntary withdrawal was more frequent among those who were randomly assigned to placebo group than those who were randomly assigned to iron group (5 *v* 1 individuals). Analyses were conducted to rule out differential attrition by sensitivity analysis (best case-worth case). No significant attrition-condition was found.

There were no significant differences between the baseline serum ferritin levels in the placebo (28.8±9.6 µg/l) and iron (26.1±8.1µg/l) receiving groups (*t* test, P = 0.668) (figure1). The percentages of donors with depleted iron stores (serum ferritin <12 µg/l) in the groups were 21.7% and 30.6%, respectively.

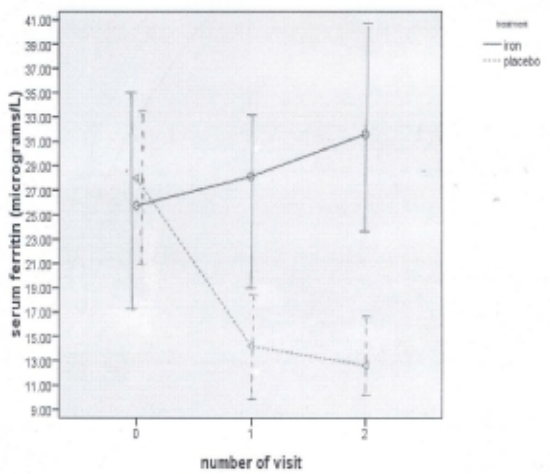

Figure 1: Mean ferritin levels at each visit. The vertical bars represent approximate 95 percent confidence intervals for the mean.

In placebo group, serum ferritin concentration decreased to 14.0±6.2 and 13.5±6.5 µg/l at visits 1 and 2, respectively (repeated measurement ANOVA followed by paired *t* test, P = 0.001). The percentage of donors with depleted iron stores increased to 56% and 58% at visits 1 and 2, respectively. The percentage of the individuals with small iron stores (serum ferritin 12-30 µg/l) decreased from 43.5% to 26.5% and 29% at visits 1 and 2, respectively (table 2, figure 1).

Table 1: Demographic information of the participants in iron and placebo groups.

	Iron-treated group (49)	Placebo group (46)	P value
Age (years)	34.2 ± 9.3 *	34.0 ± 8.0	0.158
Months since last donation	7.2 ± 2.6	7.2 ±2.1	1
Total life time donations	6.0 ± 5.0	6.0 ± 4.4	1
Never pregnant (%)	41%	38%	0.131
Frequency of pregnancy	3.0 ± 5.3	2.7 ± 1.5	0.581
Years since last pregnancy	12.4 ± 5.3	12.4 ± 5.5	1
Prior iron supplementation	72%	79%	0.102

***** Mean ± SD

Table 2: The number and percentage of donors with adequate iron stores (serum ferritin>30 µg/l), small iron stores (serum ferritin 12-30 µg/l), and depleted iron stores (serum ferritin<12 µg/l).

Serum ferritin concentration	Placebo group						Iron group					
	>30µg/l		12-30 µg/l		<12 µg/l		>30µg/l		12-30 µg/l		<12 µg/l	
	N/total	%	N/total	%	N/total	%	N/total	%	N/total	%	N/total	%
Baseline	16/46	34.8	20/46	43.5	10/46	21.7	18/49	36.7	16/49	32.7	15/49	30.6
Visit 1	6/34	17.5	9/34	26.5	19/34	56	15/41	36.6	22/41	54	4/41	9.4
Visit 2	4/31	13	9/31	29	18/31	58	20/39	51.3	15/39	38.5	4/39	10.3

In iron-treated group, serum ferritin increased to 27.5±10.3 µg/l at visit 1 (repeated measurement ANOVA followed by paired *t* test, P = 0.064), and to 31.7±13.4 µg/l at visit 2 (repeated measurement ANOVA followed by paired *t* test, P = 0.001). The percentage of donors with depleted iron stores decreased to 9.4% and 10.3% at visits 1 and 2, respectively, and that of the subjects with small iron stores increased from 32.7% to 54% and 38.5% at visits 1 and 2, respectively (table 2, figure 1).

Figure 1 also shows ferritin measurement results for donors completed the study. A repeated analysis of variance revealed significant differences between the groups (P = 0.001).

The compliance with regimens was similar on the 28th day, but on the 56th day it decreased in the iron-treated group as compared with the other group significantly (P = 0.04, table 3).

The distribution of side effects in the placebo and iron-treated groups are presented in table 4. However, there was no significant difference between the placebo and iron-treated groups in terms of the incidence of gastrointestinal (GI) or none GI adverse effects. There was a higher incidence of unpleasant taste in the group taking iron than in the placebo group (P< 0.05). Headache and weakness was more frequent in placebo group compared with the iron group without statistical significance. Nausea was the most common side effect among all the other symptoms, which was more frequent in iron-treated group. However, most donors (71.4%) in the iron-treated group did not report any side effects.

Discussion

Our results show that iron supplementation using low dose ferrous sulfate for 28 days after one unit blood donation favorably restored the iron status of female regular blood donors of childbearing age. This finding is comparable to that of other studies.[9,17,19,20,21] In contrast, in a recent study conducted by Radtke, et al., iron supplementation with ascorbic acid was prescribed to female blood donors for 4 weeks. However, after iron therapy near to 50% of blood donors who had depleted iron stores still had serum ferritin below 12µg/l.[22] In the study by Radtke, et al, ferrous gluconate 20 mg and ascorbic acid was used as daily supplementation, which might be an explanation for the differences.

In another study, iron supplementation was recommended for 8 weeks to make iron stores recovery.[23] The increase in the duration of treatment may interfere with screening programs of gastrointestinal blood loss diseases such as colon cancer.[5] Moreover, increment of supplementation period can decrease the compliance of participants.

Initial findings of the current study support short-term iron supplementation to compensate iron loss and prevent over treatment. Thus, iron supplementation in female regular blood donors as used in the present investigation, may be useful on a 4-week course. However, using supplementation for 8 weeks will

Table 3: Compliance with supplementation program in the two groups.

Days checked	Groups	Iron-treated group		Placebo group		P value
		N/Total	%	N/Total	%	
On day 28	Subjects returning for repeat sampling	41/49	84	34/36	80	0.154
	Subjects who ingested ≥25 tablets †	18/41	44	16/34	47	0.187
On day 56	Subjects returning for repeat sampling	39/49	80	31/46	67	0.109
	Subjects who ingested ≥50 tablets †	13/39	33	14/31	45	0.04

† Numbers were rounded

Table 4: Distribution of side effects in iron and placebo-treated groups during the study.

Side effect	Iron group		Placebo group		P value
	Number	%	Number	%	
GI complaints					
Heartburn	5	10.2	3	6.5	0.088
Nausea	17	34.7	9	19.6	0.078
Abdominal					
Cramps	2	4	1	2.2	0.092
Constipation	1	2	1	2.2	0.214
Diarrhea	0	0	0	0	
Other complaints					
Weakness	3	6.1	8	17.4	0.071
Headache	6	12.2	8	17.4	0.09
Unpleasant taste	9	19.6	2	4.1	0.041

probably result in a positive iron balance and make overcompensation.[20,22]

Of the 95 female blood donors, 29.5% had serum ferritin below 12 µg/l, suggesting iron deficiency or iron deficiency anemia. This finding is comparable to what has been found by other investigators.[2,4,5,23] Considering the high prevalence of anemia and iron deficiency in this group of donors, it is suggested that the current paradigms for donors safeguard are inadequate. Therefore, we should go towards supplementation programs.[17]

At the beginning of the present study, the mean values for hematological measures and demographic characteristics in the two study groups were similar, suggesting comparability of the two groups.

The total withdrawal proportions were similar for the two groups; however, voluntary withdrawal was more frequent among the placebo group than iron group. The reason for this finding is obscure, but there is no evidence for distortion of the study results due to this event.

On the 28th day, in iron-treated group the mean serum ferritin did not differ significantly from the baseline of the study. However, on the 56th day, it was significantly higher. It is well-known that iron supplementation may aggravate undiagnosed hemochromatosis or obscure diseases associated with blood loss.[5] Whether low iron stores may favorably impact the incidence of cancer and coronary heart disease remains an open question.[24] Therefore, iron supplementation in blood donors should focus on compensation of iron loss and to prevent overcompensation.[22] The results of the present trial demonstrate that a 28-day treatment with ferrous sulfate could restore iron stores in female regular blood donors without making positive iron balance. In addition to the data discussed above, in 90.6% of the donors in the iron-treated group serum ferritin increased to 12 µg/l. Although an extra 4 weeks of treatment with iron to the end of 8th week increased mean serum ferritin, it did not make any significant change in the subjects with serum ferritin of more than 12 µg/l. This might have occurred because an extra 4 weeks of treatment with ferrous sulfate adversely affected the compliance of the individuals comparing with placebo.

In regular blood donors, the mean absorption of iron was reported 14% by Lieden, et al.[20] Accordingly, during iron supplementation, up to 28th day with 50 mg ferrous sulfate on a daily schedule, the mean absorption of iron in our donors seemed to reach 196 mg. Based on our results, this amount of iron supplementation, plus the amount of iron absorbed from food during the same period, appear to be sufficient for female volunteers donating repeatedly. Moreover, as shown in few studies, the subjects with depleted iron stores absorb iron more than other subjects.[21]

The side effects of ferrous sulfate were similar in both iron and placebo groups. This can be due to bedtime drug recommendation. Nausea was the most common side-effect among all other symptoms, which was seen more in iron-treated group than the other group. This finding is similar to the results that were reported by Gordeuk, et al.[19] However, headache and weakness were more frequent in the placebo group, compared with the iron group but the difference was not statistically significant. Unpleasant taste was seen in iron-treated group significantly more than the placebo group. Such finding had been previously reported by Simon et al.[9] However, because the determination of the sample size was not made based on the incidence of side effects, similarity of the rate of side effects in iron and placebo groups might be due to this event.

The rate of compliance on day 28 was similar in two groups. However, compliance rate was decreased significantly in iron-treated group on day 56, compared with the placebo group. This finding supports short-term iron supplementation program for female blood donors in reproductive age.[22]

Our participants were from a random sample of female regular blood donors, providing our results with more applicability. Our study design provides a situation in which nearly all donors recruited in the study after blood donation had a sustained iron stores.

Although many investigators recommended carbonyl iron supplementation for blood donors because of the lower lethal dose of this form of iron compared with ferrous sulfate,[12] carbonyl iron is not available in Iran. Therefore, we recommend ferrous sulfate as iron supplementation in unit dose package.

In conclusion, we recommend low dose iron supplementation (50 mg elemental iron as ferrous sulfate) to replace iron losses from donation in female regular blood donors of childbearing age. This approach could prevent potential harm to blood donors due to iron loss, and retain these donors for future donations.[25]

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Conflict of Interest: None declared

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