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COMPARISON OF THE EFFECTS OF TREATMENT WITH ORAL IRON EVERY DAY VERSUS EVERY OTHER DAY IN FEMALE PATIENTS WITH IRON DEFICIENCY ANEMIA

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ABSTRACT

Background: Iron deficiency anemia(IDA) is a public health problem that affects all age groups, and it is a common cause of morbidity. Treatment is based on oral iron supplements, and daily therapy is associated with increased hepcidin that affects iron absorption with increased gastrointestinal side effects. **Aim:** The purpose of this study was to determine the effectiveness of daily versus alternate day supplementation of oral iron in women with IDA. **Materials and Methods:** This was a randomized controlled trial involved 160 women with a diagnosis of IDA at Hematology unit, Internal Medicine Department, Tishreen University Hospital, Lattakia, during one-year period 2022-2023. Patients were divided into four groups according to the method of therapy: group 1 received treatment with 600 mg ferrous gluconate as a single daily dose in the morning (40 patients), group 2 received treatment with 600 mg ferrous gluconate every other day in the morning (40 patients), group 3 received treatment with a 600 mg ferrous gluconate as equally divided dose daily (40 patients), and group 4 received treatment with 600 mg ferrous gluconate as divided equally dose every other day (40 patients). **Results:** Ages of the study population range from 18 to 39 years, with a mean age of 26.01±5.6. Moderate anemia represented the most frequent type (56.3%), with a significant statistical improvement in laboratory measurements in all therapeutic groups at the end of follow-up period. At the fourth week of therapy, a significant increasing in the following variables was observed frequently in the group 3 and 1 respectively; hemoglobin (3.59, 2.88 with p:0.01), mean corpuscular volume MCV (12.02,7.9 with p:0.001), hematocrit (10.18, 14 with p:0.3), and red blood cell RBC (0.71,0.38 with p:0.05). At 12 weeks, a significant increasing in ferritin observed frequently in the group 3 and 1 respectively (10.22,6.04 with p:0.001). There was a significant decreasing in red cell distribution width RDW which observed more frequently in group 3(5.98) and group 1(4.63), p:0.1. Return to normal HGB was observed in all patients(100%) in group 3 and in 37 cases(92.5%) in group 1 at 8th week of treatment. Gastrointestinal side effects developed on overage 27.5%, 10%, 12.5% and 7.5% in group 1,2,3, and 4 respectively. **Conclusion:** Oral iron supplements in daily split doses led to faster hematologic response with low frequency of gastrointestinal effects.

KEYWORDS: Alternate day therapy, anemia, iron deficiency, ferrous gluconate, gastrointestinal side effects.

INTRODUCTION

Anemia is defined as a condition in which number of red blood cells or its ability in tissue oxygen delivery is inappropriate with physiological needs of the body.[1,2,3] According to the world health organization(WHO), anemia is a reduction in hemoglobin levels below 12 g/dL in females, 13 g/dL in males and 11 g/dL in pregnant women.[4] Iron deficiency anemia(IDA) represents a serious global public health problem that affects all age groups, and WHO estimates that 42% of the children younger than 5 years and 40% of pregnant women are anemic.[4] Iron deficiency results from various factors: inadequate nutrients or absorption, blood loss such as peptic ulcers, menstrual, or chronic bleeding resulting from colon cancer, polyps or hemorrhoids.[5,6,7,8,9,10] Clinical manifestations typically include: fatigue, pica, headache, exercise intolerance, mood changes and dyspnea. In addition to, there are many physical findings including: pallor, dry skin, atrophic glossitis with loss of tongue papillae, delay in growth and development of children.[11,12,13] Correcting of potential reasons for anemia with using of oral iron compounds which provides an inexpensive and effective method for patients management. There are numerous

formulations available for therapy and evidence suggests that excessive dosing is potentially counterproductive, decreasing absorption of iron with increasing side effects.[14,15,16] Hepcidin is a peptide hormone that plays a significant role in iron metabolism. Oral iron supplements increase hepcidin which is correlated with the dosing of iron and persists for a long period of time (24 hours) leading to reduction of iron absorption. Elevated levels of unabsorbed iron might increase free radical production in intestine to levels that could cause mucosal cell damage.[17,18,19,20] Many studies have found that alternate day therapy is effective as daily doses with less frequent of side effects. The purpose of our study was: 1- to elucidate differences between daily doses and alternate day therapy in management of IDA, 2- to determine side effects of the two methods.

PATIENTS AND METHODS

This is a Randomized controlled trial of a group of women attending Department of Hematology at Tishreen University Hospital in Lattakia-Syria during one-year period 2022-2023). The inclusion criteria were: all women with proven diagnosis of iron deficiency anemia within an age range of 18-40 years who fulfilled the following hematological parameters including hemoglobin(HGB)<12 g/dL and ferritin lower than 30 mcg/L. The exclusion criteria were presence one of the following: pregnancy and lactation, inflammatory bowel diseases and celiac disease, thalassemia or thalassemia trait, allergy to oral iron supplements or receiving nutritional supplements during that last weeks before study, C-reactive protein greater than 5 mg/L, abnormal uterine bleeding, HGB lower than <8 g/dL with presence of active hemorrhage, and planning for surgical procedure or blood donation during the next three months.

Complete medical history together with the physical examination were done. Complete blood count(CBC) and ferritin were performed on admission for all women to assess presence of iron deficiency anemia. Patients were classified into three groups according to National Cancer Institute (NCI) classification: mild(lower than normal and ≥10 g/dL), moderate(8-9.9 g/dL) and severe (6.5-7.9 g/dL). Oral iron as ferrous gluconate(dose: 600 mg ferrous gluconate containing 70 mg elemental iron) was given in various ways of administrations as follows; group 1 one dose per day(40cases), group 2 every other day dosing(40 cases), group 3 divided into two doses daily(40 cases), and group 4 divided into two doses every other day dosing(40 cases). Hematological parameters including: hemoglobin(HGB), mean corpuscular volume(MCV), hematocrit(HCT), red cell distribution width(RDW), red blood cell(RBC), and ferritin were measured at regular times(4, 8, and 12 weeks) and compared with baseline values in all groups.

Ethical consideration: All patients were provided a complete and clear informed consent after discussion about the study. This study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations(SD), Frequency and percentages. One way Anova was used to compare between the groups. Friedman test was used to test for differences between groups when the dependent variable being measured is ordinal. Wilcoxon rank-sum test was used to compare two independent samples. All the tests were considered significant at a 5% type I error rate($p<0.05$), β:20%, and power of the study:80%.

RESULTS

The study included a group of 160 women with proven diagnosis of iron deficiency anemia who fulfilled the criteria of the study. As shown in table (1), age ranged from 18 to 39 years, with the mean age was 26.01±5.6 years. Using of National Cancer Institute (NCI) classification, patients were divided into three groups as follows; mild in 44 cases(27.4%), moderate in 90 cases(56.3%), and severe in 26 cases(16.3%).

Table 1: Demographic characteristics of the study population.

Variables	Results
Age (years)	26.01±5.6(18-39)
Severity of anemia	
Mild	44(27.4%)
Moderate	90(56.3%)
Severe	26(16.3%)

On admission, there were no statistical significant differences between treatment groups regarding values of HGB, MCV, HCT and ferritin ($p>0.05$). As the data in table 2 indicate that effect of oral iron in increasing HGB is duration of treatment dependent, in which the mean values of HGB were on admission:(9.24±1.1), (9.09±1.05), (9.07±1.2), and (9.14±1.02) in group 1,2,3,4 respectively and increased significantly after 4,8,12 weeks in group 1(12.12±1.03, 13.25±0.6, 13.71±0.2,p:0.0001), group 2(9.99±1.03, 10.80±1.01, 11.61±0.9,p:0.0001), group 3(12.66±0.8, 13.69±0.2, 13.73±0.1,p:0.0001) and group 4(10.46±0.9, 11.43±0.8, 12.47±0.7,p:0.0001). At the 4th week, increasing in HGB levels was higher in group 3(3.59 g/dL) and group 1(2.88 g/dL) compared to group 4(1.32 g/dL) and group 2(0.9 g/dL), p:0.01. In addition to, significant increasing in HGB was observed in group 3(4.62 g/dL) and group 1(4.01 g/dL) compared to group 4(2.29 g/dL) and group 2(1.71 g/dL), p:0.01 at the 8th week of treatment.

There was significant increasing in MCV levels after 4,8,12 weeks of treatment in group 1(73.76±4.4,78.54±5.08,86.57±1.9,p:0.0001), group 2 (70.35±3.5,74.45±3.5,77.82±3.4,p:0.0001), group 3(78.02±1.8, 81.25±2.5, 83.30±2.02, p:0.0001) and group 4(71.37±3.9, 75.12±3.7, 78.62±2.9, p:0.0001).

Improvement in MCV levels was observed highly in group 3 and group 1 compared to group 4 and group 2 at 4^{th}, 8^{th}, 12^{th} week(p:0.0001). RBC increased significantly at the end of treatment compared to pre-treatment levels; group 1 (5.15±0.1 versus 4.1±0.3,p:0.0001), group 2(4.59±0.2 versus 3.84±0.2,p:0.0001), group 3(5.10±0.1 versus 3.91±0.2,p:0.0001), and group 4(4.65±0.2 versus 3.93±0.2,p:0.0001). Improvement in RBC levels was observed highly in group 3 and group 1 compared to group 4 and 2 at various points of time, but without significant difference, p>0.05. The level of RDW continued to decrease in all groups, and the mean level of RDW was significantly lower at the post-treatment point(12 weeks) than at the pre-treatment point as follows; group 1(12.10±0.7 versus 19.50±3.3,p:0.0001), group 2(15.62±2.04 versus 22.60±4.1,p:0.0001), group 3(12.15±1.07 versus 21.65±4.4,p:0.0001), and group 4(13.12±1.6 versus 20.30±3.7,p:0.0001). Decreasing in RDW levels was highly observed in group 3 and group 1 than group 4 and group 2 at various points of time without presence of significant difference, p>0.05. Treatment increased HCT levels significantly after 4,8,12 weeks in group 1(40.57±3.6, 41.42±3.3, 44.15±2.3,p:0.0001), group 2(28.45±2.6, 32.10±3.3, 35.35±3.3,p:0.0001), group 3(35.65±2.7, 39.75±2.4, 42.07±1.7,p:0.0001) and group 4(29.45±3.3, 32.55±3.2, 36.10±3.1,p:0.0001. Increasing in HCT levels was highly observed in group 1 and group 3 compared to group 2 and 4,p>0.05. Additionally, ferritin levels were increased significantly by the end of 12 weeks compared to baseline values as follows;(12.87±3.5 versus 6.83±2.2,p:0.0001) in group 1,(11.65±2.7 versus 6.18±2.9,p:0.0001) in group 2,(16.59±2.1 versus 6.37±2.9) in group 3, and(9.02±3.1 versus 5.35±2.2,p:0.0001) in group 4. increasing in ferritin levels was higher in group 3(10.22) and group 1(6.04) compared to group 2(5.47) and group 4(3.67), p:0.001.

Table 2: Comparison of hematological measurements between baseline and 3 months after treatment in all groups.

Variables	Group 1	Group 2	Group 3	Group 4	P value
HGB					
Baseline	9.24±1.1	9.09±1.05	9.07±1.2	9.14±1.02	0.9
4 weeks	12.12±1.03	9.99±1.03	12.66±0.8	10.46±0.9	0.0001
8 weeks	13.25±0.6	10.80±1.01	13.69±0.2	11.43±0.8	0.0001
12 weeks	13.71±0.2	11.61±0.9	13.73±0.1	12.47±0.7	0.0001
p-value	0.0001	0.0001	0.0001	0.0001	
MCV					
Baseline	65.86±4.6	66.45±4.2	66±5.4	65.25±4.1	0.7
4 weeks	73.76±4.4	70.35±3.5	78.02±1.8	71.37±3.9	0.001
8 weeks	78.54±5.08	74.45±3.5	81.25±2.5	75.12±3.7	0.0001
12 weeks	86.57±1.9	77.82±3.4	83.30±2.02	78.62±2.9	0.0001
p-value	0.0001	0.0001	0.0001	0.0001	
RBC					
Baseline	4.1±0.3	3.84±0.2	3.91±0.2	3.93±0.2	0.0001
4 weeks	4.49±0.3	4.07±0.2	4.62±0.2	4.19±0.2	0.0001
8 weeks	4.94±0.2	4.35±0.2	4.95±0.1	4.40±0.2	0.0001
12 weeks	5.15±0.1	4.59±0.2	5.10±0.1	4.65±0.2	0.0001
p-value	0.0001	0.0001	0.0001	0.0001	
HCT					
Baseline	26.75±3.7	25.15±2.8	25.47±3.7	25.27±3.1	0.1
4 weeks	40.57±3.6	28.45±2.6	35.65±2.7	29.45±3.3	0.05
8 weeks	41.42±3.3	32.10±3.3	39.75±2.4	32.55±3.2	0.0001
12 weeks	44.15±2.3	35.35±3.3	42.07±1.7	36.10±3.1	0.0001
p-value	0.0001	0.0001	0.0001	0.0001	
RDW					
Baseline	19.50±3.3	22.60±4.1	21.65±4.4	20.30±3.7	0.003
4 weeks	14.87±2.1	19.65±2.8	15.67±1.6	17.77±2.8	0.0001
8 weeks	13±1.1	17.57±2.2	13.50±1.3	15.32±2.08	0.0001
12 weeks	12.10±0.7	15.62±2.04	12.15±1.07	13.12±1.6	0.0001
p-value	0.0001	0.0001	0.0001	0.0001	
Ferritin					
Baseline	6.83±2.2	6.18±2.9	6.37±2.9	5.35±2.2	0.08
12 weeks	12.87±3.5	11.65±2.7	16.59±2.1	9.02±3.1	0.002
p-value	0.0001	0.0001	0.0001	0.0001	

As shown in table(3), return to normal values of HB was recorded after 8 weeks in 92.5%, 12.5%, 100%, and 25% in group 1,2,3,4 respectively and after 12 weeks in 100%, 35%, and 70% in group 1,2,4 respectively.

Regarding of side effects that observed in group 1, 2, 3,4 were respectively as follow; (heartburn 17.5%, metallic taste 2.5%), (heartburn 2.5%, metallic taste 7.5%), (constipation 2.5%, diarrhea 2.5%, heartburn 7.5%, metallic taste 5%), and (heartburn 2.5%, metallic taste 5%).

Table 3: Comparison of final hemoglobin and side effects between all groups.

Variables	Group 1	Group 2	Group 3	Group 4
Return to normal HB				
4 weeks	22(55%)	1(2.5%)	29(72.5%)	2(5%)
8 weeks	37(92.5%)	5(12.5%)	40(100%)	10(25%)
12 weeks	40(100%)	14(35%)	0(0%)	28(70%)
Side effects				
No symptoms	29(72.5%)	36(90%)	35(87.5%)	37(92.5%)
Emesis	0(0%)	0(0%)	0(0%)	0(0%)
Constipation	2(5%)	0(0%)	1(2.5%)	0(0%)
Diarrhea	0(0%)	0(0%)	1(2.5%)	0(0%)
Heartburn	7(17.5%)	1(2.5%)	3(7.5%)	1(2.5%)
Metallic taste	1(2.5%)	3(7.5%)	2(5%)	

DISCUSSION

This is Randomized Controlled trial in 160 women with proven diagnosis of iron deficiency anemia attending hematologic clinic during one year assessed for efficiency of alternate day supplementation of oral iron in management of anemia versus daily dose as well as side effects in all patients.

This study showed the main findings: First, moderate anemia was detected in approximately 60% of the patients, and there were no significant differences between groups regarding of baseline values of HGB, MCV, HCT and ferritin($p>0.05$). Second, significant increase in levels of RBC, HGB, MCV, HCT and decrease in RDW were achieved in all treatment groups. Third, there was significant increase in ferritin levels, but without replenish iron stores in all groups. Increasing levels of HGB was significantly higher in group 3 compared to group 1 at 4^{th} and 8^{th} week, but without significant difference at the end of treatment. Additionally, increasing MCV levels was significant in group 3 compared to other groups during study period and increasing HCT levels was observed highly in group 3 and 1 at 4^{th} week without significant difference between two groups. Decrease in RDW was observed highly in group 3 and 1 at 4^{th} week without significant difference between two groups. Finally, side effects were less frequent in group 3 compared to 1. Previous findings might be explained by the following: most cases of anemia were of moderate form, erythropoiesis is enhanced and suppress elevated levels of hepcidin after oral iron, in which elevated levels is associated with inhibition of iron absorption. Side effects were lower in split dose, in which low dose is associated with increase in absorption compared to high dose and remains lower amount of unabsorbed iron in intestinal lumen. These findings are comparable with results of previous studies.

Stoffel et al(2017) performed two studies: first study included women with iron deficiency anemia treated with oral iron formulation(21 women on daily dose for 14 days and 19 women on alternate day dosing for 28 days), and second study included (10 women on daily dose and 10 women on split dose of iron). First study revealed that iron absorption was significantly higher in group 2, concentration of hepcidin was lower in this group with low rate of gastrointestinal side effects. Second study revealed an increase in concentration of hepcidin with the dose split through the day($p:0.01$) without presence of significant difference between two groups regarding of iron absorption($p:0.3$). Headache represented the most frequent side effect in two groups without presence of significant differences regarding gastrointestinal effects.[21]

Oflas et al(2019) demonstrated in a study included 150 women with iron deficiency anemia treated with oral iron formulation(group 1 on split dose, group 2 on daily dose and group 3 on alternate day dosing for one month) presence of significant increasing in HGB and ferritin in three groups and increase in ferritin was significant in group 1. Gastrointestinal side effects were occurred more frequently in group 1(68%) compared to group 2(24%) and 3(10%).[22]

Kaundal et al(2019) showed in a study included 62 patients with iron deficiency anemia treated with oral iron formulation(group 1 on split dose, group 2 on alternate day dosing) that increase levels of HGB, MCV and MCH were observed significantly in group 1 than 2 at 3 weeks and 6 weeks. Gastrointestinal side effects were occurred more frequently in group 1(38.7% versus 22.7%).[23]

Mehta et al(2019) demonstrated in a study included 40 patients with iron deficiency anemia (group 1 on alternate day dosing, group 2 on daily dose) that increase level of HGB was occurred significantly in group 1 with less frequent of side effects.[24]

Karakoc et al(2020) showed in a study performed in group of pregnant women treated with oral iron formulation: group 1 on daily dose(111) and group 2 on alternate day dosing(106) that increase in level of HGB

was significant in group 2 with less frequent of side effect in this group(p:0.0001).[25]

In summary, we obtain favorable results in management of IDA when oral iron is given in daily divided doses with lower side effects.

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