Comparison of Efficiency and Side Effects of Daily and Alternate Day Oral Iron

Ibrahim Nahit Sendur and Umit Yavuz Malkan *

Posted Date: 18 July 2023

doi: 10.20944/preprints202307.1234.v1

Keywords: Iron deficiency anemia; oral iron; side effects

Article

Comparison of Efficiency and Side Effects of Daily and Alternate Day Oral Iron

İbrahim Nahit Sendur [1] and Umit Yavuz Malkan [2,*]

[1] Diskapi Yildirim Beyazit Training and Research Hospital, Department of Internal Medicine
[2] Hacettepe University, Faculty of Medicine, Department of Hematology
* Correspondence: umitmalkan@hotmail.com; Tel: +90-5327780087

Abstract: Introduction: In the recent years alternate day dosing has been recommended in iron deficieny treatment. The aim of this study is to compare the efficacy and side effects of oral iron treatments given daily 1x1, alternate day 1x1 and 2x1 alternate day dosing in iron deficieny anemia patients. Methods: A total of 52 patients with a diagnosis of iron deficiency anemia with serum ferritin level of 25 µg/L or less were included in this retrospective study. Statistical analyzes were done with SPSS V.25. Results: The patients included in our study were between the ages of 18-51. All of the patients included in the study were female. A statistically significant increase was found between 0-14 days($p<0.001$), 14-28 days($p<0.001$) and 0-28 days($p<0.001$) hemoglobin values in all patients. There was no statistically significant difference between 0-14 days ($p=0.397$) and 0-28 days($p=0.310$) ferritin values in all patients. A statistically significant difference was found between 14-28 days($p<0.001$) ferritin values. When the rate of change of hemoglobin and ferritin values between the groups was compared and no statistically significant difference was observed between the groups. The rate of change of ferritin values for 14-28 days was significant ($p=0.012$). There was no significant difference in the frequency of symptoms in the 14th day and 28th day controls for each group ($p>0.05$). The incidence of metallic taste and bloating symptoms was found to be statistically significant in the third control in the group with 2x1 drug use alternate day ($p=0.094$). Discussion: The only difference in efficacy was observed in ferritin values between 14th and 28th days. The increase in ferritin values was higher in the group that used 1x1 oral iron every day. However, since no difference was observed between the groups in terms of ferritin and hemoglobin values on days 0 and 28, all three groups were considered equally efficient. Side effects were mainly gastrointestinal side effects. Since the group that received 2x1 oral treatment alternate day had a statistically significantly higher rate of side effects, the patients' treatment tolerance will be lower compared to the other groups. In conlusion, there is no difference in efficacy and side effects between the patient groups receiving 1x1 daily and 1x1 alternate day oral iron therapy, so 1x1 use alternate day is the most appropriate treatment method for oral iron therapy in terms of patient tolerance, adherence to treatment and pharmacoeconomics.

Keywords: iron deficiency anemia; oral iron; side effects

1. INTRODUCTION

Anemia affects 33% of the world population. The most important cause of anemia is iron deficiency (1). All iron deficiencies with or without anemia, whether symptomatic or not, should be treated (2). Oral ferrous sulfate (FeSO4) is recommended for first step treatment. In treatment, 60-120 mg of elemental iron per a day is generally used (3). Iron deficiency and iron deficiency anemia are a global health problem that we encounter frequently in daily practice. Although the prevalence of iron deficiency anemia is decreasing, it is already one of the leading causes of anemia globally (4). Iron absorption is 5-28% in fasting and 2-13% on a full stomach. Therefore, high doses of iron are generally used in oral iron replacement therapy. However, excess iron that cannot be absorbed causes serious side effects by triggering inflammation in the gastrointestinal tract. The most important side effects

 doi:10.20944/preprints202307.1234.v1

of excess iron; constipation, burning and tenderness in the stomach, nausea, vomiting, metallic taste in the mouth. These side effects usually cause treatment non-compliance and discontinuation of the treatment (5).

Stoffel et al., in a study of young women with mild iron deficiency, compared daily oral iron therapy with every other day oral iron therapy in one study, and in the other compared oral iron taken once daily with dosing twice or more per day (6). When the oral iron dose divided into the day was compared with the oral iron taken once a day, no difference was observed in terms of total iron absorption. However, it has been shown that oral iron taken in divided doses during the day causes a greater increase in hepcidin levels (7). Hepcidin plays an important role in the regulation of iron absorption, and oral iron intake causes an increase in hepcidin levels. An increase in hepcidin level decreases iron bioavailability (8). As the oral iron dose increases, hepcidin level increases more and iron absorption continues to decrease further. Oral iron taken in two or more divided doses per day is thought to negatively affect iron absorption by increasing hepcidin levels. The study by Stoffel et al. also showed that total iron absorption was higher in oral iron treatment taken every other day than in daily treatment. However, it was stated that the incidence of gastrointestinal side effects was observed less in the use of iron every other day (6).

In recent studies, it has been predicted that new treatment regimens can replace classical oral iron therapy, with the results that the side effect profile is safer in oral iron treatment with alternate days without a significant difference between ferritin level and hemoglobin level between iron treatment used daily and iron treatment used daily (6). However, since the studies are still new, the number of patients is insufficient and the patient follow-up period is short, there is a need for a more comprehensive study on this subject (9). Since it has the same treatment efficacy, has few side effects and is advantageous in terms of pharmacoeconomics, it seems appropriate to increase the number of studies on iron treatment every other day and to use it in daily practice. The recommended daily treatment dose of iron in adults, ranges between 150-200 mg of elemental iron. For a long time, this amount of iron was met by giving one or more iron pills daily in patients who preferred oral iron therapy. However, recent studies suggest that alternate-day oral iron therapy is more successful than daily oral iron therapy. The goal of the study is to determine the most appropriate oral iron treatment dose for the Turkish population, considering the efficacy and side effects. We retrospectively analyzed the files of patients diagnosed with iron deficiency anemia who were given oral iron therapy at various doses. The aim of this study is to compare the efficacy and side effects of oral iron treatments given daily 1x1, alternate day 1x1 and 2x1 alternate day dosing in iron deficieny anemia patients.

2. MATERIALS AND METHODS

In this study daily and every other day iron therapy was compared. Patients were divided into three groups which are; oral iron treatments given daily 1x1, alternate day 1x1 and 2x1 alternate day dosing. The primary outcome of the study was to determine the efficacy of oral iron treatment dosing and efficacy. This efficacy was determined by monitoring hemoglobin, transferrin saturation and ferritin levels. The secondary outcome of the study was the side effects of oral iron treatment dosing. These side effects are metallic taste, nausea, bloating, constipation, diarrhea and/or vomiting, and other side effects. This research was designed as a retrospective study.The ethics committee approval date of our research is 06.07.2020 and decision no: 91/02. Age, gender, weight, additional disease histories, disease diagnosis dates, laboratory result values at the time of diagnosis, laboratory result values on the 14th and 28th days, and side effect profiles of the patients included in the study were noted.

Inclusion criteria for the study include being between the ages of 18-65, serum ferritin level 25 µg/L or less, hemoglobin level above 7 g/dl, CRP level below 5 mg/L, Body mass index being 18.5-26.5 kg/m2, not using chronic drugs (except for contraceptives), not having major chronic diseases, not being pregnant or breastfeeding, not donating blood for the past 4 months, not smoking, not using vitamin and mineral supplements. Exclusion criteria from the study included gastric surgery

 doi:10.20944/preprints202307.1234.v1

history, malabsorbion syndrome (celiac disease, Whipple disease, bacterial overgrowth, atrophic gastritis), active bleeding, or gastrointestinal bleeding.

Patients between the ages of 18-65 and diagnosed with iron deficiency anemia with a serum ferritin level of 25 µg/L or less, who applied to the University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital Internal Medicine Outpatient Clinic, were included in this study and their information was recorded. The cases given oral iron therapy at different doses were analyzed retrospectively. Three different groups of patients who were given different doses of oral iron therapy were determined. These groups are; 1x1 (100 mg elemental iron-ferrous fumarate) oral iron treatment daily, 1x1 (100 mg elemental iron-ferrous fumarate) oral iron treatment every other day, and 2x1 (200 mg elemental iron-ferrous fumarate) oral iron treatment every other day were determined. Blood parameters at the time of diagnosis, day 14 and day 28 were compared retrospectively. Patients were questioned in terms of side effect profile at each control examination and side effects were recorded.

Statistical Analysis

All statistical analyses were performed with IBM©,SPSS© Statistics Version for Windows (Armonk, NY: IBM Corporation, 2017). Categorical data of the patients were analysed by Fisher's Exact test or Chi-square test. Distribution analyses of the continuous data of the patients were performed with the Kolmogorov-Smirnov test. Parametric dependent continuous variables were analysed by paired T-test, non-parametric dependent continuous variables were analysed by Wilcoxon test. Parametric independent continuous variables were analysed by T-test or ANOVA test, and non-parametric independent continuous variables were analysed by Mann-Whitney U or Kruskal-Wallis method. $P<0.05$ was accepted as the limit of statistical significance.

3. RESULTS

A total of 52 patients were included in the study. Nineteen patients in the group with 1x1 drug use every day, 18 patients in the group with 1x1 drug use every other day and 15 patients in the group with 2x1 drug use every other day were included in the study. All 52 (100%) of the patients included in the study were women. The mean age of the patients included in the study was 40 years. When all patients were divided into groups, the mean age was 19 years in the group using 1x1 drug every day, 42.5 years in the group using 1x1 drug every other day and 35 years in the group using 2x1 drug every other day. Blood parameters of all patients were evaluated on days 0, 14 and 28 without separating them into groups.

A statistically significant increase was found between hemoglobin values on days 0-14 ($p<0.001$), 14-28 ($p<0.001$) and 0-28 ($p<0.001$) in all patients. In all patients, a statistically significant increase was found between 0-14 day ($p=0.04$) and 0-28 day ($p<0.001$) in serum iron values. There was no statistically significant difference in serum iron levels between 14th and 28th day ($p=0.936$). A statistically significant decrease in unsaturated iron binding capacity was found between days 0-14 ($p<0.001$) and 0-28 ($p<0.001$) in all patients. No statistically significant difference was found between the unsaturated iron binding capacity values on day 14-28 ($p=0.612$). There was no statistically significant difference between ferritin values on day 0-14 ($p=0.397$) and day 0-28 ($p=0.310$) in all patients. A statistically significant increase was found between 14-28 days ($p<0.001$) ferritin values (Table 1). Age, complete blood count, renal function tests, liver function tests, acute phase reactants and haemolysis parameters of all groups were evaluated on day 0, day 14 and day 28 (Table 2). Then, for specific parameters (hemoglobin, iron, unsaturated iron binding capacity, ferritin), both within-group changes and between-group changes were evaluated.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 July 2023 doi:10.20944/preprints202307.1234.v1

Table 1. Blood parameters of all patients at first, second and third control visits.

PARAMETERS	1. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)	2. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)	3. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)
Age	40 (18-51)	40 (18-51)	40 (18-51)
White Blood Cell (x10^3/µl)	6,2 (3,9-10.4)	6 (4,3-10,5)	6.15 (3,60-9,70)
Red Blood Cell (x10^6/µl)	4,4 (4.2-5.3)	4.6 (4-5,6)	4,4 (4-5,4)
Haemoglobin (g/dl)	11,3 (7-13)	11,7 (7-13,6)	12,2 (8,2-15)
Haematocrit (%)	36 (28-95)	36 (33-41)	36 (31-41)
MCV (fl)	79,1 (60-88)	78 (65-89)	80.4 (62-88)
MCH (pg)	24,5 (17-28)	24 (18-29)	25 (19-30)
MCVbk (g/dl)	30,5 (28-33)	31 (17-33)	31,5 (28-37)
RDW (%)	15 (12,1-20)	17,05 (13-23)	17,35 (13-26)
Platelet (x10^3/µl)	262,5 (198-470)	265,5 (186-336)	262 (218-344)
Vitamin B12(pg/ml)	299 (212-562)	N/A	N/A
Folate (ng/ml)	5,74 (2.30-12)	N/A	N/A
Haptoglobulin (mg/dl)	1,36 (0,60-3,47)	N/A	N/A
AST (U/L)	16 (9-24)	16 (10-35)	15,5 (10-68)
ALT (U/L)	11,5 (6-25)	13 (8-48)	13,4 (7-89)
Indirect billirubin (mg/dl)	0,24 (0,14-2)	0,225 (0,11-0,86)	0.21 (0,08-0,25)
Glucose (mg/dl)	88 (79-103)	85,5 (79-105)	95 (75-100)
Urea (mg/dl)	22 (12-28)	24.5 (10-30)	22 (10-29)
Creatinine (mg/dl)	0,6 (0,4-0,7)	0,5 (0,4-0,7)	0,6 (0,4-1,15)
Sodium (mEq/L)	139 (134-141)	139 (136-142)	140 (133-145)
Potassium (mEq/L)	4,25 (3,8-4,6)	4,3 (3,8-4,7)	4,5 (3,5-5)
CRP (mg/L)	1,05 (0,1-3,5)	0,75 (0,2-6)	1,15 (0,1-7)
LDH (U/L)	181,5	178	175

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 July 2023 doi:10.20944/preprints202307.1234.v1

	(111-223)	(147-259)	(116-213)
Reticulocyte (%)	1,5 (0,66-1,6)	1,9 (1-2,59)	1,65 (1-3,4)
Iron (µg/dl)	37 (13-751)	61 (19-4034)	57 (12-3280)
Serum iron binding capacity (µg/dl)	363 (101-519)	330,5 (6-500)	331 (41-506)
Ferritin (µg/dl)	6 (1,39-53)	25,25 (3,67-131)	23,35 (5.25-110)

Table 2. First, second and third control parameters of all patients divided into groups.

PARAMETERS	1. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)	2. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)	3. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)
Age			
Medication use 1x1 every day	19 (20-51)	19 (20-51)	19 (20-51)
Medication use 1x1 every other day	42,5 (18-49)	42,5 (18-49)	42,5 (18-49)
Medication use 2x1 every other day	35 (19-50)	35 (19-50)	35 (19-50)
White Blood Cell ($x10^3/\mu l$)			
Medication use 1x1 every day	8,4 (5,1-11,7)	7,6(4,1-11,8)	7,17 (4,4-11,8)
Medication use 1x1 every other day	6,25 (3,5-10,2)	5,45(4,3-10,8)	5,25 (3,6-10,6)
Medication use 2x1 every other day	6,3 (4,6-10,4)	6,5 (5,1-10,5)	6,3 (5-9,7)
Red Blood Cell ($x10^6/\mu l$)			
Medication use 1x1 every day	4,5 (4-5,89)	4,7 (3,8-5,7)	4,6 (4,2-5,32)
Medication use 1x1 every other day	4,45 (3,5-5,2)	4,6 (3,8-5,2)	4,8 (4-5,4)
Medication use 2x1 every other day	4,4 (4,3-6)	4,5 (4-5,6)	4,6 (4-5,4)
Hemoglobin (g/dl)			
Medication use 1x1 every day	11,6 (7,6-13)	11,7 (7,9-13,3)	12,8(8,4-15)
Medication use 1x1 every other day	11,25 (7-12,9)	11,8 (7-13,1)	12 (8,2-13,4)
Medication use 2x1 every other day	11 (7,4-12,6)	11,7 (8,4-13,60)	12,1 (9,3-14,3)
Hematocrit (%)			
Medication use 1x1 every day	37 (28-40)	39(30-42,1)	40 (32-46)
Medication use 1x1 every other day	36 (25-95)	37 (26-41)	36,5(30-43)
Medication use 2x1 every other day	36 (28-39)	35 (33-41)	35 (31-41)
MCV (fl)			
Medication use 1x1 every day	78 (59-89)	81,9 (19,3-89,1)	83,8 (62-93)
Medication use 1x1 every other day	78 (58-85)	78 (58-89)	79,5(39-87)
Medication use 2x1 every other day	72 (60-88)	74 (65-87)	75 (62-88)
MCH (pg)			
Medication use 1x1 every day	24 (16-28)	25 (15-29)	26(16-34,2)
Medication use 1x1 every other day	25,4 (21,9-28)	24,4 (15,4-29)	25 (24,5-29)
Medication use 2x1 every other day	24 (17-28)	23 (18-29)	23.6 (19-30)
MCHC (g/dl)			
Medication use 1x1 every day	31 (27-36)	31,1 (25-33)	31,9(26-33,6)
Medication use 1x1 every other day	24 (15,1-28)	31 (26,1-33)	32 (30-33)
Medication use 2x1 every other day	30 (28-33)	31 (17-33)	31,3 (28-37)

 doi:10.20944/preprints202307.1234.v1

RDW (%)			
Medication use 1x1 every day	15(12,8-20,7)	18 (10,5-26,5)	16,9 (12-24)
Medication use 1x1 every other day	15,5 (12,1-27,9)	16,5 (13,1-29)	16 (13,1-21)
Medication use 2x1 every other day	16 (13-20)	20 (13-23)	20 (13-26)
Platelet (x10³/µl)			
Medication use 1x1 every day	327 (199-486)	297 (191-451)	311 (184-620)
Medication use 1x1 every other day	267 (198-413)	261,5 (178-477)	252 (248-265)
Medication use 2x1 every other day	220 (207-470)	230 (186-336)	270 (218-334)
Vitamin B12 (pg/ml)			
Medication use 1x1 every day	305 (209-443)	N/A	N/A
Medication use 1x1 every other day	264 (195-512)	N/A	N/A
Medication use 2x1 every other day	317 (212-443)	N/A	N/A
Folate (ng/ml)			
Medication use 1x1 every day	6,18 (3,67-14,20)	N/A	N/A
Medication use 1x1 every other day	7 (2,39-20)	N/A	N/A
Medication use 2x1 every other day	5 (2,3-8,01)	N/A	N/A
Haptoglobulin (mg/dl)			
Medication use 1x1 every day	1,65 (0,76-3,47)	N/A	N/A
Medication use 1x1 every other day	1,27 (0,6-1,78)	N/A	N/A
Medication use 2x1 every other day	0,96 (0,6-2)	N/A	N/A
AST (U/L)			
Medication use 1x1 every day	16 (10-24)	165(9-21)	15 (5-20)
Medication use 1x1 every other day	13 (10-21)	14 (9-35)	17 (11-68)
Medication use 2x1 every other day	15 (9-20)	14 (10-21)	14 (10-25)
ALT (U/L)			
Medication use 1x1 every day	11,5 (6,9-25)	13 (6-24)	13 (5-27)
Medication use 1x1 every other day	10 (6-23)	11 (7,3-48)	13 (10-89)
Medication use 2x1 every other day	13 (9-17)	13 (10-19)	16 (7-29)
Indirect bilirubin (mg/dl)			
Medication use 1x1 every day	0,28 (0,06-0,83)	0,2 (0,04-0,76)	0,16 (0,05-0,6)
Medication use 1x1 every other day	0,20 (0,5-1,04)	0,18 (0,08-0,84)	0,17 (0,14-0,5)
Medication use 2x1 every other day	0,35 (0,14-2,0)	0,15 (0,11-0,86)	0,18 (0,03-0,28)
Glucose (mg/dl)			
Medication use 1x1 every day	88 (81-100)	88 (79-115)	86 (67-97)
Medication use 1x1 every other day	90,5(75-113)	89 (79-111)	92,5 (79-115)
Medication use 2x1 every other day	87 (79-95)	84 (84-103)	88 (77-100)
Urea (mg/dl)			
Medication use 1x1 every day	24 (9-30)	20(11-34)	21 (10-35)
Medication use 1x1 every other day	21,5 (12-31)	23 (14-38)	25 (22-29)
Medication use 2x1 every other day	22 (20-27)	25 (10-30)	21 (15-24)
Creatinine (mg/dl)			
Medication use 1x1 every day	0,6 (0,4-0,95)	0,6 (0,4-0,94)	0,66 (0,4-0,88)
Medication use 1x1 every other day	0,6 (0,5-1,05)	0,5 (0,4-0,7)	0,6 (0,4-0,7)
Medication use 2x1 every other day	0,6 (0,5-0,7)	0,5 (0,5-0,7)	0,5 (0,4-0,6)
Sodium (mEq/L)			
Medication use 1x1 every day	139(135-140)	139 (134-142)	139 (133-145)
Medication use 1x1 every other day	139 (134-142)	139 (136-142)	138 (136-142)
Medication use 2x1 every other day	138 (136-141)	140 (139-142)	140 (136-142)
Potasium (mEq/L)			
Medication use 1x1 every day	4,4(3,68-4,87)	4,5 (3,64-5)	4,5 (3,7-5,2)
Medication use 1x1 every other day	4,3 (3-4,8)	4,25 (3,8-4,8)	4,1 (4-4,7)
Medication use 2x1 every other day	4,3 (3,9-4,6)	4,3 (4,1-4,7)	4,5 (3,5-4,6)

 doi:10.20944/preprints202307.1234.v1

CRP (mg/L)			
Medication use 1x1 every day	1,3(0,4-6,7)	0,3 (1,79-5,9)	1,11 (0,5-5,9)
Medication use 1x1 every other day	1,5(0,3-4,1)	1,5 (0,2-4,3)	1,4 (0,4-1,9)
Medication use 2x1 every other day	1,6 (0,10-3,5)	2,5 (0,2-6)	1,7 (0,1-7)
LDH (U/L)			
Medication use 1x1 every day	164 (114-223)	170 (130-242)	173 (143-224)
Medication use 1x1 every other day	175 (111-273)	166 (121-259)	170 (116-193)
Medication use 2x1 every other day	185 (115-210)	180 (155-232)	175 (130-205)
Reticulocyte (%)			
Medication use 1x1 every day	1,44 (0,61-2,16)	1,82 (0,93-3,75)	1,61 (0,86-3,3)
Medication use 1x1 every other day	1,29 (0,6-4,1)	1,55(0,6-2,4)	1,6 (1,1-3,4)
Medication use 2x1 every other day	1,5 (0,7-1,6)	1,8 (1,2-2,4)	1,9 (1-2,1)
Iron (µg/dl)			
Medication use 1x1 every day	52,1(13-751)	131(30,3-4034)	130 (18-3280)
Medication use 1x1 every other day	38 (13-314)	54,5 (21-878)	62 (12-898)
Medication use 2x1 every other day	31,6 (14-328)	39 (19-131)	41,6 (16-471)
Serum iron binding capacity (µg/dl)			
Medication use 1x1 every day	357 (212-465)	298 (6-401.8)	308 (50-506)
Medication use 1x1 every other day	385 (280-494)	338 (21-455)	350 (44-489)
Medication use 2x1 every other day	366 (101-519)	351 (140-500)	320 (41-407)
Ferritin (ng/dl)			
Medication use 1x1 every day	6,8 (1,38-31)	25,5 (3,67-45)	25,3 (6,15-61)
Medication use 1x1 every other day	5 (1,7-53)	24 (6,7-54)	20,5 (5,25-50)
Medication use 2x1 every other day	6(1,4-46)	26 (7-131)	32 (13-110)

Blood parameters of all patients were analysed in groups. A significant increase was found between hemoglobin values on days 0-14 ($p<0.001$), 14-28 ($p<0.001$) and days 0-28 ($p<0.001$) in patients in group 1. An important increase was found between hemoglobin values on day 0-14 ($p<0.001$), day 14-28 ($p<0.001$) and day 0-28 ($p<0.001$) in patients in group 2. A substantial increase was found between hemoglobin values on days 0-14 ($p<0.001$), 14-28 ($p<0.001$) and 0-28 ($p=0.001$) in patients in group 3. When the serum iron values of all patients divided into groups were analysed, it was found that the serum iron value was 52.15 (13-751) µg/dl on day 0, 131 (30.3-4034) µg/dl on day 14 and 130 (18-3280) µg/dl on day 28 in the group using 1x1 drug every day (Group 1). In group 1 patients, an increase was found between 0-14th day ($p=0,094$) and 0-28th day ($p=0,02$) serum iron values. No significant difference was found between the 14-28th day ($p=0,601$) values. In group 2 patients, an important increase was found between serum iron values on days 0-14 ($p=0.003$) and 0-28 ($p=0.004$). No significant difference was found between the 14-28th day ($p=0,586$) values. No significant difference was found between the serum iron values on days 0-14 ($p=0.776$), 14-28 ($p=0.955$) and 0-28 ($p=0.363$) (Table 3).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 July 2023 doi:10.20944/preprints202307.1234.v1

Table 3. Significance values of the differences of the parameters at 0., 14., 28. days in the intragroup temporal plane, without considering the difference in the rate of change of the parameters between the groups.

PARAMETERS	1. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)	2. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)	3. CONTROL MEDIAN VALUES (MINIMUM AND MAXIMUM)	CHANGE BETWEEN 1st and 2nd CONTROL P-VALUE	CHANGE BETWEEN 2nd and 3rd CONTROL P-VALUE	CHANGE BETWEEN 1st and 3rd CONTROL P-VALUE
Serum Iron (µg/dl)						
Medication use 1x1 every day	52,1 (13-751)	131 (30,3-4034)	130 (18-3280)	0,094	0,601	0,002
Medication use 1x1 every other day	38 (13-314)	54,5 (21-878)	62 (12-898)	0,003	0,586	0,004
Medication use 2x1 every other day	31,6 (14-328)	39 (19-131)	41,6 (16-471)	0,776	0,955	0,363
Iron binding capacity (µg/dl)						
Medication use 1x1 every day	357 (212-465)	298 (6-401,8)	308 (50-506)	0,001	0,647	0,015
Medication use 1x1 every other day	385 (280-494)	338 (21-455)	350 (44-489)	0,001	0,981	0,001
Medication use 2x1 every other day	366 (101-519)	351 (140-500)	320 (41-407)	0,460	0,125	0.125
Ferritin (µg/dl)						
Medication use 1x1 every day	6,87(1,39-31)	25,5(3,67-45)	25,3(6,15-61)	0,056	0,001	0,05
Medication use 1x1 every other day	5(1,7-53)	6,7(24-54)	20(5,25-50)	0,307	0,002	0,263
Medication use 2x1 every other day	6(1,4-46,6)	26(7-131)	32(13-110)	0,358	0,001	0,122

When the unsaturated iron binding capacity values were analysed, in group 1 patients, a significant decrease was found in unsaturated iron capacity values on day 0-14 (p=0.001) and day 0-28 (p=0.015). No significant difference was found between the 14-28th day (p=0,647) values. A substantial decrease was found between the unsaturated iron capacity values on days 0-14 (p=0.001) and 0-28 (p=0.001) in group 2 patients. No significant difference was found between day 14-28 (p=0.981) values. No significant difference was found between the unsaturated iron capacity values on day 0-14 (p=0.460), day 14-28 (p=0.125) and day 0-28 (p=0.125) in group 3 patients (Table 3).

In group 1 patients, a substantial increase was found between 14-28th day (p<0.001) ferritin values. No significant difference was found between 0-14th day (p=0.05) and 0-28th day (p=0.056) ferritin values. An increase was found between 14-28th day (p=0.02) ferritin values in group 2 patients. No significant difference was found between 0-14th day (p=0.307) and 0-28th day (p=0.263) ferritin values. A significant increase was found between 14th-28th day (p=0.001) ferritin values in group 3 patients. No significant difference was found between 0-14th day (p=0.358) and 0-28th day (p=0.122) ferritin values (Table 3).

The rate of change pattern of parameters (hemoglobin, iron, unsaturated iron binding capacity, ferritin) in all patient groups was analysed. There was a statistically significant difference between 28th day - 14th day ferritin values (p=0.012). 14th day – day zero unsaturated iron binding capacity (p=0,085) and 14th day – day 0 transferrin saturation (p=0,085) values were statistically borderline significant.

After the patients were divided into groups, hemoglobin value increases were calculated (Table 4). The increases were evaluated separately by comparing the groups with each other. The rate of change in hemoglobin values between the groups was calculated as 0-14th day (p=0.386), 14-28th day (p=0.210) and 0-28th day (p=0.984) and no statistically significant difference was observed between the groups.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 July 2023 doi:10.20944/preprints202307.1234.v1

Table 4. Investigation of the rate of change in hemoglobin values between groups on days 0-14-28.

PARAMETERS	MEAN (MİN-MAX)	P-Values
Hb Change Between 1st and 3rd Control Visit (g/dl) (Hb Change Between 0th day-28th day Control Visits)		
Medication use 1x1 every day	0,9(-0,1, 3,7)	<0,001
Medication use 1x1 every other day	1(-0,3, 5,6)	0,002
Medication use 2x1 every other day	1,4(-0,5, 3,3)	0,001
Hb Change Between 1st and 2nd Control Visit (g/dl) (Hb Change Between 0th day-14th day Control Visits)		
Medication use 1x1 every day	0,6(-1,3, 1,3)	<0,001
Medication use 1x1 every other day	0,65(-0,3-4,2)	<0,001
Medication use 2x1 every other day	0,9(-0,9, 2,6)	<0,001
Hb Change Between 2nd and 3rd Control Visit (g/dl) (Hb Change Between 14th day-28th day Control Visits)		
Medication use 1x1 every day	0,6(-0,1, 2,4)	<0,001
Medication use 1x1 every other day	0,55(-0,6, 1,4)	<0,001
Medication use 2x1 every other day	0,4(-0,1, 1,8)	<0,001

After the patients were divided into groups, increases in serum iron levels were calculated (Table 5). The increases were evaluated by comparing the groups with each other. When the rate of change of serum iron values between the groups was compared, it was calculated as 0-14th day (p=0.102), 14-28th day (p=0.585) and 0-28th day (p=0.141) and no significant difference was observed between the groups.

Table 5. Evaluation of the rate of change in serum iron values between groups on days 0-14-28.

PARAMETERS	MEAN (minimum-maximum)	P-Values
Serum Iron Change Between 1st and 3rd Control Visit (µg/dl) (Serum Iron Change between day 0 and day 28 Control Visits)		
Medication use 1x1 every day	58,65(-63,3055)	0,002
Medication use 1x1 every other day	24(-5,647)	0,004
Medication use 2x1 every other day	7(-302,456)	0,363
Serum Iron Change Between 1st and 2nd Control Visit (µg/dl) (Serum Iron Change Between 0th day-14th day Control Visits)		
Medication use 1x1 every day	12,15(-355,3089)	0,094
Medication use 1x1 every other day	20(-19,564)	0,003
Medication use 2x1 every other day	4(-299,110)	0,776
Serum Iron Change Between 2nd and 3rd Control Visit (µg/dl) (Serum Iron Change Between 14th day-28th day Control Visits)		
Medication use 1x1 every day	1,5(-93,353)	0,601
Medication use 1x1 every other day	-5(-420,502)	0,586
Medication use 2x1 every other day	0,7(-44,452)	0,955

After the patients were divided into groups, unsaturated iron binding capacity values were calculated (Table 6). The increases were evaluated by comparing the groups with each other. When the rate of change of unsaturated iron binding capacity values between the groups was compared, it was calculated as 0-14th day (p=0.141) and 0-28th day (p=0.328) and no significant difference was observed between the groups. However, statistically borderline significance was observed between the groups in the rate of change of unsaturated iron binding capacity values on the 14th -28th day (p=0.085).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 July 2023 doi:10.20944/preprints202307.1234.v1

Table 6. Investigation of the rate of change of unsaturated iron binding capacity values between groups on days 0-14-28.

PARAMETERS	MEAN (MİN-MAX)	P-Values
Change in Unsaturated Iron Binding Capacity between 1st and 3rd Control Visit (µg/dl) (Change in Unsaturated Iron Binding Capacity between day 0 and day 28 Control Visits)		
Medication use 1x1 every day	-44(-415,187)	0,015
Medication use 1x1 every other day	-38(-256,25)	0,001
Medication use 2x1 every other day	-42(-478,251)	0,125
Change in Unsaturated Iron Binding Capacity between 1st and 2nd Control Visit (µg/dl) (Change in Unsaturated Iron Binding Capacity between 0th day-14th day Control Visits)		
Medication use 1x1 every day	-35(-421,22)	0,001
Medication use 1x1 every other day	-35,5(-439,23)	0,001
Medication use 2x1 every other day	-10(-150,275)	0,460
Change in Unsaturated Iron Binding Capacity between 2nd and 3rd Control Visit (µg/dl) (Unsaturated Iron Binding Capacity between 14th day-28th day Control Visits)		
Medication use 1x1 every day	1,5(-93,353)	0,647
Medication use 1x1 every other day	-11(-224,354)	0,981
Medication use 2x1 every other day	-24(-459,36)	0,125

After the patients were divided into groups, ferritin value increases were calculated (Table 7). When the rate of change of ferritin values between the groups was compared, it was calculated as 0-14th day (p=0,572) and 0-28th day (p=0,258) and no significant difference was observed between the groups. However, statistically significant difference was observed between the groups in the rate of change of ferritin values on the 14th -28th day (p=0.012).

Table 7. Investigation of the rate of change of ferritin values between groups at 0.-14.-28. days.

PARAMETERS	MEAN (MİN-MAX)	P-Values
Ferritin Change Between 1st and 3rd Control Visit (ng/dl) ((Ferritin Change Between 0th day-28th day Control Visits)		
Medication use 1x1 every day	21(-8,35)	0,05
Medication use 1x1 every other day	12(-45,48)	0,263
Medication use 2x1 every other day	28(-22,9,107,48)	0,122
Ferritin Change Between 1st and 2nd Control Visit (ng/dl) (Ferritin Change Between 0th day-14th day Control Visits)		
Medication use 1x1 every day	9(-8,3, 0,43)	0,056
Medication use 1x1 every other day	19(-37,52)	0,307
Medication use 2x1 every other day	13,6(-22,129)	0,358
Ferritin between 2nd and 3rd Control Visit (ng/dl) (Ferritin between 14th day-28th day Control Visits)		
Medication use 1x1 every day	5(-11, 22)	<0,001
Medication use 1x1 every other day	-5(-29,2, 23)	0,002
Medication use 2x1 every other day	3(-66, 47)	0,001

When the side effect profile of all groups was analysed, diarrhoea and vomiting symptoms were not observed in any of the patients. Nausea, vomiting, metallic taste and bloating symptoms were analysed separately for each group. There was no significant difference in the incidence of symptoms in the 14th and 28th day controls for each group (p>0.05). The incidence of metallic taste and bloating symptoms was found to be statistically borderline significant (p=0.094) in the 3rd control in the group with 2x1 drug use every other day (Table 8).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 July 2023 doi:10.20944/preprints202307.1234.v1

Table 8. Side effect profile of all patients divided into groups at seconds and third controls.

PARAMETERS	MEDİCATİON USE 1X1 EVERY	MEDİCATİON	MEDİCATİON USE 2X1 EVERY	P-VALUES	MEDİCATİON	MEDİCATİON	MEDİCATİON USE 2X1 EVERY	P-VALUES
Nausea								
Yes	0	1	1	0,542	1	2	4	0,18
No	19	17	14		18	16	11	
Metallic taste								
Yes	0	0	1	0,284	1	1	4	0,094
No	19	18	14		18	17	11	
Bloating								
Yes	1	0	1	0,564	1	1	4	0,094
No	18	18	14		18	17	11	
Constipation								
Yes	1	1	0	0,655	0	1	2	0,254
No	18	17	15		19	17	13	

4. DISCUSSION

The standard treatment of iron deficiency anaemia in the guidelines is the use of 60 mg oral iron-containing tablets 2-3 times a day (10). However, it has been proven in recent studies that the excess iron given increases the level of hepcidin and therefore decreases iron absorption, and for this reason, iron treatment has been recommended every other day (11). In addition, intermittent iron therapy has been shown to be effective in preschool children and in the pregnant population (12, 13). The mucosal block theory was first proposed in 1943 by Hahn et al. in a study on dogs (14). According to this theory, the iron dose given after the first dose was absorbed less than the first dose. It was shown that enterocytes exposed to high doses of iron could not absorb iron sufficiently and it was shown that 5-6 days should pass and new enterocytes should take part in absorption in order to ensure absorption at the same rate. Therefore, it was thought that weekly administration of iron treatment could increase absorption (14). In later times this theory was supported by various animal experiments (15). In a study conducted by Granick et al. in 1946, high doses of iron were given to guinea pigs and it was shown that ferritin crystals were formed in duodenal mucosal cells and these crystals could persist in the cells for 3-6 days (16). This study suggested that ferritin may play a role in iron absorption. Later in 1963, the mucosal block theory was modified by Crosby et al. and it was determined that the iron content in the dueodonal mucosa played a role in iron absorption in experimental animals (17). In the 1960s, iron absorption mechanisms began to be investigated in humans. In 1998, a study by Hallberg et al. showed the opposite result of animal experiments. According to this study, contrary to animal experiments, the first dose of iron given did not affect the subsequent doses and did not reduce iron absorption (18).

In the study conducted by Young et al. in 2009, the role of hepsidine in iron homeostasis was demonstrated. In this study, it was shown that there was a negative correlation between hepsidin level and iron absorption in young women (19). In the same period, Zimmermann et al. demonstrated that hepsidine was an important predictor of dietary iron bioavailability in young women (8). In 2017, Sangkhae and Nemeth showed that hepatic BMP-SMAD pathway decreases the expression of hepsidine, which is a regulatory hormone of iron homestasis, in iron deficiency. It was stated that the expression of ferroportin and DMT-1 in enterocytes increased with the decrease in circulating hepsidine level and thus iron absorption increased (20).

In the study conducted by Moretti et al. in 2015, 54 female patients with iron deficiency without anaemia (hemoglobin>11.7 g/dl and ferritin <20 ng/dl) received oral ferrous sulphate labelled at

 doi:10.20944/preprints202307.1234.v1

various doses for two days. The aim of the study was to show acute elevation of hepsidine after iron replacement. After administration of 60 mg, 80 mg, 160 mg and 240 mg elemental iron, a significant increase in plasma hepcidin level was found in the first 24 hours ($p<0.05$). It was shown that fractionated iron absorption decreased with increasing dose ($p<0.01$). However, total iron absorption was found to increase with dose increase ($p<0,01$) (11). In the same study, significant differences were observed in plasma hepcidin levels measured at 10:00, 16:00 and 08:00 the next morning in the group given 2x60 mg iron ($p<0.01$). After the first dose, iron absorption at noon dose decreased by 26% and iron absorption the next morning decreased by 46% compared to the first dose ($p<0.01$). In terms of total iron absorption, no statistically significant difference was found between the group given 2x60 mg and the group given 1x60 mg. Transferrin saturation (%) values measured at the 4th hour after iron replacement at various doses increased statistically significantly with increasing dose (11). In our study, a significant increase in transferrin saturation was observed in group 1 ($p=0.015$) and group 2 ($p=0.001$) patients between days 0 and 28 in the temporal plane. When the rate of change in transferrin saturation was evaluated between the groups, a statistically significant difference was found between days 0 and 14 in group 1 and group 2. The study by Moretti et al. was shorter in terms of evaluation period (2 days) compared to our study (11).

Stoffel et al. in their first study in 2017, they divided 40 female patients with iron deficiency without anaemia into two groups (7). The first group received 60 mg elemental iron every day for 14 days (group A) and the second group received iron every other day for 28 days (group B). Iron absorption was statistically significantly increased in the group given iron every other day (16.3% and 21.8%, $p<0.01$). Total iron absorption was similar in both groups ($p<0.05$). Serum hepcidin level was significantly increased in group A patients (7). In the second study conducted by the same team, it was planned to investigate the effect of dividing the doses during the day on hepcidin levels and iron absorption. Patients were divided into randomised groups. Group 1 received 120 mg elemental iron at 08:00, while group 2 patients received a total of 120 mg elemental iron, 60 mg at 08:00 and 60 mg at 18:00. There was a significant increase in serum hepcidin level in both groups ($p<0.001$). The increase in hepsidine in the group given iron 2 times a day was found to be higher than in the group given a single daily dose ($p=0.013$). In the group that received single daily dose of iron, serum hepsidine and fractionated iron absorption levels were correlated ($p=0.035$ for day 1, $p=0.001$ for day 2, $p=0.001$ for day 3). In the group receiving iron replacement in two doses per day, hepsidin and fractionated iron absorption were correlated on day 1 ($p=0.013$), but no correlation was found on days 2 and 3 ($p=0.17$ for day 2, $p=0.33$ for day 3). No increase in fractionated and total iron absorption was observed in split dosing (7).

In the study by Stoffel et al. published in 2019, it was shown that in 16 women with iron deficiency anaemia, high-dose oral iron (100 mg, 200 mg) treatment increased serum hepsidine levels for 24 hours, but this effect did not last for 48 hours (6). It has been shown that absorption of fractionated iron decreases the following day but reaches basal absorption level after 48 hours. This contradicts with the mucosal block theory. It was proved in this study that the absorption of fractionated iron was less in patients receiving 200 mg iron compared to those receiving 100 mg iron. Patients were followed up for 6 days in this study. Labelled ferrous sulphate was given to the patients on the 2nd, 3rd and 5th days. After administration of 100 mg iron to the first group and 200 mg iron to the second group, serum hepsidin levels were evaluated on day 2, day 3 and day 5. It was shown that serum hepsidin levels increased in both groups in a time-dependent manner ($p<0.001$). In both doses, serum hepsidine level was significantly increased on day 3 compared to days 2 and 5 ($p<0.002$ for day 2, $p<0.001$ for day 5). There was no significant difference in serum hepsidine levels between days 2 and 5. At the same time, fractionated and total iron absorption, which were analysed in both doses, were significantly increased on day 2 and day 5 compared to day 3 ($p<0.001$). No significant difference was found in fractionated and total iron absorption between day 2 and day 5, regardless of dose. When ferritin level was analysed for both doses, ferritin level was found to be significantly increased on day 3 and day 5 compared to day 2 ($p<0.05$). Serum iron level and transferrin saturation were significantly increased on day 3 and day 5 compared to day 2 ($p<0.05$), but no significant difference was found between day 3 and day 5. Total iron binding capacity was found to be

 doi:10.20944/preprints202307.1234.v1

significantly decreased on day 3 and day 5 compared to day 2 ($p<0.05$, $p<0.01$), but again no significant difference was found between day 3 and day 5. When the group receiving 100 mg iron was evaluated in terms of side effect profile, symptoms such as nausea, vomiting and diarrhoea were seen 40% less. However, no statistically significant difference was found between the two groups in terms of side effects ($p=0.105$) (6). In conclusion, when combined with the first study in 2017, it has been proven that every other day dosing scheme increases the absorption of fractionated iron in iron replacement in patients with iron deficiency with or without anaemia, and this absorption is higher in the low dose regimen.

In our study, when ferritin levels were evaluated in the intragroup temporal plane, no statistically significant difference was found for group 1 ($p=0.05$), group 2 ($p=0.2$) and group 3 ($p=0.122$) on days 0 and 28. However, a statistically significant increase was observed for group 1 ($p<0.001$), group 2 ($p<0.002$) and group 3 ($p=0.001$) on the 14th and 28th days.When the rate of ferritin change was compared between the groups, the increase in ferritin was higher in the group receiving 1x1 every day (median value for the group receiving 1x1 every day: 5(-11,22)). These results suggested that ferritin increase was significant after hemoglobin levels increased. When serum iron levels were evaluated in the temporal plane, a significant increase in iron levels was found in group 1 ($p=0.002$) and group 2 ($p=0.004$). No significant difference was found in group 3 ($p=0,363$). When unsaturated iron binding capacity was evaluated, a statistically significant decrease was found at the end of the 28th day in group 1 ($p=0.013$) and group 2 ($p=0.001$) patients. In group 3 patients, no significant decrease was found in terms of unsaturated iron binding capacity ($p=0.123$). In terms of side effects, vomiting and diarrhoea symptoms were not observed in any patient in our study. There was no significant difference between the groups in nausea and constipation symptoms. On the second and third control days, metallic taste ($p=0.09$) and bloating ($p=0.09$) were found more in group 3 patients.

Kaundal et al. randomly divided a total of 62 patients with iron deficiency anaemia into two groups in their study published in 2019 (21). One group received oral iron treatment twice a day with a total of 120 mg elemental iron/day ($n=31$) and the other group received oral iron treatment every other day with a total of 120 mg elemental iron every other day ($n=31$) and hemoglobin increase, hepcidin level and side effect profile were analysed. In the study, the increase of hemoglobin value ≥ 2 gr/dl at the end of the third week was taken as a reference. The percentage of achievement of this reference was 33.3% in the group given iron twice a day, while this rate was 6.5% in the group given iron 1x1 every other day and this difference was found to be statistically significant ($p<0.001$). There was no significant difference between the 2 groups in terms of plasma hepcidin levels ($p=0.8$). In terms of side effects, nausea was observed 22.5% in the group with 1x1 every other day use, whereas it was observed 38.7% and significantly more frequently in the group with 2x1 every other day iron use ($p=0.03$). No significant difference was observed between the two groups in terms of dyspepsia, vomiting, constipation and diarrhea (21). In this study, a result contrary to previous studies was found. this may be due to the fact that anaemia of any severity was included in the study. The median hemoglobin value of the patients participating in this study was 8.9 g/dl and this median value is lower than similar studies in the literature. In addition, the fact that the hepsidin level did not change in this study contradicts the finding of increased hepsidin level in patients with daily iron intake in previous studies. Furthermore, the finding that hepsidin level did not change in this study contradicts with the finding of increased hepsidin level in patients with daily iron intake in previous studies (6).

Karakoç et al. conducted a study comparing the efficacy of daily and every other day iron therapy in 264 pregnant women in the second trimester of pregnancy (14-28 weeks) (22). The patients were given 100 mg of ferrous sulphate every day and every other day. Hemoglobin and ferritin levels were compared at the end of 2 months. A statistically significant increase was found in hemoglobin and ferritin levels at the end of the second month in both groups ($p<0.05$). This study was conducted in the temporal plane and has deficiencies in terms of not comparing the hemoglobin and ferritin levels between the two groups. In this study, in terms of side effect profile, the frequency of side effects was 41.1% in the group receiving daily medication, whereas it was 15.7% in the group receiving iron every other day. When a comparison was made between the two groups in terms of

side effect profile, a statistically significant result was obtained (p=0.005). In our study, a statistically significant increase was found in hemoglobin levels at the end of the 28th day in patients in all three groups (p<0.001). No difference was observed when the level of hemoglobin change between the groups was evaluated. Treatment response was observed in all three treatment protocols.

The limitations of our study are the relatively small number of patients, the lack of male patients and the retrospective design of the study. However, our study is valuable in terms of being a study conducted in the current field, including real-life data and containing findings compatible with the literature. In addition, unlike other studies, the data of three different treatment modalities were evaluated in our study and the changes and responses of these modalities were evaluated both within and between each other.

5. CONCLUSION

In conclusion, in our study, the classical oral iron replacement therapy for iron deficiency was compared with alternative treatment modalities. Hemoglobin and ferritin values were evaluated for efficacy. The only difference in terms of efficacy was observed in ferritin values between 14th and 28th days. It was found that the increase in ferritin values between 14th and 28th days was higher in the group using 1x1 oral iron therapy every day. However, since there was no difference between the groups in terms of hemoglobin values and there was no difference between the groups in terms of ferritin values on days 0 and 28, all three groups were evaluated as equal in terms of efficacy.

Side effects were evaluated mainly in terms of gastrointestinal side effects. Since the group receiving 2x1 every other day oral iron therapy had a higher rate of side effects, which was statistically borderline significant, we anticipate that patient tolerance will be lower compared to the other groups. Since there was no difference in efficacy and side effects between the groups receiving 1x1 every day and 1x1 every other day oral iron therapy, we think that 1x1 every other day oral iron is the most appropriate treatment method in terms of patient tolerance, treatment compliance and pharmacoeconomics. At the same time, our study is one of the studies evaluating the effect of oral iron dose and frequency of use on hepcidin levels and the compatibility of these findings with clinical studies. As a result of our study, when both the response to treatment and the frequency of side effects are evaluated, the use of 1x1 oral iron every other day comes to the forefront in terms of equal efficacy, pharmacoeconomics and patient compliance despite the use of a lower dose. Studies to date have demonstrated the efficacy of every other day oral iron therapy in terms of iron absorption, treatment response, patient compliance and side effect profile. However, these data still need to be supported by larger prospective randomised controlled trials.

Author Contributions: INS and UYM was responsible for the study design, data interpretation, and manuscript writing. INS treated the patients, collected the samples, and provided patient data. UYM contributed to interpretation and critically reviewing the manuscript. All authors contributed to the revision of the manuscript and approved the final version.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Statement of Ethics: All of the ethical considerations were strictly handled in accordance with the Helsinki Declaration. This study protocol was reviewed and approved by the Ethics committee of University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital. The ethics committee approval date of our research is 06.07.2020 and decision no: 91/02.

Consent to participate statement: All of the study patients gave informed consent.

Conflicts of Interest Statement: The authors have no conflicts of interest to declare.

References

1. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood, The Journal of the American Society of Hematology. 2014;123(5):615-624.
2. Auerbach M, Deloughery T. Single-dose intravenous iron for iron deficiency: a new paradigm. Hematology 2014, the American Society of Hematology Education Program Book. 2016;2016(1):57-66.
3. CDC A. Recommendations to prevent and control iron deficiency in the United States. MMWR Recomm Rep. 1998;47(RR-3):1-29.
4. Camaschella C. Iron-deficiency anemia. New England journal of medicine. 2015;372(19):1832-1843.
5. Cook JD, Reddy MB. Efficacy of weekly compared with daily iron supplementation. The American journal of clinical nutrition. 1995;62(1):117-120.
6. Stoffel NU, Zeder C, Brittenham GM, Moretti D, Zimmermann MB. Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. Haematologica. 2020;105(5):1232.
7. Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. The Lancet Haematology. 2017;4(11): e524-e533.
8. Zimmermann MB, Troesch B, Biebinger R, Egli I, Zeder C, Hurrell RF. Plasma hepcidin is a modest predictor of dietary iron bioavailability in humans, whereas oral iron loading, measured by stable-isotope appearance curves, increases plasma hepcidin. The American journal of clinical nutrition. 2009;90(5):1280-1287.
9. Sheikh AB, Javed N, Ijaz Z, Barlas V, Shekhar R, Rukov B. Iron deficiency anemia in males: a dosing dilemma? Journal of Community Hospital Internal Medicine Perspectives. 2021;11(1):46-52.
10. Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. American journal of hematology. 2016;91(1):31-38.
11. Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood, The Journal of the American Society of Hematology. 2015;126(17):1981-1989.
12. Peña-Rosas JP, De-Regil LM, Malave HG, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. Cochrane Database of Systematic Reviews. 2015(10).
13. De-Regil LM, Jefferds MED, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. Cochrane Database of Systematic Reviews. 2011(12).
14. Hahn P, Bale W, Ross J, Balfour W, Whipple G. Radioactive iron absorption by gastro-intestinal tract: influence of anemia, anoxia, and antecedent feeding distribution in growing dogs. The Journal of Experimental Medicine. 1943;78(3):169.
15. Fairweather-Tait SJ, Swindell TE, Wright A. Further studies in rats on the influence of previous iron intake on the estimation of bioavailability of Fe. British Journal of Nutrition. 1985;54(1):79-86.
16. Granick S. NAL Mucosa as a direct response to iron feeding. The function of ferrinin the regulation of iron absorption.
17. Crosby WH. Editorial review: the control of iron balance by the intestinal mucosa. Blood. 1963;22(4):441-449.
18. Hallberg L. Combating iron deficiency: daily administration of iron is far superior to weekly administration. The American journal of clinical nutrition. 1998;68(2):213-217.
19. Young MF, Glahn RP, Ariza-Nieto M, Inglis J, Olbina G, Westerman M, et al. Serum hepcidin is significantly associated with iron absorption from food and supplemental sources in healthy young women. The American journal of clinical nutrition. 2009;89(2):533-538.
20. Sangkhae V, Nemeth E. Regulation of the iron homeostatic hormone hepcidin. Advances in nutrition. 2017;8(1):126-136.
21. Kaundal R, Bhatia P, Jain A, Jain A, Nampoothiri RV, Mishra K, et al. Randomized controlled trial of twice-daily versus alternate-day oral iron therapy in the treatment of iron-deficiency anemia. Annals of Hematology. 2020;99(1):57-63.

 doi:10.20944/preprints202307.1234.v1

22. Karakoc G, Orgul G, Sahin D, Yucel A. Is every other day iron supplementation effective for the treatment of the iron deficiency anemia in pregnancy? The Journal of Maternal-Fetal & Neonatal Medicine. 2022;35(5):832-836.