Original Article

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Alternate day oral iron replacement versus daily intake in women with iron-deficiency anemia in Basrah

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ABSTRACT

Background: Iron-deficiency anemia (IDA) remains a major global health concern, disproportionately affecting women of reproductive age. Conventional daily iron supplementation, though effective, is often associated with poor adherence due to gastrointestinal side effects. Emerging evidence suggests that alternate-day dosing may enhance iron absorption and tolerability, but comparative efficacy data in clinical settings remain limited. **Aim**: This study aimed to compare the hematological and iron store responses of women with IDA in Basrah, Iraq, between alternate-day and daily oral iron supplementation regimens. **Methods**: A total of 97 women with confirmed IDA (hemoglobin [Hb] < 12 g/dL, serum ferritin < 15 ng/mL) were enrolled in a prospective follow-up cohort study. The participants were divided into two groups: Group B (n = 48) received 100 mg of elemental iron daily, while Group A (n = 49) received the same dose every other day. Serum ferritin and hematological parameters (Hb, red blood cell [RBC] count, hematocrit) were assessed at baseline, three weeks, six weeks, and three months. ANOVA and paired t-tests were used for statistical analysis, with a significance level of $P < 0.05$. **Results**: Compared to the daily group, the alternate-day group exhibited a significantly higher mean increase in serum ferritin (28.6 ± 4.2 ng/mL vs. 22.3 ± 3.8 ng/mL, $P = 0.001$) and hemoglobin (2.8 ± 0.5 g/dL vs. 2.1 ± 0.4 g/dL, $P = 0.001$) at three months. The alternate-day group demonstrated earlier and more sustained improvements in iron reserves ($P < 0.01$ at all follow-ups), but both regimens increased RBC counts. **Conclusion**: In women with IDA, alternate-day iron supplementation is more effective in restoring hemoglobin and iron stores than daily dosing, possibly due to improved absorption and reduced hepcidin inhibition. These findings suggest potential benefits for patient adherence and clinical outcomes, supporting the use of alternate-day regimens as a superior therapeutic approach. To validate these results, further randomized controlled trials are necessary.

Keywords: Iron-deficiency anemia, alternate-day dosing, daily iron supplementation, hemoglobin, serum ferritin, hepcidin

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INTRODUCTION

Iron-deficiency anemia (IDA) is the most prevalent nutritional deficiency globally, affecting over 2 billion individuals, with women and children being the most vulnerable groups. According to estimates from the World Health Organization (WHO), 30% of non-pregnant women and 42% of pregnant women suffer

from anemia, predominantly caused by iron deficiency.[1,2]

IDA can arise from chronic blood loss, insufficient dietary intake, or malabsorption disorders like celiac disease and inflammatory bowel disease. In women, the predominant cause is menstrual blood loss, with an average monthly loss of 35 mL of blood, equating to an iron loss of 0.5 to 0.68 mg per day.[3–5]

The clinical manifestations of IDA can vary widely, from being asymptomatic to presenting with symptoms such as weakness, fatigue, irritability, headaches, vertigo, syncope, reduced cognitive function, and diminished productivity. Additional symptoms may include tachycardia, cardiac murmur, shortness of breath, difficulty in concentrating, reduced exercise and work capacity, and peculiar cravings like pagophagia. In severe instances, IDA can lead to reactive thrombocytosis, impairing blood flow and increasing the risk of thrombotic events.[6,7] Laboratory tests, particularly serum ferritin levels, are critical for diagnosis, with levels below 15 ng/mL strongly indicative of IDA.[8,9]

Traditional oral iron supplementation, such as ferrous sulfate, is a standard treatment, but side effects such as nausea, constipation, and gastric irritation often result in poor compliance.[10,11] Alternate day dosing has emerged as another viable alternative, supported by research suggesting enhanced iron absorption due to reduced hepcidin activity and improved tolerability.[12] This study aims to compare the efficacy of alternate-day and daily iron supplementation regimens in improving hematological parameters and iron stores in women suffering from IDA in Basrah.

MATERIALS AND METHODS

Study Design and Setting

This follow-up cohort study was conducted at Al-Sader Teaching Hospital, within the medical department, from September 2022 to September 2023. The study design was specifically chosen to observe changes in iron absorption in women with IDA over an extended time frame.

Study Population

The study included 97 menstruating women aged 12 to 48 years who had regular menstrual cycles. These participants were divided into two groups based on the dosing schedule of iron supplements: alternate days (Group A) and daily (Group B). Group A received iron supplements every other day, while Group B received them daily. This division facilitated a direct comparison of the efficacy of iron absorption between the two groups.

Inclusion Criteria

Participants included in the study were

1. menstruating women (ages 12 to 48) with regular menstrual cycles;
2. women diagnosed with IDA within the last six months;
3. individuals not currently receiving any form of iron supplementation; and
4. participants who were willing to adhere to the study protocol

Exclusion Criteria

The study excluded individuals who

1. were men;
2. had known cases of malabsorption or hemoglobinopathy;
3. had active gastrointestinal (GIT) bleeding;
4. had hemoglobin levels less than seven;
5. had experienced cardiac failure;
6. were pregnant;
7. were diagnosed with cancer;
8. were on nonsteroidal anti-inflammatory drugs (NSAIDs);
9. had a history of gastric surgery; and
10. suffered from chronic diseases known to influence iron metabolism (e.g., chronic kidney disease)

Outcomes Measurement

The outcomes measured included changes in serum ferritin and hemoglobin levels as indicators of iron absorption.

Patient Evaluation

Patients underwent a thorough evaluation, including detailed medical history, physical examination, and laboratory investigations. The medical history focused on menstrual and dietary habits, previous illnesses, and medication use. The physical examination primarily assessed signs of anemia and related conditions, while the laboratory investigations included complete blood count, serum ferritin, hemoglobin levels, white blood cells, and mean corpuscular volume (MCV).

Data Collection

Data were collected at baseline and three-week, six-week, and three-month intervals. This data encompassed demographic information, medical history, physical examination findings, laboratory results, and questionnaire responses. Data collection was standardized to ensure consistency across both groups.

RESULTS

The study comprised 97 menstruating women between the ages of 12 and 48 (mean age: 31 ± 8 years). The participants were divided into two groups: Group A alternate-day supplementation with 49 individuals (51%)—and Group B daily supplementation with 48 participants (49%). Table 1

A comparison of the ages of participants in the iron supplementation study indicated a significant age difference (P-value = 0.003). The daily supplementation group had an average age of 24.86 years (SD = 9.012), while the alternate-day group had an average age of 19.83 years (SD = 7.38). Table 2

The hemoglobin levels of the participants, which were measured at different times , are thoroughly compared in Table 3. At the time of administration, the mean hemoglobin levels of the daily (10.16 ± 1.35) and alternate-day (10.39 ± 1.048) groups are comparable, with a non-significant P-value of 0.365, suggesting that there is no statistical difference at the outset. The gap between the two groups widens substantially as the study advances, despite both groups exhibiting an increase in hemoglobin levels. The increases are not statistically significant after three weeks and six weeks (P-values of 0.219 and 0.047, respectively). However, by three months, the mean hemoglobin level of the alternate-day group (11.89 ± 0.26) significantly exceeds that of the daily group (11.39 ± 0.93), as substantiated by a P-value of 0.001.

The alternate-day group (-1.50 ± 0.86) exhibits a minor advantage over the daily group (-1.22 ± 1.22) in terms of the mean difference in hemoglobin levels from the baseline to three months. Both groups experienced a significant increase in hemoglobin levels, as indicated by the asterisks. Furthermore, the correlation coefficients (0.471 for daily and 0.744 for alternate days) indicate a more robust positive correlation between the supplementation regimen and elevated hemoglobin levels in the alternate-day group.

Table 1: Baseline characteristics of participants.

Characteristic	Group A (n = 49)	Group B (n = 48)	P-Value
Age (years, mean ± SD)	31.2 ± 7.9	30.8 ± 8.1	0.67
BMI (kg/m², mean ± SD)	23.8 ± 3.2	23.6 ± 3.1	0.74
Baseline hemoglobin (g/dL)	10.39 ± 1.05	10.16 ± 1.35	0.365
Baseline ferritin (ng/mL)	12.5 ± 6.7	11.9 ± 7.1	0.52

Table 2: Age distribution of 97 patients among the studied groups.

Variables	Daily	Alternate days	P- value
Number of patients	49	48	
Age (years) (Mean ± SD)	24.86 ± 9.012	19.83 + 7.38	0.003

Table 3: Hemoglobin level distribution of 97 patients among the studied groups.

	Time	Daily	Alternative day	p-value
Hemoglobin levels	At administration	10.16 ± 1.35	10.39 ± 1.048	0.365
	After 3 weeks	10.59 ± 1.42	10.88 ± 0.82	0.219
	After 6 weeks	11.01 ± 1.04	11.35 ± 0.93	0.047
	After 3 months	11.39 ± 0.93	11.89 ± 0.26	0.001
	Mean difference	-1.22 ± 1.22	-1.50 ± 0.86	
	Correlation	0.471	0.744	

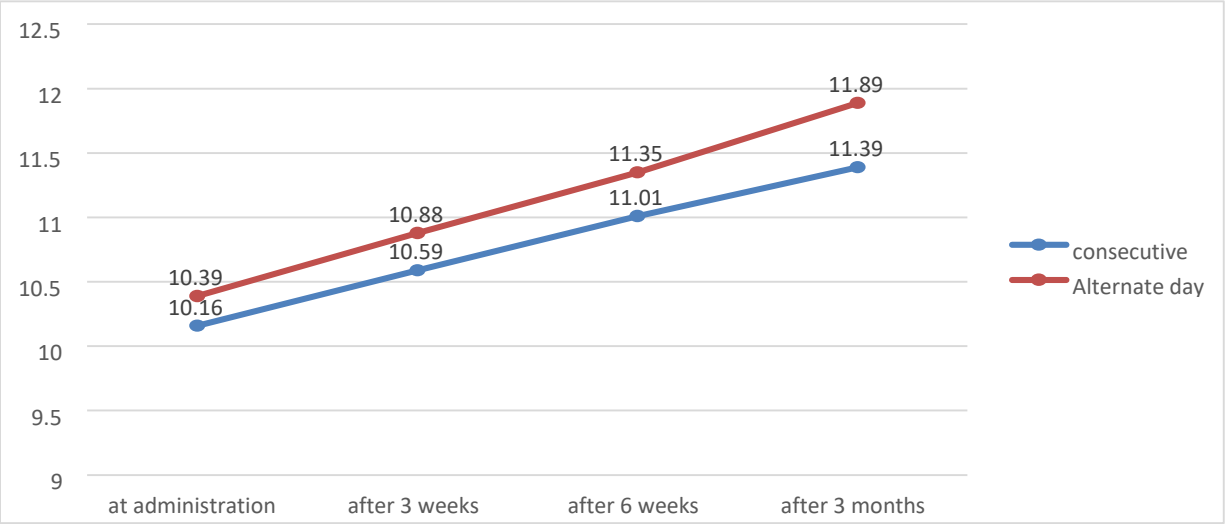

Figure 1: Hemoglobin level curve line during the follow-up period

Table 4 illustrates the variations in red cell count (RCC), white blood cell count (WBC), and platelet count between the two groups. The initial counts of RCC are comparable between the two groups (P-value = 0.334). The alternate-day group exhibits a more substantial increase over time, as evidenced by the fact that the P-values decrease to 0.016 and 0.003 at six weeks and three months, respectively, indicating statistically significant differences at later stages. The correlation coefficients indicate a stronger relationship in the alternate-day group (0.875) than in the daily group (0.567), as evidenced by the more substantial increase in the alternate-day group (-0.29 ± 0.25) compared to the daily group (-0.104 ± 0.44).

Initially, there is no significant difference in the WBC count (P-value = 0.403). However, a significant divergence is observed at three weeks (P-value = 0.040), favoring the alternate-day group. Nevertheless, this significance is not maintained at six weeks and three months, as the P-values increase once more. The mean differences are minor and consistently negative in both groups; however, the alternate-day group exhibits a stronger correlation (0.916) than the daily group (0.403). The platelet count indicates an initial significant difference (P-value = 0.027), with the daily group starting with a higher count. This significance diminishes over time, with no discernible difference by three months (P-value = 0.221). The mean difference in the alternate-day group (27.22 ± 26.43) is significantly lower than that of the daily group, as evidenced by a correlation coefficient of 0.959.

The data on MCV is presented in Table 5. At the beginning of the study, the MCV of the alternate-day group is significantly higher (78.23 ± 10.24) than that of the daily group (72.92 ± 12.03) (P-value = 0.022). However, the alternate-day group consistently maintains higher values, with statistical significance maintained or increased at each time point (P-values: 0.027 at three weeks, 0.017 at six weeks, and 0.008 at three months). Both groups exhibit increases in MCV as time progresses. This pattern indicates that the alternate-day group exhibits a more pronounced or effective response to iron supplementation over time.

The mean difference in MCV from the beginning to the end of the study period suggests a decrease in the daily group (-4.65 ± 10.51) and the alternate-day group (3.99 ± 2.56), both of which are marked as significant with asterisks. This distinction is further emphasized by the correlation coefficients, which demonstrate a very strong correlation (0.968) between the supplementation regimen and variations in MCV in the alternate-day group, as opposed to a moderate correlation (0.492) in the daily group. This data suggest that the alternate-day supplementation schedule may be more effective in modifying MCV, a critical indicator of red blood cell size and an indirect indicator of the body's availability and utilization of iron.

Participants' serum ferritin levels, which are a critical indicator of body iron stores, are compared in Table 6. The levels are marginally higher in the alternate-day group (12.43 ± 9.51) than in the daily group (9.99 ± 6.41) at the time of administration, although the difference is not statistically significant (P-value=0.142). Serum

ferritin levels increased in both groups throughout the study; however, the alternate-day group experienced a more significant rate of increase. This is indicative of the progressively narrowing P-values, which culminate in a highly significant difference at three months (P-value = 0.001), where the alternate-day group achieves a significantly higher level (53.82 ± 7.33) than the daily group (40.53 ± 7.67).

The alternate-day group (-41.38 ± 8.46) significantly outperformed the daily group (-30.53 ± 8.78) in terms of the mean difference in serum ferritin levels from the beginning to the end of the study period, as indicated by the asterisks denoting statistical significance. The two groups are further distinguished by the correlation coefficients between the change in serum ferritin levels and the supplementation regimen. The daily group exhibits a weak correlation (0.232), while the alternate-day group has a moderate, significant correlation (0.521).

Table 4: Red cell count, white blood cells, and platelet count distribution of 97 patients among the studied groups.

Variables		Daily	Alternate-day	P-value
Red cell count	At administration	4.56 ± 0.52	4.66 ± 0.51	0.334
	After 3 weeks	4.61 ± 0.52	4.74 ± 0.49	0.215
	After 6 weeks	4.67 ± 0.40	4.89 ± 0.48	0.016
	After 3 months	4.66 ± 0.44	4.95 ± 0.49	0.003
	Mean difference	-0.104 ± 0.44	-0.29 ± 0.25	
	Correlation	0.567	0.875	
White blood cell count	At administration	7.007 ± 2.01	6.68 ± 1.79	0.403
	After 3 weeks	7.66 ± 2.42	6.77 ± 1.72	0.040
	After 6 weeks	7.58 ± 1.53	7.002 ± 1.63	0.074
	After 3 months	7.49 ± 1.43	7.22 ± 1.67	0.384
	Mean difference	-0.49 ± 1.94	-0.54 ± 0.71	
	Correlation	0.403	0.916	
Platelet count	At administration	327.86 ± 89.0	287.31 ± 88.87	0.027
	After 3 weeks	330.08 ± 88.59	294.44 ± 89.86	0.052
	After 6 weeks	341.00 ± 96.66	305.90 ± 94.47	0.074
	After 3 months	337.18 ± 87.97	314.54 ± 93.09	0.221
	Mean difference	-9.32 ± 74.91	-27.22 ± 26.43	
	Correlation	0.642	0.959	

Table 5: Mean corpuscular volume distribution of 97 patients among the studied groups.

Variable		Daily	Alternate-day	P-value
Mean corpuscular volume	At administration	72.92 ± 12.03	78.23 ± 10.24	0.022
	After 3 weeks	75.49 ± 6.96	79.51 ± 10.30	0.027
	After 6 weeks	76.64 ± 6.73	80.95 ± 10.33	0.017
	After 3 months	77.58 ± 6.90	82.23 ± 9.75	0.008
	Mean difference	-4.65 ± 10.51	-3.99 ± 2.56	
	Correlation	0.492	0.968	

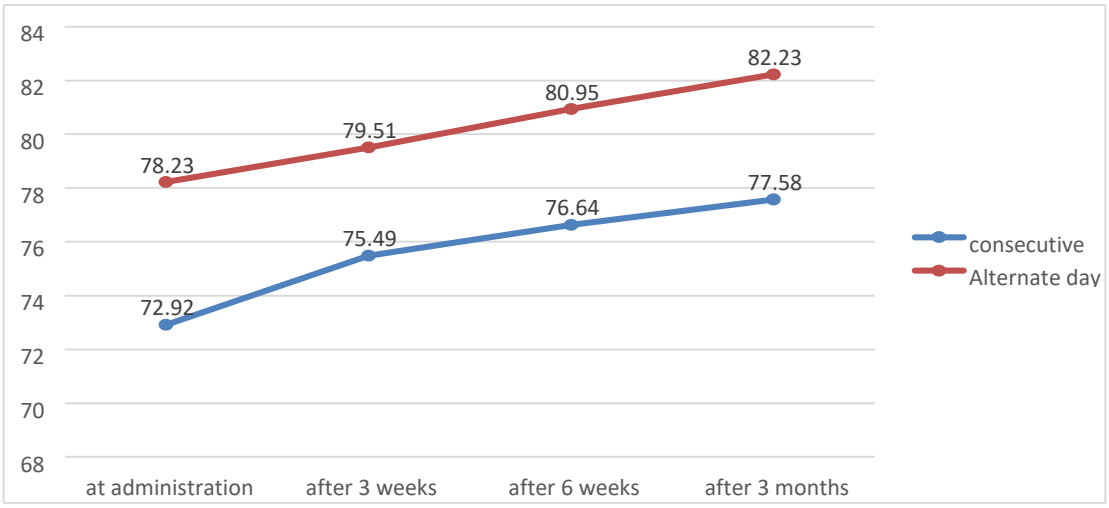

Figure 2: Mean corpuscular volume curve line during the follow-up period.

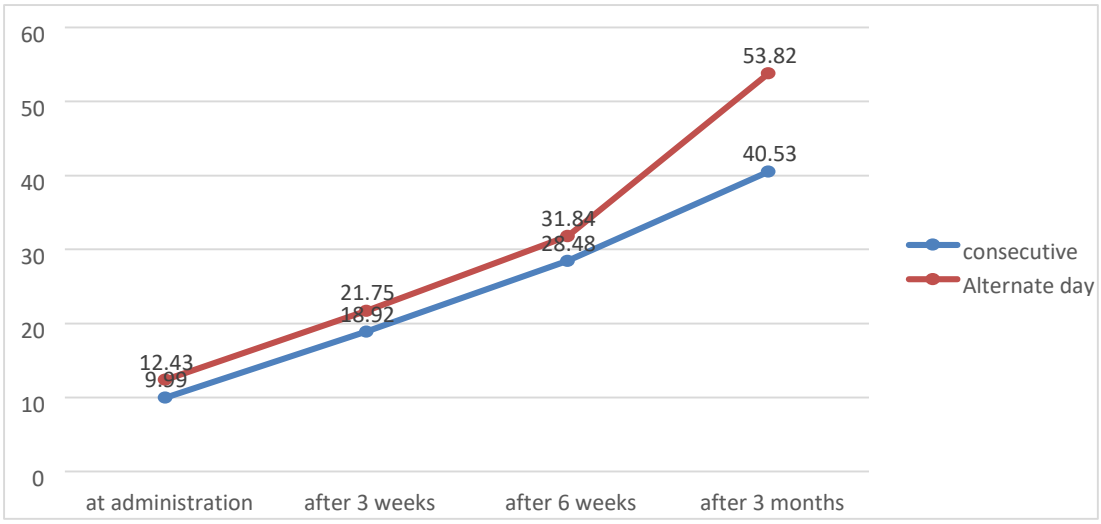

Figure 3: Serum ferritin level curve line during the follow-up period.

Table 6: Serum ferritin level distribution of 97 patients among the studied groups.

Variable	Time	Daily	Alternative day	P-value
Serum ferritin level	At administration	9.99 ± 6.41	12.43 ± 9.51	0.142
	After 3 weeks	18.92 ± 7.41	21.75 ± 10.83	0.136
	After 6 weeks	28.48 ± 7.70	31.84 ± 11.76	0.098
	After 3 months	40.53 ± 7.67	53.82 ± 7.33	0.001
	Mean difference	-30.53 ± 8.78	-41.38 ± 8.46	
	Correlation	0.232	0.521	

DISCUSSION

This study assessed the effectiveness of daily iron supplementation regimens compared to alternate-days regimens on key hematological markers in two separate participant groups. The considerable age disparity between these groups (P-value = 0.003) may influence the metabolic and physiological responses to iron supplementation, indicating that age-related factors could influence the reported results.

The study found that the hemoglobin levels of the groups were relatively similar at the onset; however, after a duration of three months, the alternate-day plan caused a statistically significant increase in hemoglobin levels (P-value = 0.001). The stronger positive relationship between the supplementation plan and higher hemoglobin levels was seen in the alternate-day group (0.744) compared to the daily group (0.471). This suggests that the alternate-day plan may be more effective in promoting erythropoiesis. This is consistent with existing research conducted by McCormick et al. and Abdelgawad et al., which have demonstrated the effectiveness of alternate-day dosing regimens.[13,14] Additionally, a meta-analysis by Stoffel et al. that compared daily iron supplementation with intermittent supplementation highlighted the efficacy of this approach, along with a general reduction in reported side effects.[15]

The study also examined changes in RCC, WBC, and platelet count. The alternate-day group exhibited a more significant increase in RCC, with P-values decreasing to 0.016 and 0.003 at six weeks and three months, respectively. This indicates a robust response to iron supplementation, potentially enhancing oxygen transport capacity and overall physical performance. The fact that the drop in platelet count was strongly linked to iron supplementation (0.959) in the group that took it on alternate days shows that it does have an impact on how platelets behave, even if that impact weakens over time. Given that IDA leads to more severe anemia and lower ferritin levels, indicative of advanced iron deficiency, it can cause reactive thrombocytosis. Iron supplementation effectively reduces elevated platelet counts, underscoring the importance of addressing iron deficiency not only to correct anemia but also to resolve associated hematological abnormalities such as thrombocytosis.[16,17]

Additionally, serum ferritin levels, a critical marker of body iron stores, significantly favored the alternate-day group at three months (P-value = 0.001), reflecting a more pronounced increase in stored iron. The moderate significant correlation (0.521) in the alternate-day group between the supplementation regimen and change in serum ferritin levels further differentiates the effectiveness of the alternate-day supplementation strategy. This finding resonates with the research conducted by Siebenthal et al., who explored iron supplementation patterns in 150 Swiss women, comparing daily dosing with alternate-day regimes. Their study revealed that median serum ferritin levels were higher in the alternate-day group four months post-treatment than in the daily-day group three months post-treatment. Moreover, administering the same total dose of iron on alternate days for six months did not lead to a more substantial increase in serum ferritin compared to daily dosing for three months.[18]

Furthermore, Stoffel et al. determined that while administering a daily dose of 60 mg to women who were iron-depleted but not anemic, the outcomes indicate that for women with IDA, administering higher iron doses ranging from 100 to 200 mg on alternate days leads to improved fractional iron absorption (FIA) when compared to daily dosing.[19] This phenomenon could be explained by multiple theories. The alternate-day regimen, which involves spacing iron doses, could be more effective than daily dosing due to a phenomenon known as the “mucosal block.” This study uggests that when enterocytes, the absorptive cells in the intestine, are exposed to a large dose of iron, they temporarily lose their ability to absorb more iron until they are replaced by new cells. This cellular turnover typically takes about five to six days. Consequently, if iron is administered daily, absorption efficiency could be diminished because the enterocytes are still in their “blocked” state and unable to process additional iron efficiently. In contrast, providing iron doses at weekly intervals aligns better with the natural turnover rate of enterocytes, potentially enhancing iron absorption. Additionally, if the increase in serum hepcidin (S Hep)—a hormone that regulates iron absorption—returns to baseline levels after 48 hours, any remaining inhibition of absorption would align with the mucosal block theory, supporting the idea that less frequent dosing might overcome this regulatory hurdle and improve iron uptake.[20,21]

Moreover, FIA is known to decrease significantly with the increase in iron doses. High doses of unabsorbed iron remaining in the gut can lead to adverse effects, potentially harming the gastrointestinal tract. This issue suggests that lower doses of iron, administered in a manner that avoids daily intake, may be more tolerable for patients. Improved tolerance could lead to better compliance with the supplementation regimen, making it more effective in the long term.[22]

CONCLUSIONS

The alternate-day iron supplementation regimen demonstrates multiple benefits, including enhanced hemoglobin levels, RCC, and iron reserves, as indicated by serum ferritin levels. The results indicate that the timing and frequency of iron supplementation may be essential for optimizing its advantages.

Limitations

The study possesses certain limitations. The sample size is relatively small and targets a certain demographic, eliminating individuals with disorders that impact iron metabolism, thereby restricting generalizability. The study, conducted at a single hematology center with a limited follow-up duration, may not accurately represent long-term effects or be generalizable to wider groups. Furthermore, dependence on self-reported compliance and subjective assessments may generate bias. Future research could mitigate these limitations by incorporating a larger sample size and more diverse participant demographic, extending the follow-up duration, and utilizing objective adherence monitoring.

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