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Efficiency of intravenous iron carboxymaltose in patients with iron-deficiency anemia due to heavy menstrual bleeding: a single-center experience

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Abstract. – OBJECTIVE: Heavy menstrual bleeding (HMB) is the most common cause of iron deficiency anemia (IDA) in premenopausal women. Clinical studies have shown that iron carboxymaltose (ICM) is an appropriate, effective, and well-tolerated treatment option for clinical situations associated with iron deficiency (ID).

PATIENTS AND METHODS: This study took 78 out of 400 consecutive patients diagnosed with IDA due to HMB and intolerant or insufficient response of oral iron. All patients were administered the total calculated dose of ICM separately, based on the body weight and current hemoglobin (Hb) level. All the anemia parameters of the patients were compared before and after treatment.

RESULTS: All anemia parameters, including median Hb, ferritin, and transferrin saturation, significantly increased four weeks after treatment. Pre- and post-treatment mean Hb levels were 8.9 (± 1.7) g/dL and 12.3 (± 1.2) g/dL, respectively. The mean ferritin level of the patients before treatment was 3.93 (± 2.7) ng/mL. After treatment, the mean ferritin level was 244 (± 185) ng/mL. The mean transferrin saturation levels before and after treatment were 5.7% (± 5.0) and 43.1% (± 20.9), respectively. Although no serious side effects were observed in all patients, headache was detected in 2 patients (2.6%), urticaria in 3 patients (3.8%), and flushing in 2 patients (2.6%).

CONCLUSIONS: ICM is an effective and safe treatment option for patients with IDA due to HMB, in which oral iron therapy is insufficient or intolerant. In fact, without waiting for the failure or intolerance of oral iron therapy, moving ICM to the frontline could be cost-effective and more convenient to patients with HMB and health care providers.

Key Words:
Iron deficiency anemia, Ferric carboxymaltose, Hypermenorrhea, Heavy menstrual bleeding.

Introduction

Anemia still maintains its importance as a major public health problem today. It has been shown to affect 1.93 billion people all over the world, that is 27% of the world's population[1]. The World Health Organization (WHO) defines anemia as a lower-than-normal erythrocyte count in the blood or Hb concentration in the erythrocyte[2]. Definition of anemia is Hb concentration less lower than 13 g/dL in men (age ≥ 15 years), Hb level less lower than 12 g/dL in non-pregnant women, and Hb level less lower than 11 g/dL in pregnant women (≥ 15 years old)[3]. ID is the most common cause of anemia and is detected in approximately half of the anemia patients[4]. In developed countries, IDA occurs in 2% to 5% of adult men and postmenopausal women. Chronic blood loss from the gastrointestinal tract is the most common cause of IDA in adult men and postmenopausal women[5]. The most common cause of IDA in premenopausal women is menstrual blood loss[6]. IDA causes symptoms such as weakness, fatigue, difficulty concentrating, decreased work efficiency and cognitive ability, headache, loss of appetite, pica, exertional dyspnea, hair loss, brittle nails, and restless legs syndrome[7,8]. Iron is primarily stored in the form of ferritin in the body. Ferritin value varies with age and gender. According to the WHO, the criteria for diagnosis of ID is ferritin lower than 15 µg/ml in healthy individuals aged 5 years and older[9]. Some of the international guidelines use 30 µg/mL as the ferritin threshold[10,11]. The sensitivity of this threshold value is estimated to be 92% and the specificity as 98%[12]. Since ferritin is an acute-

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phase protein, it may increase independently of iron concentration in acute and chronic inflammatory diseases, malignant diseases, and liver diseases. In these cases, even with ferritin levels of 50 μg/mL and above, there might still be iron deficiency[3,13]. If ID is not treated, it causes IDA. Transferrin saturation (the ratio of serum iron to serum iron-binding capacity), combined with ferritin, better reflects ID. Iron is mostly bound to its circulating carrier protein transferrin. In ID, the total iron-binding capacity increases and this results in lower transferrin saturation. The normal range for serum iron is 60-150 μg/dL. Serum iron should be measured after overnight fasting, as it may temporarily be affected by dietary or pharmacological iron absorption. The normal range of total iron-binding capacity and transferrin saturation is 300-360 μg/dL and 20-50%, respectively. The threshold for transferrin saturation, which indicates an iron deficiency, is usually 16%. However, in the presence of inflammation, a threshold value of 20% is used[14].

IDA should always be treated, whether symptomatic or not[15]. Nowadays, oral iron preparations are the first option in the treatment of IDA. However, the necessity for long-term treatments, the inability to maintain a treatment because of gastrointestinal side effects, and the need to continue long-term efficiency limit the administration of oral iron preparations. ICM is a non-dextran-based intravenous iron formulation designed to mimic physiological ferritin, consisting of a polynuclear iron (I) hydroxide core stabilized by carboxymaltose[16,17].

IDA is a serious public health problem, especially affecting premenopausal women. The present research aims to demonstrate the efficacy and safety of intravenous ICM treatment in women of childbearing age who have HMB and for whom oral iron therapy is insufficient or intolerable.

Patients and Methods

The research was carried out at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Hematology between January 2019 and February 2021. This study was conducted according to the Declaration of Helsinki with ethical principles, and it was approved by the Institutional Review Board of 'Dr. Abdurrahman Yurtasalan Ankara Oncology Training and Research Hospital'.

This retrospective study 78 out of 400 consecutive patients diagnosed with IDA and treated with iron carboxymaltose, who applied to the hematology outpatient clinic. All patients signed the informed consent form. Patients who met all the following inclusion criteria were included in the study: (1) female patients aged 18 years and older with a hemoglobin concentration lower than 12 mg/dl; (2) patients whose serum ferritin at the time of the screening was lower than 30 ng/mL and their C-reactive protein level were normal according to the range established by the central laboratory (3) patients with hypermenorrhea at each of the consecutive menstrual cycles during the past 6 cycles; (4) patients in whom the main cause of IDA was judged as hypermenorrhea, menorrhagia, and menometrorrhagia; (5) outpatients; and, (6) patients for whom oral iron therapy given due to IDA was insufficient or who cannot could not tolerate oral iron.

Patients who met any of the following exclusion criteria were excluded from the study: (1) patients less than 18 years old; (2) patients whose body weight was lower than 35 kg; (3) patients with hematopoietic stem cell diseases; (4) patients undergoing gastroctaemia or bariatric surgery; (5) patients diagnosed with inflammatory bowel disease (Ulcerative Colitis, Chron); (6) patients diagnosed with celiac; (7) patients with hemoglobinopathy; (8) patients with malignancy; (9) patients with chronic kidney diseases; (10) patients with perioperative anemia; (11) patients with chronic heart failure; (12) patients during pregnancy and in the postpartum period 13) patients within 6 months after gastrointestinal bleeding; (14) patients using drugs that may affect the evaluation of the efficacy of ICM (e.g., erythropoiesis stimulation agent formulations, drugs containing progesterone, gonadotropin-releasing hormone agonists/antagonists, ethisterone-derived drugs).

For the assessment of efficacy, laboratory tests related to IDA [i.e., hemoglobin, ferritin, mean corpuscular volume (MCV), erythrocyte distribution width (RDW), serum iron, serum total iron-binding capacity (TIBC)] were investigated. The percentage saturation of transferrin with iron was calculated by dividing the serum iron concentration by the total iron-binding capacity (TIBC) and multiplying by 100. The measurement values were evaluated before the initiation of ferric carboxymaltose administration and four weeks after treatment. Furthermore, concomitant diseases of the patients, such as gastrointestinal diseases (gastritis, ulcer, hemorrhoids), gyneco-

logical diseases (uterine benign anomalies, myoma…), and drug adverse events were assessed.

The total dose of ferric carboxymaltose was calculated separately for each patient depending on the patient's hemoglobin level and body weight. 2000 mg ferric carboxymaltose was administered for women with Hb lower than 10 g/dL and a body weight 70 kg (group 1); 1500 mg ferric carboxymaltose was administered for women with Hb lower than 10 g/dL and body weight lower than 70 kg (group 2). Patients with Hb 10 g/dL or more and body weight of 70 kg received 1500 mg ferric carboxymaltose (group 3); patients with Hb 10 g/dL or more and body weight lower than 70 kg received 1000 mg ferric carboxymaltose (group 4). The patients were administered ferric carboxymaltose until the total calculated iron dose was achieved in at least 1-week intervals, with a maximum dose of 1000 mg of iron per week. Ferric carboxymaltose was administered as an intravenous infusion diluted in 250 ml sterile 0.9% sodium chloride solution for 15 minutes. All patients were observed for adverse effects for at least 30 minutes following each ferric carboxymaltose administration.

The demographics and other baseline characteristics of this study are shown in Table I.

Statistical Analysis

Data were analyzed using the SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data. Categorical data were expressed as ratiosand numerical data as median and mean±standard deviation. The Shapiro Wilk test was used to determine the distribution normality of data. In a comparison between groups, the "Student *t*-test" was used for normally distributed numerical variables. The Mann-Whitney U test was used to compare differences between two independent groups for non-normally distributed numerical variables. Comparison of categorical variables was analyzed using the "Chi-square significance test" or "Fisher's Exact test". The level of significance was predetermined to be $p < 0.05$.

Results

This study took 78 out of 400 consecutive patients diagnosed with IDA due to heavy menstrual bleeding. All patients who met the study criteria were administered the total calculated dose of ferric carboxymaltose depending on the patients' Hb levels and body weight. The mean age of the patients was 38.2 (± 8.2). All anemia parameters including median hemoglobin level, ferritin value, and transferrin saturation significantly increased in the four weeks after the treatment.

Pre-treatment and post-treatment median hemoglobin concentration were 8.9 (± 1.7) g/dL, and 12.3 (± 1.2) g/dL, respectively. The mean change in hemoglobin before and after treatment was 3.4 (± 1.7) g/dl. The proportion of patients achieving an increase in Hb ≥ 2 g/dL was 89% (70 patients). After the treatment, the proportion

Table I. Patients' characteristics and laboratory features.

Characteristics	Group 1 (Hb < 10, ICM: 2 gr) (n: 30)	Group 2 (Hb < 10, ICM: 1.5 gr) (n: 22)	*p* 1 *vs.* 2	Group 3 (Hb > 10, ICM: 1 gr) (n: 10)	Group 4 (Hb > 10, ICM: 1 gr) (n: 16)	*p* 3 *vs.* 4
Age ± SD, (years)	39.3 ± 8.8	37.8 ± 6.0	0.477	42 ± 8.7	34 ± 8.4	0.034
BMI±SD (kg/m^2) mean	25.1 ± 2.6	23.8 ± 2.6	0.055	26.1 ± 3.5	24.2 ± 2.4	0.120
Concomitant disease						
Diabetes	1 (3.3 %)	1 (4.5 %)	0.573	1 (10%)	1 (6.3%)	0.399
Hypothyroidism	1 (3.3 %)	2 (9.1 %)		3 (10%)	0	
Hemorrhoids	0	2 (9.1%)		0	3 (18.8%)	
Gastritis	3 (10)	3 (13.6 %)		4 (40%)	5 (31.3%)	
Vit B12 deficiency	1 (3.3%)	0		0	0	
Hemoglobin (g/dl) mean ± SD	7.8 ± 2.6	8.2 ± 1.0	0.199	10.8 ± 0.9	10.9 ± 0.9	0.838
Hematocrit (%) mean ± SD	28.3 ± 3.4	29.3 ± 3.0	0.294	35.5 ± 2.7	35.1 ± 2.9	0.747
Serum Ferritin (ml/ng) mean ± SD	3.7 ± 3.0	3.0 ± 2.5	0.412	5.1 ± 2.8	4.9 ± 1.7	0.804
Serum Iron mean ± SD	15.3 ± 12.9	17.8 ± 14.8	0.530	32.4 ± 12.4	32.8 ± 19.7	0.953
Serum Iron binding Capacity mean ± SD	411 ± 41	410 ± 63	0.921	408 ± 58	384 ± 51	0.273

$p < 0.05$ is considered significant.

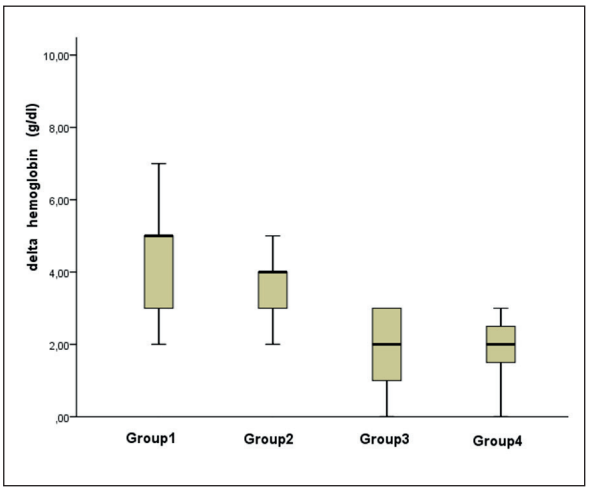

Figure 1. The post-treatment Hb levels of the patients were grouped according to the pre-treatment Hb levels and the treatment dose.

of subjects with normalized hemoglobin was 46% (36 patients). The post-treatment Hb levels of the patients are given in Figure 1, grouped according to the pre-treatment Hb levels and the treatment dose.

The mean ferritin levels of the patients pre-and post-treatment were 3.93 (± 2.7) ng/mL and 244 (± 185) ng/mL, respectively. The mean change in serum ferritin was 240 (±185) ng/mL. The mean baseline transferrin saturation was 5.7% (± 5.0). After treatment, the median transferrin saturation was 43.1% (± 20.9). The median change in transferrin saturation was 37.4% (± 21.3). The pre-and post-treatment biochemical parameters of the patients are given in Table II. The Hb, hematocrit, and ferritin levels were assessed separately, according to the groups and the rates of changing before and after the treatment (given in Table I). Although no serious side effects were observed in all patients, headache was observed in 2 patients (2.6%), urticaria in 3 patients (3.8%), and flushing in 2 patients (2.6%).

Discussion

Heavy menstrual bleeding occurs in 18-38% of childbearing-aged women. This can lead to iron deficiency or iron deficiency anemia[6]. Iron deficiency (serum ferritin ≤ 15 ng/mL) was found in 29.2% of adolescents and women with heavy menstrual bleeding[18]. Gastrointestinal side effects were significantly observed in patients with iron deficiency anemia treated with oral iron preparations[19]. These gastrointestinal side effects have occurred especially with ferrous sulfate[20]. Although oral iron is seen as the first-line treatment of iron deficiency anemia, intravenous iron has been found to be superior in efficacy compared to oral iron in many clinical situations. Intravenous iron is administered to patients who cannot tolerate oral iron because of its side effects and to patients for whom oral iron therapy is not effective due to poor iron absorption[21]. Intravenous iron is used as standard front-line therapy for inflammatory bowel diseases in Europe[22]. Moreover, intravenous iron supplementation was found to be effective in iron deficiency anemia in patients undergoing bariatric surgery[23,24].

Ferric carboxymaltose is taken up by reticuloendothelial cells, then gradually released into the serum. Thus, the risk of direct release of cytotoxic free ionic iron into the blood is minimized and a large amount of iron supplementation is provided at the same time[16,17]. Ferric carboxymaltose allows for the administration of a large amount of iron (15 mg/kg; maximum 1000 mg/infusion) by a rapid infusion without requiring a test dose[25].

Although self-limiting infusion reactions rarely occur during intravenous iron administration, intravenous iron provides effective treatment and ease of use in some clinical situations to patients and healthcare personnel[15]. In the past, serious side effects have been especially observed with iron dextran infusion, but rarely seen with ferric carboxymaltose. In randomized controlled trials, ferric carboxymaltose effectively replenished

Table II. Pre-treatment and post-treatment biochemical parameters of patients.

Pre-treatment median Hb level	8.9 (± 1.7) g/dL
Post-treatment median Hb level	12.3 (± 1.2) g/dL
The median change in Hb level	3.4 (±1.7) g/dl
The proportion of patients who achieved ≥ 2 g/dL Hb increase	% 89 (70 patients
The proportion of subjects with normalized Hb after treatment	% 46 (36 patients)
Pre-treatment median ferritin level	3.93 (± 2.7) ng/mL
Post-treatment median ferritin level	244 (± 185) ng/mL
The median change in ferritin level	240(± 185) ng/mL
Pre-treatment median transferrin saturation	% 5.7 (± 5.0)
Post-treatment median transferrin saturation	% 43.1 (± 20.9)
The median change in transferrin saturation level	% 37.4 (± 21.3)

Table III. Change in hematological parameters one month after the treatment.

Characteristics	Group 1 (Hb < 10, ICM: 2 gr) (n: 30)	Group 2 (Hb < 10, ICM: 1.5 gr) (n: 22)	Group 3 (Hb > 10, ICM: 1.5 gr) (n: 10)	Group 4 (Hb>10, ICM: 1 gr) (n: 16)
Delta Hb (g/dl)	4.5 ± 1.6	3.7 ± 1.2	1.8 ± 1.0	1.9 ± 0.9
Delta Hematocrit (%)	11.9 ± 4.2	9.9 ± 3.1	3.9 ± 2.5	5.1 ± 2.4
Delta Serum Ferritin	240 ± 177	170 ± 102	378 ± 260	250 ± 199
Delta Serum Iron	62 ± 30	68 ± 31	69 ± 24	53 ± 35
Delta Serum Iron binding Capacity	-195 ± 77	-191 ± 83	-202 ± 64	-145 ± 86

Delta indicates changes in hematological parameters one month after the treatment.

iron stores and improved anemia with a low risk of hypersensitivity reaction and was generally well-tolerated in a variety of clinical conditions with iron deficiency, including chronic kidney diseases, inflammatory bowel diseases, perioperative anemia, postpartum anemia[25].

In addition, the necessity of long-term treatments with oral preparations increases the total cost[26]. In recent years, the administration of intravenous iron has increased in heavy uterine bleeding for whom oral iron is not sufficient or in pregnant women who cannot tolerate or respond to oral iron[15]. ICM is an effective and well-tolerated treatment option in patients suffering with iron deficiency anemia due to hypermenorrhea[27]. ID and IDA cause a serious disease burden in women but can be treated rapidly with intravenous iron carboxy maltose. In reproductive-aged women diagnosed with iron deficiency anemia with intolerance to oral iron therapy, Hb level needed to be rapidly increased and Hb, ferritin, and transferrin saturation were found to be significantly superior with iron carboxymaltose therapy[26]. Furthermore, the efficacy and safety of intravenous iron carboxymaltose were demonstrated in 996 premenopausal women with iron deficiency anemia due to heavy menstrual bleeding or postpartum period[28]. The present study revealed similar findings to previous studies; iron stores were effectively renewed with ferric carboxymaltose, and hemoglobin concentration, ferritin level, and transferrin saturation were significantly increased[27-29].

In the present study, no serious side effects were observed in all patients. Minor side effects were observed in 7 patients. Headache was observed at a rate of 2.6%, urticaria at a rate of 3.8%, and flushing at a rate of 2.6%. Urticaria and flushing were resolved with the administration of 45.5 mg of pheniramine hydrogen maleate. Headache was mild or moderate in all cases. In general, the headache went away in a short time. No significant change was observed in the vital signs of the patients. For prophylaxis, 45.5 mg of pheniramine hydrogen maleate was administered to the patients who developed urticaria and flushing, in their second administration of ferric carboxymaltose infusion. These side effects were not observed in the patients during the second administration. The limitation of the present study is that hypophosphatemia, which can be observed with ferric carboxymaltose, was not evaluated. This is due to the retrospective nature of the study.

Conclusions

Ferric carboxymaltose is an effective and safe treatment that could be administered in patients with iron deficiency anemia due to hypermenorrhea, menorrhagia, and menometrorrhagia. Oral iron is not absorbed enough to compensate for losses in women with abnormal uterine bleeding, thus without waiting for failure or intolerance of oral iron therapy, ferric carboxymaltose might be administered.

Furthermore, drug cost-effectivity might be achieved by administrating high-dose ferric carboxymaltose treatment once or twice. A long-term treatment with oral iron preparations not only increases the cost of medication but also increases the frequency of admission to the hospital. In addition, it should not be ignored that the laboratory tests made in each admission contributed to the costs, and it should not be forgotten that each admission also increases the workload of the hospital staff.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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