



OPEN Comparative analysis of oral iron therapy regimens in premenopausal women with iron deficiency anemia

Lütfullah Çaştur[✉] & Cundullah Torun[✉]

Iron deficiency anemia (IDA) is prevalent among women of reproductive age. Treatment aims to replenish iron stores and normalize hemoglobin levels, with oral iron therapy being the preferred route in most cases. This study aimed to compare the efficacy and side effects of three common oral treatment regimens in premenopausal women with IDA. An observational study was conducted on patients initiated on oral ferrous glycine sulfate therapy (100 mg elemental iron). Patients were divided into three groups based on treatment regimen: alternate-day ($n = 40$), daily single-dose ($n = 41$), and daily twice dose ($n = 40$). Hemoglobin, ferritin, and transferrin saturation levels were measured before and after one month of therapy. The primary outcome was to compare laboratory changes from baseline to post-treatment within and between groups. The secondary outcome was to compare the frequency of gastrointestinal side effects. The mean age was 41.2 ± 8 years, with a mean hemoglobin level of 10.4 ± 1.1 g/dl, and a mean ferritin level of 7 ± 3.2 ng/mL at the time of diagnosis. After one month of therapy, hemoglobin, ferritin, and transferrin saturation levels significantly increased in all groups ($p < 0.001$ for all). However, the increase in hemoglobin and ferritin levels was significantly lower in the alternate-day group compared to the other groups ($p < 0.001$). Gastrointestinal side effects were more prevalent in the daily twice group (66.1%) compared to the alternate-day (16.7%) and daily single-dose (23.4%) groups ($p < 0.001$). Daily single-dose oral ferrous glycine sulfate therapy emerged as an effective and well-tolerated treatment regimen for premenopausal women with IDA.

Keywords Iron deficiency, Anemia, Ferrous glycine sulfate, Hepcidin, Oral replacement

Iron deficiency anemia (IDA) ranks among the leading nutritional deficiencies and affects approximately one-third of women of reproductive age¹. It is well known that IDA has a significant impact on quality of life². The objective of treatment is to restore iron stores and normalize hemoglobin levels. Oral iron therapy is preferred over the intravenous route except in conditions such as pregnancy, heart failure, chronic kidney disease, inflammatory bowel disease, and bariatric surgery^{3,4}.

Of the various iron salts available, ferrous sulfate stands out as the most frequently utilized. The standard prescription for IDA usually entails consuming 2–3 tablets of ferrous sulfate daily, which aligns with the traditionally recommended daily dosage of 100–200 mg of elemental iron⁵.

However, it was demonstrated at the beginning of the millennium that high-dose iron therapy leads to an increase in a peptide called hepcidin, which in turn reduces iron absorption, and unabsorbed iron causes more gastrointestinal system irritation. This revelation indicated that the standard treatment deviated from the ideal treatment^{6,7}. However, the optimal dosage and frequency of ideal treatment remain subjects of ongoing research. This study aimed to compare the effectiveness and side effects of the three most commonly implemented treatment regimens (alternate day, daily, and twice daily dosing) in daily clinical practice for premenopausal women with iron deficiency anemia.

Methods

Patients and study design

This single-center observational study included premenopausal women aged 18–50 diagnosed with iron deficiency anemia, who initiated oral ferrous glycine sulfate therapy at a tertiary care hospital between April and

Department of Internal Medicine, Istanbul Medeniyet University, Fahrettin Kerim Gökay Street, Kadıköy, 34722 Istanbul, Turkey. ✉email: cundullaht@gmail.com

July 2023. The study received approval from the Istanbul Medeniyet University Goztepe Training and Research Hospital Ethics Committee (decision no: 2023/0168, date: 15.03.2023). Patients were screened weekly via the hospital electronic system during the specified period, ensuring prompt contact within a week of initiating iron therapy. They were invited to participate in the study via telephone. Informed consent was obtained from all participants, and the study adhered to the principles of the Helsinki Declaration.

Iron deficiency anemia was defined as hemoglobin levels below 11.5 g/dL and ferritin levels below 15 µg/L⁸. Patients with malignancy, inflammatory bowel disease, chronic kidney failure, chronic liver failure, heart failure, a history of gastric or intestinal surgery, and pregnant women were excluded from the study. Written consent was obtained from eligible patients, who then participated in face-to-face interviews at the internal medicine outpatient clinics. During these interviews, patients' medical histories were detailed, and those with menometrorrhagia were excluded from the study. Ultimately, 148 patients were included in the study. The study flowchart, detailing the inclusion and exclusion criteria, is shown in Fig. 1.

Although there is variability among physicians in our hospital regarding the preferred preparations for oral treatment of IDA, the treatment regimen is commonly chosen in three ways. Patients prescribed a preparation containing 567 mg of ferrous glycine sulfate, equivalent to 100 mg of elemental iron, were included in the study and divided into three groups based on their treatment regimens. The first group comprised patients prescribed alternate-day oral iron therapy, the second group daily single doses, and the third group daily twice doses. The total elemental iron intake for the patients was as follows:

Group 1: 1 × 1 (100 mg) elemental iron per 2 days, total 1500 mg/month.

Group 2: 1 × 1 (100 mg) elemental iron per day, total 3000 mg/month.

Group 3: 2 × 1 (200 mg) elemental iron per day, total 6000 mg/month.

One month after the initiation of oral iron therapy, patients were scheduled for blood sample collection. The primary outcome was to evaluate the difference in hemoglobin, ferritin, and transferrin saturation changes between baseline and post-treatment within each group and among the groups. The secondary outcome was to determine the frequency of gastrointestinal system (GIS) side effects.

Complete blood count, serum iron, total iron binding capacity (TIBC), transferrin saturation, and ferritin values were measured in a fasting state. These tests were conducted in the same laboratory and using the same device. At the end of 1 month, GIS side-effects were examined. Both intragroup and intergroup statistical analyses were conducted on the pre-treatment and post-treatment blood parameters.

Statistical analysis

Continuous data were presented as mean and standard deviation. The Wilcoxon Signed-Rank Test was used to evaluate differences between dependent variables. The Kruskal-Wallis H-Test was utilized for intergroup comparisons, and for variables where significant differences were found among groups, the Bonferroni-corrected Mann-Whitney-U Test was employed to determine which groups were significantly different. A Chi-squared test was conducted to assess the association between the treatment regimens and the occurrence of side effects. The results were considered statistically significant when the p-value was less than 0.05. Patient data collected in the study were analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 29.0 for MacOS (IBM Corp., Armonk, NY).

Results

A total of 121 premenopausal women diagnosed with iron deficiency anemia were included in the study. The mean age was found to be 41.2 ± 8 years, with a mean hemoglobin level of 10.4 ± 1.1 g/dL, a mean ferritin level of 7 ± 3.2 ng/mL, and a mean transferrin saturation of 0.09 ± 0.08 at the time of diagnosis. In patients with baseline C-reactive protein (CRP) measurement ($n = 95$), no signs of inflammation were found, with a median CRP of 0.85 mg/L (min-max: 0.51–1.30 mg/L). After treatment, the mean hemoglobin level was 11.9 ± 0.9 g/dL, the mean ferritin level was 22.2 ± 10 ng/mL, and the mean transferrin saturation was 0.463 ± 1.48 .

In Groups 1, 2, and 3, 2 (4.8%), 6 (12.8%), and 19 (32.2%) patients, respectively, discontinued the recommended treatment due to gastrointestinal side effects. After excluding these patients from the analysis, Groups 1, 2, and 3 comprised 40, 41, and 40 patients, respectively. Age, baseline hemoglobin, and ferritin levels were similar among the groups ($p > 0.05$ for each). Hemoglobin, ferritin, and transferrin saturation levels significantly increased after treatment in all three groups ($p < 0.001$ for each) (Table 1).

Changes in laboratory values before and after treatment are shown in Table 2. The increase in hemoglobin and ferritin levels was significantly higher in Groups 2 and 3 compared to Group 1, while the increase in transferrin saturation was significantly higher in Group 2 compared to both Group 1 and Group 3 ($p < 0.0001$ and $p = 0.001$, respectively).

Overall gastrointestinal side effects were significantly more common in Group 3 (66.1%) compared to Group 1 (16.7%) and Group 2 (23.4%) ($p < 0.001$). There was no significant difference in side effect frequency between Group 1 and Group 2 ($p = 0.430$) (Table 3). Gastrointestinal side effects leading to treatment discontinuation were also more frequent in Group 3 (32.2%) compared to Group 1 (4.8%) and Group 2 (12.8%) ($p = 0.001$).

Discussion

In premenopausal women with iron deficiency anemia, one-month oral iron therapy across three treatment regimens (alternate-day—group 1, daily single—group 2, and daily twice—group 3) resulted in significant increases in hemoglobin levels. The increase in hemoglobin levels in group 2 and group 3 was similar, while in group 1, the increase in hemoglobin levels was lower compared to the other groups. The frequency of side effects leading to treatment non-compliance was similar in group 1 and group 2, while it was higher in group 3.

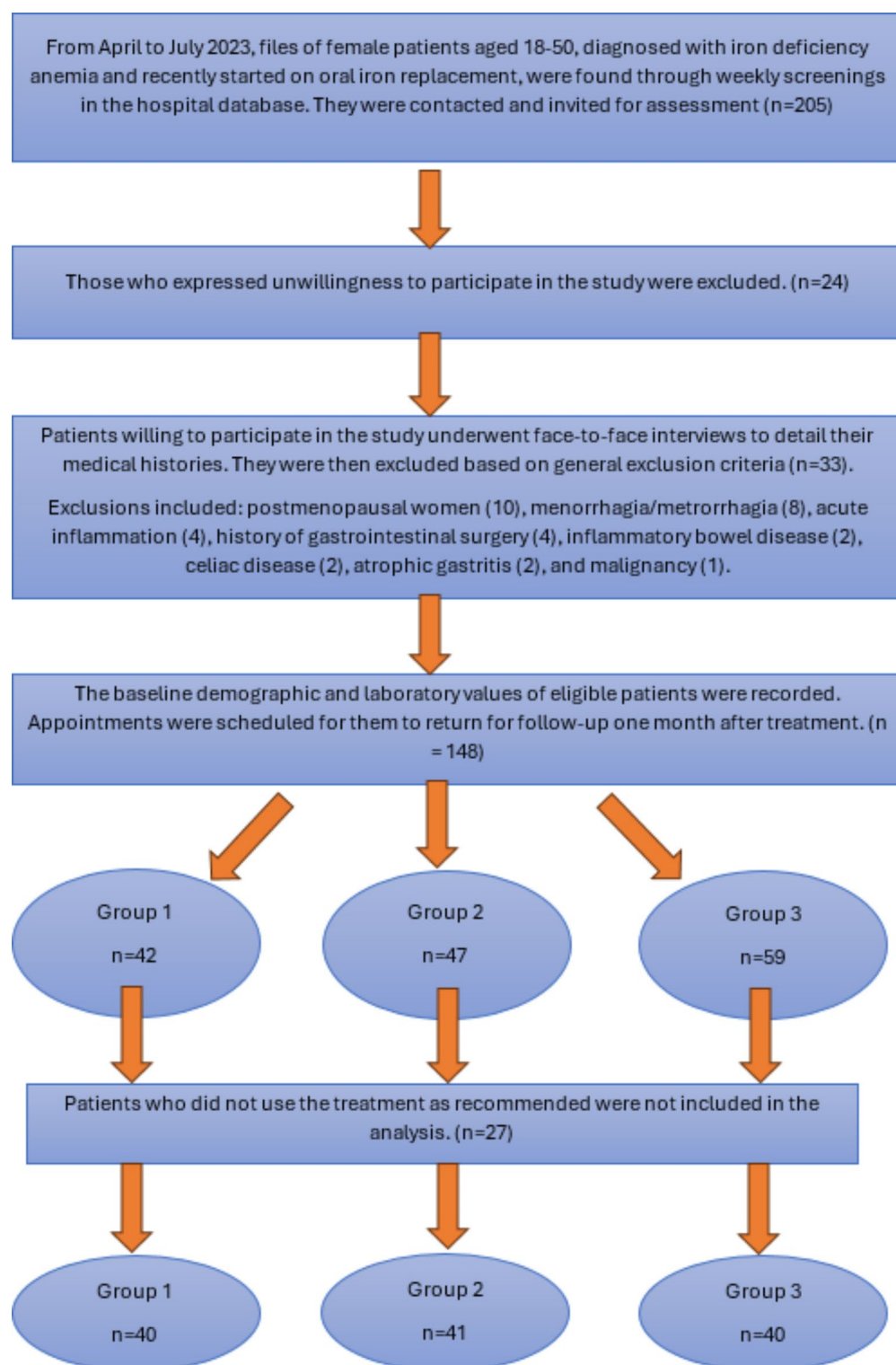


Fig. 1. The study flowchart, detailing the inclusion and exclusion.

Oral iron replacement therapy is a simple and effective approach for treating iron deficiency, except in cases of non-adherence, intolerance, unresponsiveness, or severe anemia⁹. In 2015, a systematic review focused on iron-deficient but non-anemic endurance athletes explored the impact of iron supplementation on serum ferritin, serum iron, transferrin saturation, and hemoglobin concentration. A meta-analysis of 17 relevant studies revealed significant improvements in serum ferritin, serum iron, and transferrin saturation following iron treatments ($p < 0.001$ for each)¹⁰. In our study, the significant increase in hemoglobin and iron parameters across all treatment regimens after one month of therapy also corroborates findings from existing studies.

Variables	Alternate day	Once daily	Twice daily
Baseline Hemoglobin (g/dl)	10.6 ± 1	10.3 ± 1	10.3 ± 1.2
Posttreatment Hemoglobin (g/dl)	11.7 ± 1	12 ± 0.8	11.9 ± 0.8
P value	< 0.001	< 0.001	< 0.001
Baseline transferrin saturation (%)	0.1 ± 0.08	0.08 ± 0.11	0.09 ± 0.04
Posttreatment transferrin saturation (%)	0.33 ± 0.62	0.78 ± 1.4	0.28 ± 0.52
P value	< 0.001	< 0.001	< 0.001
Baseline Ferritin (ng/mL)	7.1 ± 2.6	6.9 ± 3.6	7.2 ± 3.3
Posttreatment Ferritin (ng/mL)	17.6 ± 5.6	25.7 ± 11.6	23.3 ± 10.1
P value	< 0.001	< 0.001	< 0.001

Table 1. Comparison of baseline and 1-month post-treatment laboratory values within each treatment group.

Variables	Alternate day (n = 40)	Once daily (n = 41)	Twice a dily (n = 40)	p value	Difference
Age (year)	41 ± 7.6	39.9 ± 9.3	42.7 ± 6.7	0.431	
Basal laboratory results					
Hemoglobin (g/dl)	10.6 ± 1	10.3 ± 1	10.3 ± 1.2	0.275	
Transferrin saturation (%)	0.1 ± 0.08	0.08 ± 0.1	0.09 ± 0.04	0.005	1–2
Ferritin (ng/mL)	7.1 ± 2.6	6.9 ± 3.6	7.2 ± 3.3	0.740	
Posttreatment laboratory results					
Hemoglobin (g/dl)	11.7 ± 1	12 ± 0.8	11.9 ± 0.8	0.072	
Transferrin saturation (%)	0.33 ± 0.62	0.78 ± 2.40	0.28 ± 0.52	0.008	2–3
Ferritin (ng/mL)	17.6 ± 5.6	25.7 ± 11.6	23.3 ± 10.1	< 0.001	1–2;2–3
Changes in laboratory results					
Hemoglobin (g/dl)	1 ± 0.6	1.7 ± 0.8	1.6 ± 1	< 0.001	1–2;1–3
Transferrin saturation (%)	0.22 ± 0.61	0.69 ± 2.39	0.19 ± 0.52	0.001	1–2;2–3
Ferritin (ng/mL)	10.5 ± 5.2	18.9 ± 9.9	16.1 ± 10.4	< 0.001	1–2;1–3

Table 2. Comparison of baseline and 1-month post-treatment laboratory values between different treatment groups

	Gastrointestinal side effects (n, %)
Group 1 (Total)	7 (16.7)
Nausea	4 (9.5)
Abdominal pain	2 (4.8)
Constipation	1 (2.4)
Group 2 (Total)	11 (23.4)
Nausea	5 (10.6)
Abdominal pain	3 (6.4)
Constipation	1 (2.1)
Diarrhea	2 (4.3)
Group 3 (Total)	39 (66.1)
Nausea	17 (28.8)
Abdominal pain	8 (13.6)
Constipation	6 (10.2)
Diarrhea	8 (13.6)

Table 3. Incidence of gastrointestinal side effects across different iron therapy regimens. Chi-squared = 30.845, $p < 0.001$.

The discovery of the hepcidin/ferroportin axis has paved the way for advancements in oral iron administration schedules. A pilot study conducted by Moretti and colleagues on non-anemic premenopausal women with iron deficiency suggested that administering oral iron on an alternate-day schedule could be as effective as the traditional daily schedule involving divided doses¹¹. In one part of their study Moretti et al. demonstrated that administering twice-daily doses of 60 mg or more led to elevated serum hepcidin levels following the initial

dose, accompanied by a 35–45% reduction in iron absorption from the subsequent dose. Recently, in a study conducted on women with non-anemic iron deficiency, Karczewski et al. found a dose-dependent effect of iron supplementation on plasma hepcidin levels¹². Similarly, another study involving iron-depleted women without anemia revealed that administering iron supplements daily in divided doses raised serum hepcidin levels and decreased iron absorption¹³. In our study, despite patients in group 2 receiving only half the elemental iron supplementation compared to those in group 3, the increase in ferritin and hemoglobin levels was similar. This could be explained by the high hepcidin levels and reduced absorption during the second dose intake on the same day for patients in group 3. This result suggests that daily 200 mg oral iron therapy may cause an increase in hepcidin levels substantial enough to surpass the expected endogenous suppression of hepcidin during anemia. Studies measuring iron absorption and hepcidin levels should validate these results.

In our study, significant increases in ferritin and hemoglobin levels were observed after one month of alternate-day iron therapy, yet this increase was significantly lower compared to other groups. In a 2-month randomized controlled trial conducted by Pasupathy et al., there was no significant difference observed between alternate-day and daily iron administration in terms of improving hemoglobin levels¹⁴. However, at the end of the study, while the total amount of iron intake was the same for both groups, it might be the reason for this different result that in our study, after one month, the group receiving alternate doses had half the elemental iron intake of the daily single dose group and one-fourth of the twice daily dose group. In a study conducted by Uçan et al., four groups were formed for the treatment of iron deficiency anemia: daily single dose (3 gr/month), daily double dose (6 gr/month), alternate-day single dose (1.5 gr/month), and alternate-day double dose (3 gr/month). As a result, daily single dose and alternate-day double dose therapy significantly contributed to the increase in hemoglobin values¹⁵. Similar to our study, it was observed that when the total dose of alternate-day therapy was lower than daily single dose therapy, the increase in hemoglobin was significantly lower. These findings suggest that alternate-day therapy can achieve effective hemoglobin improvement similar to consecutive-day therapy only when an adequate dose of elemental iron is provided. In a review by Stoffel et al. discussing the optimal frequency and dosage of oral iron therapy, it was suggested that if alternate-day therapy is to be implemented and the rate of hemoglobin response is significant, the dose administered should be twice the daily recommended amount¹⁶.

In our study, it is noteworthy and intriguing that despite patients in group 3 receiving twice the elemental iron intake compared to group 2 after one month of treatment, the transferrin saturation values increased significantly more in group 2. These results differ from those of the studies mentioned above and the study by Oflaz et al., which was conducted with a design quite similar to ours, thus prompting further questions¹⁷. Although hepcidin may reduce iron absorption in subsequent doses, cumulatively, higher iron absorption would be expected in group 3. The absence of a significant change in ferritin levels but a difference in transferrin saturation values among groups highlights the need for further studies measuring iron absorption.

Approximately one-fifth of the participants included in the study were unable to complete the study due to adverse effects. Oral iron supplements are known to be associated with a higher incidence of gastrointestinal side effects compared to IV iron or placebo⁷. One potential explanation is that iron not absorbed could lead to inflammation in the gut and alterations in the gut microbiota due to iron exposure¹⁸. Previous research has explored the associations between excessively high doses of iron replacement and gastrointestinal side effects¹⁹. Given the relationship between hepcidin levels and the amount of unabsorbed iron, and considering that hepcidin's effect lasts for approximately 48 h, it is predicted that extending the time between doses could reduce the frequency of side effects²⁰. In our study, the higher frequency of side effects leading to treatment discontinuation in the group receiving twice daily therapy supports this idea. However, even in the group receiving the lowest dose of iron therapy (group 3), 16.7% of patients still reported various side effects. This raises the question of whether even lower doses, which were not included in our study, should be considered for treating iron deficiency. Notably, this question has already been addressed by Simic et al., who conducted a study involving 36 women with non-anemic iron deficiency treated with a low-dose iron regimen (12 mg of elemental iron daily). After two months of treatment, they observed significant increases in both ferritin and hemoglobin levels, with only one patient reporting side effects²¹. This promising result highlights the potential of low-dose iron therapy and underscores the need for larger confirmatory studies.

A strength of the study is the comparison of the three most commonly used treatment regimens in clinical practice. However, the absence of a prospective design and randomization resulted in baseline differences in transferrin saturation levels between the groups, marking the study's most significant limitation. Furthermore, although oral iron therapy is typically recommended for several months, our study only reports on the outcomes after one month of treatment, which represents another limitation.

Conclusion

When considering both efficacy and side effects, daily single-dose therapy with ferrous glycine sulfate (providing 100 mg of elemental iron) appears to be an appropriate treatment regimen for premenopausal women with iron deficiency anemia. However, considering that iron deficiency anemia treatment typically requires several months, further studies are needed to evaluate the effectiveness of lower doses and longer treatment intervals in long-term trials.

Data availability

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

L.C. And C.T. wrote the main manuscript text. L.C. prepared tables and C.T. prepared Fig. 1. All authors reviewed manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to C.T.

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