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# Once Weekly Low-dose Iron Supplementation Effectively Improved Iron Status in Adolescent Girls

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**Abstract** Iron supplementation has been suggested as a strategy for prevention and treatment of iron deficiency (ID) and iron deficiency anemia (IDA) in many countries, but non-compliance of daily regimens and common dosage remain as major challenges. The aim of this study was to investigate the effects of low dose once weekly iron supplementation in adolescent girls. The study was designed as a community-based, randomized, supplementation trial. The initial sample consisted of 200 female high school students, aged 14–16 years old, of whom 193 students concluded the study. They were randomly selected and assigned into either iron-supplemented group (ISG) or iron-unsupplemented group (IUG). The ISG received 150 mg ferrous sulfate once weekly for 16 weeks, whereas the IUG received nothing. Weight, height, and hematological parameters were measured and compared between the two groups before and after the intervention. There was no significant difference between the initial measures of the two groups before the intervention. After 16 weeks of intervention, mean of hemoglobin and serum ferritin improved significantly in ISG compared to IUG. At the beginning of the study, percent of anemia, IDA, and ID in ISG were 12.5%, 8.3%, and 30.2%, whereas these figures for IUG in this period of study were 14.4, 10.3, and 38.2, respectively, which were not significantly different between the two groups. However, percentages of the above items at the end of study in ISG were 2.1%, 0%, and 21.9%, respectively. In contrast to IUG, all cases of IDA

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were abolished in the ISG. Our study showed that once weekly supplementation of 150 mg ferrous sulfate for 16 weeks significantly improved iron status in female adolescents and effectively treated IDA. There is no need for higher dosage of iron for supplementation that may cause adverse effects and bear higher costs.

**Keywords** Iron deficiency · Iron deficiency anemia · Anemia · Iron supplementation · Administration and dosage · Adolescent girls

## Introduction

Iron deficiency anemia (IDA) is actually the most common nutritional anemia worldwide and still a public health problem in developing countries. It is generally assumed that more than 50% of the cases of anemia are due to iron deficiency (ID) [1–3]. There are many possible causes of IDA. This condition can mainly arise from inadequate iron intake or absorption. Other causes include increased iron requirement for growth of blood volume (e.g., during infancy, adolescence, pregnancy, or lactation), increased excretion (e.g., in excessive menstrual blood or hemorrhage from injury), or chronic blood loss (e.g., due to bleeding ulcer, bleeding hemorrhoids, parasites, or malignant disease) [4]. Also, defective release of iron from its stores in the body and defective iron use due to a chronic inflammation or other chronic disorders are known as contributing factors to IDA. So, infants, preschool children, adolescents, women of childbearing age, and particularly pregnant women are at a greatest risk of developing this kind of anemia [2, 5].

Many consequences have been reported for ID and especially IDA. They include impaired motor development and coordination, impaired language development and scholastic achievement, psychological and behavioral effects (inattention, fatigue, insecurity, etc.), and decreased physical activity in infants and children. IDA consequences in pregnant women are increased maternal morbidity and mortality, increased fetal morbidity and mortality, and increased risk of low birth weight [4, 6, 7]. Globally, ID ranks number 9 among 26 risk factors which are indicated in the global burden of disease 2000. Also, in 2002, IDA was considered to be among the most important contributing factors to the global burden of disease [8, 9]. IDA is a major public health problem in Iran, especially among pregnant women and adolescent girls. Some studies in various areas of Iran reported the prevalence of ID in 14- to 20-year-old girls as 27–39% and showed that 10–15% of Iranian girls are suffering from IDA [10–12].

Several strategies have been suggested for preventing IDA, including dietary modification, fortification of staple food with iron, infection control, and iron supplementation [13]. However, each recommended strategy must be adapted with the patient variables like culture, socio-economic situation, attitude, behavior, and dietary pattern. In some situations, iron supplementation is the best approach as it can specifically target high-risk group, be safe and flexible, and get implemented quite rapidly [5, 14, 15]. Variations in deployment of iron supplementation in terms of duration, dose, type and form of prescribed product, and frequency of administration have resulted to different findings. Route and frequency of administration with along the dosage of iron play an important role in gaining the patient's compliance and achieving the desired level of clinical effectiveness [16].

Despite numerous studies conducted so far, there is no consensus on the best duration and dosage of iron supplementation. Regarding the important role of these two factors on the overall effectiveness and compliance of this approach, conducting some complementary studies are needed. In some studies, administration of ferrous sulfate as low as 200 mg once

weekly for 2 months has been reported to be more effective than daily plan [17, 18]. With the aim of finding the effectiveness of even lower dosage, this study was designed to investigate the effects of supplementing 30 mg elemental iron as 150 mg ferrous sulfate once weekly for a 16-week period on iron status of 14–16-year-old female high school students in Yazd, Iran. This study can be distinguished from the similar ones by using low-dose iron once weekly for supplementation.

## Materials and Methods

*Study Design and Location* The study was designed as a community-based randomized, supplementation trial. The study protocol was approved by the Research Council and Ethics Committee at Shahid Sadoughi University of Medical Sciences in Yazd. The study was carried out in some girls' high schools of Yazd city in central Iran between October 2007 and November 2008.

*Subjects and Procedures* Eight girls' high schools were randomly selected and assigned to either iron-supplemented group (ISG) or iron-unsupplemented group (IUG). The first graders in each high school were called and invited to participate from the alphabetically sorted registration list to accumulate 25 students in each high school. The total number of students was 100 in each group at the beginning of the study when participants were 14 to 16 years old (ISG mean age ± SD: 15.17±0.76, IUG: 15.21±0.64). The subjects were followed up for 16 weeks. ISG students received weekly one 150-mg coated-tablet of ferrous sulfate on the first working day of each week for 16 weeks, whereas IUG received no supplementation throughout the study. The tablets were products of Shahre Daru pharmaceutical company (Shahre Daru Laboratories Co. Ltd. Tehran, Iran) and were distributed by the school health officer among the participants each week under supervision of the schoolmaster. The students in ISG were told to consume the prescribed tablet with a cup of water at the break between their two classes in the morning.

*Measurements* Weight and height of the girls were taken at the beginning of the trial (baseline) by a health worker using a Detecto mechanical medical scale (Detecto scales INC, Brooklyn, NY, USA) which was regularly calibrated and controlled against standard weights. Girls were allowed to have their high school uniform on. The standing height of girls was measured by the height-measuring rod of the scale. Weight was measured to the nearest 0.25 kg and height to the nearest 1.0 cm. The body mass index (BMI) was calculated as weight in kilograms (kg) divided by the square of height in meters ($m^2$) and was rounded to the nearest tenth.

Students who had hepatic or neural diseases or received or donated blood within the previous 2 weeks were excluded because of potential effects on their iron status indicators. About 5 ml of fasting venous blood was taken from each subject, 2 ml for cell blood count (CBC), and the remainder for serum tests. The sample tubes were sealed with parafilm, kept at 4–5°C, and sent to the Yazd Central Laboratory to be analyzed for CBC, hemoglobin (Hb), hematocrit (Hct), mean corpuscular value (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and serum ferritin. CBC test was run on the same day with a Sysmex KX21N (Sysmex Corporation, Kobe, Japan) blood analyzer, and serum ferritin was assayed by enhanced chemiluminescence immunoassay method. In this study, ID is defined as serum ferritin below 12 μg/L, anemia as Hb value below 12 g/dl, and IDA as coincidence of ID and anemia [11]. The cutoff point

of Hct, MCV, MCH, and MCHC were considered 35%, 80 fl, 27 pg, and 32 g/L, respectively.

At the end of the trial, to assess the compliance and side effects of the intervention, the supplemented students were asked about consuming and any possible adverse reactions.

*Statistical Analysis* Results are given as mean ± SD and frequency distribution tables. The Kolmogorov–Smirnov test was used for checking the normal distribution of quantitative variables. For comparing the mean of the normally distributed indices between the two groups, we used Student's *t* test; and for other indices, Mann–Whitney *U* test was used. Fisher's exact and McNemar tests were used for comparing categorical variables. The *P* value ≤0.05 was considered as significant. All *P* values were two-tailed. Statistical Package for the Social Sciences (SPSS) version 11 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

*Ethical Considerations* An informed consent was obtained from each participant at the beginning of the trial. They could quit the study freely, whenever desired. The research Ethics Committee of Shahid Sadoughi University of Medical Sciences approved the study protocol.

## Results

A total of 200 high school girls were recruited in the two study groups of this trial, of whom 193 concluded the study. Four girls from ISG and three girls from IUG stepped out on grounds of travel, illness, or some personal reasons (Fig. 1).

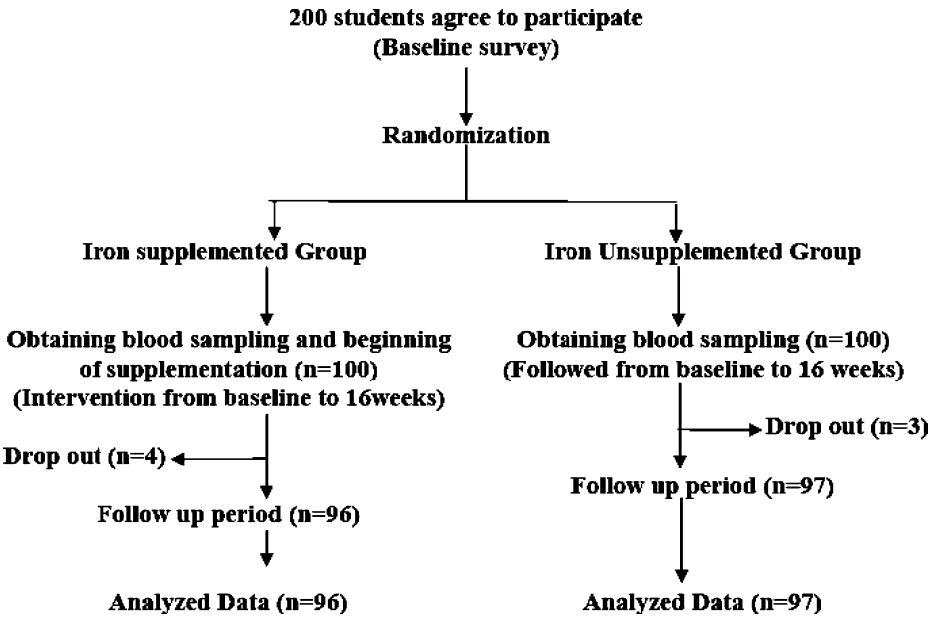


**Fig. 1** Sampling scheme for the study

The mean of quantitative variables of the study including age, weight, height, BMI, and hematological parameters before starting the intervention are shown in Table 1. No significant difference was noticed between the baseline measures of the groups.

The hematological parameters at the end of intervention are shown in Table 2. According to these data, except for white blood cells (WBC), MCV, MCH, and MCHC, the mean of other variables were significantly different between the two groups, as mean of Hb in ISG and IUG were 14.56±1.20 and 13.32±1.25 g/dl, respectively, that showed a significant difference ($P$ value <0.001). Similarly, mean of serum ferritin got significantly different ($P$ value=0.008) in ISG and IUG (35.59±32.87 and 23.73±16.60 μ/L, respectively).

Table 3 shows the percentage of anemia, IDA, ID, and other hematologic indices according to standard cutoff points at the beginning and end of the study among the two groups. At the beginning of study, percent of anemia, IDA, and ID in ISG were 12.5%, 8.3%, and 30.2%, whereas these figures for IUG were 14.4, 10.3, and 38.2, respectively, which were not significantly different between the two groups. However, percentages of these measures in ISG at the end of the study were 2.1%, 0%, and 21.9%, respectively.

Table 4 shows the frequency distribution of hematological indices before and after the intervention in the two groups. According to these data, the frequency of all measures except for serum ferritin significantly changed after the intervention in ISG, whereas in IUG, only MCV and MCH showed significant changes after 16 weeks of intervention. The subjects in ISG reported no remarkable adverse effects.

## Discussion

Our findings showed significant improvement in iron status after 16 weeks of intervention in ISG. Percentage of anemia in this group reduced from 12.5% at baseline to 2.1% at the end of intervention. Also, IDA reduced from 8.3% to nil (0%) during this period, and ID rate decreased from 30.2% to 21.9%.

It has been well demonstrated that preventing ID and its consecutive anemia is not possible without iron supplementation, especially in people at higher risk like pregnant

**Table 1** Mean of Quantitative Variables of the Two Groups at the Beginning of the Study

| Variable | Iron-supplemented group ($n$=96) | Iron-unsupplemented group ($n$=97) | $P$ value[a] |
|---|---|---|---|
| Age (years) | 15.17±0.76 | 15.21±0.64 | 0.70 |
| Weight (Kg) | 53.98±11.41 | 55.02±11.27 | 0.52 |
| Height (cm) | 158.65±7.03 | 159.63±5.71 | 0.28 |
| BMI (kg/m$^2$) | 21.48±4.47 | 21.56±4.08 | 0.89 |
| Ferritin (μ/l) | 23.92±17.70 | 22.18±18.70 | 0.50 |
| WBC (K/μL) | 7.77±2.08 | 7.89±2.13 | 0.69 |
| RBC (M/μL) | 4.87±0.33 | 4.82±0.27 | 0.18 |
| Hb (g/dl) | 12.92±0.95 | 12.84±0.87 | 0.51 |
| Hct (%) | 38.82±3.56 | 39.08±2.40 | 0.56 |
| MCV(fl) | 80.28±4.88 | 81.21±3.64 | 0.13 |
| MCH (pg) | 26.56±2.12 | 26.70±1.60 | 0.59 |
| MCHC (g/dl) | 33.54±5.04 | 32.86±0.95 | 0.19 |

[a] Student's $t$ test

**Table 2** Mean of Hematologic Variables of the Two Groups at the End of the Study

| Variable | Iron-supplemented group ($n$=96) | Iron-unsupplemented group ($n$=97) | $P$ value |
|---|---|---|---|
| Ferritin (μ/L) | 35.59±32.87 | 23.73±16.60 | 0.008[a] |
| WBC (K/UL) | 7.32±1.75 | 7.66±8.49 | 0.70[b] |
| RBC (M/UL) | 5.08±0.38 | 4.81±0.49 | <0.001[b] |
| Hb (g/dl) | 14.56±1.20 | 13.32±1.25 | <0.001[b] |
| Hct (%) | 42.94±2.79 | 39.62±4.03 | <0.001[b] |
| MCV(fl) | 84.72±5.09 | 84.33±4.90 | 0.58[b] |
| MCH (pg) | 28.73±2.22 | 29.00±2.94 | 0.55[a] |
| MCHC (g/dl) | 33.90±1.20 | 34.37±0.37 | 0.06[a] |

[a] Mann–Whitney $U$ test

[b] Student's $t$ test

women. For getting the best compliance by the subjects and maintaining its efficacy, various approaches have been proposed and evaluated. Route and frequency (daily, once weekly, and twice weekly) of administration, product form and dosage, content of elemental iron, and also logistics and distribution network are the most important determinants in overall effectiveness of such supplementation [19].

**Table 3** The Frequency of Anemia, IDA, and ID According to Cutoff Point of Each Hematologic Index at the Beginning and End of the Study

| Period of study (variable) | Iron-supplemented group | Iron-unsupplemented group | $P$ value[b] |
|---|---|---|---|
| The beginning of study | | | |
| Hb <12 (g/dl) | 12 (12.5)[a] | 14 (14.4) | 0.42 |
| Ferritin <12 (μ/dl)[d] | 29 (30.2) | 38 (39.2) | 0.12 |
| Hct <35 (%) | 6 (6.3) | 5 (5.2) | 0.42 |
| MCV <80 (fl) | 41 (42.7) | 27 (27.8) | 0.02 |
| MCH <27 (pg) | 51 (63.1) | 55 (56.7) | 0.30 |
| MCHC <32 (g/dl) | 15 (15.6) | 12 (12.4) | 0.32 |
| Present IDA[e] | 8 (8.3) | 10 (10.3) | 0.41 |
| The end of study | | | |
| Hb <12 (g/dl) | 2 (2.1) | 14 (14.4) | <0.001 |
| Ferritin <12 (μ/dl) | 21 (21.9) | 27 (27.8) | 0.21 |
| Hct <35 (%) | 0 (0) | 11 (11.3) | <0.001 |
| MCV <80 (fl) | 14 (16.6) | 17 (17.5) | 0.36 |
| MCH <27 (pg) | 16 (16.5) | 18 (18.8) | 0.41 |
| MCHC <32 (g/dl) | 6 (6.3) | 7 (7.2) | 0.50 |
| Present IDA | 0 (0) | 7 (7.2) | 0.007 |

[a] Number (percent)

[b] Fisher's exact test

[c] Anemia

[d] Iron deficiency

[e] Iron deficiency anemia

**Table 4** The Frequency Distribution of Each Hematologic Indices Before and after the Intervention in Two Groups

| Groups | Iron-supplemented group | | | Iron-unsupplemented group | | |
|---|---|---|---|---|---|---|
| Variable | The beginning | The end | *P* value[b] | The beginning | The end | *P* value[b] |
| Hb <12 (g/dl)[c] | 12 (12.5)[a] | 2 (2.1) | 0.01 | 14 (14.4) | 6 (6.2) | 0.07 |
| Ferritin <12 (μ/dl)[d] | 29 (30.2) | 21 (21.9) | 0.2 | 38 (39.2) | 27 (27.8) | 0.06 |
| Hct <35 (%) | 6 (6.3) | 0 (0) | 0.03 | 5 (5.2) | 11 (11.3) | 0.14 |
| MCV <80 (fl) | 41 (42.7) | 14 (16.6) | <0.001 | 27 (27.8) | 17 (17.5) | 0.01 |
| MCH <27 (pg) | 51 (53.1) | 18 (18.8) | <0.001 | 55 (56.7) | 16 (16.5) | <0.001 |
| MCHC <32 (g/dl) | 15 (15.6) | 6 (6.3) | 0.04 | 12 (12.4) | 7 (7.2) | 0.2 |
| Present IDA[e] | 8 (8.3) | 0 (0) | 0.008 | 10 (10.3) | 5 (5.2) | 0.2 |

[a] Number (percent)

[b] McNemar test

[c] Anemia

[d] Iron deficiency

[e] Iron deficiency anemia

Many studies have suggested daily administration of iron supplement as an effective method [20–25], but due to lower coverage, insufficient logistics, and low compliance of consumers which are reported by some other studies [5, 26–29], weekly regimens have been reported to be more effective with higher compliance since the mid 1990s [16, 18, 20].

In a similar study to ours, Engstrom et al. recruited three groups of 6–12-year-old children for 24 weeks. The first group received 12.5 mg elemental iron as ferrous sulfate on a daily basis, the second group 25 mg weekly, and the third group got no supplementation to serve as control group. Daily supplementation was reported to be more effective than weekly plan. No significant difference was seen in hemoglobin concentration between the weekly group and the control group. In the current study, despite shorter period of intervention, mean of hemoglobin, ferritin, and rate of anemia were significantly different between the supplemented and unsupplemented groups [30].

In two other studies, administration of 200 mg ferrous sulfate once weekly for 2 months in children of 5–10 years old has been reported to be more effective than daily plan [17, 18]. In contrast, we supplemented iron with lower dosage but longer duration.

In a study by Sungthong et al., effects of daily and weekly supplementation on anemia status and intelligence quotient were compared [31]. They administered 60 mg elemental iron (twofold more than our dosage) weekly, for 16 weeks (similar to our study). They showed that mean of hemoglobin concentration in both daily and weekly groups increased significantly. Ferritin and hemoglobin concentrations in the weekly group were significantly higher than those of the control group. Their findings support our results, although the dosage of supplemented iron in current study is around half of theirs.

Siddiqui et al. compared daily against weekly supplementation of 200 mg ferrous sulfate for 2 months in 5- to 10-year-old children suffering from ID. Both methods improved hematological parameters including hemoglobin, ferritin, and serum iron, though the weekly method was reported as more cost effective [17]. In another trial by Jovan et al., pregnant women were supplemented with 120 mg ferrous sulfate for 14 weeks, either once or twice weekly. They reported no significant difference between the two groups [32].

Another study on administering 60 mg elemental iron once weekly for 12 weeks did not reveal meaningful effects on blood parameters [33].

It is obvious that for comparing results of various studies on iron supplementation, some variables like duration, dosage, study population, route of administration, and product form should be taken into account. By comparing the results of current study with similar ones, response of ID anemic patients to supplementation was outstanding, so that at the end of the study, all the subjects with this problem recovered. This extraordinary result can be justified by close supervision of health workers and schoolmasters on supplementation program in the target schools. The role of supervision on the supplementation efficacy has been highlighted by some studies [28]. In addition, no remarkable side effect due to iron consumption was reported by the subjects. The good organization and supervision of the trial with lack of side effects yielded a compliance rate of 96% that can justify the desirable achieved results.

One of the limitations of this study was lack of diet record and assessment of diet changes during the trial, which may have had effects on the results to some extent. Meanwhile, lack of placebo utilization in unsupplemented group can be regarded as another limitation.

In this study, supplementation of 30 mg elemental iron once per week is shown to be effective. Further studies for determining minimum effective dose are needed. As a conclusion, weekly supplementation of 150 mg ferrous sulfate for 16 weeks in female adolescents effectively prevented ID and IDA, so there is no need for higher dosage that may cause adverse effects and additional costs.

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