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Original article

Prevalence and Significance of Leukopenia Induced by Intravenous Iron Therapy in a Large Cohort of Females with Iron Deficiency Anemia (IDA)

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Abstract. *Introduction:* Iron deficiency anemia (IDA) is the most common cause of anemia in both developed and developing countries. Leukopenia is an infrequent side effect of iron therapy reported in the literature as sporadic cases. *Objective:* To assess the prevalence of leukopenia, neutropenia and/or lymphocytopenia and its possible clinical impact if any, after intravenous iron therapy in adult patients with IDA. *Patients and Methods:* This is a retrospective study conducted in Hamad Medical Corporation, Doha (Qatar). The clinical and biochemical data of 1.567 females (mean age: 29.5 years) with IDA who attended the Hematology Clinic and were treated with intravenous (i.v.) iron therapy were collected and analysed. Complete and differential blood counts and iron profile were studied before and after i.v. iron therapy. In addition, cases who developed infections during the time of leukopenia were noted and checked for possible complications. *Results:* 30 cases (1.91%) developed leukopenia,15 cases (0.95%) developed neutropenia and 12 cases (0.76%) developed lymphocytopenia. All had normal white blood cell counts before treatment. Two patients (6.66%) had infection. One had upper respiratory tract infection and the other had urinary tract infection, the latter was treated with antibiotics. There was no reported other infection during or after i.v. iron therapy. *Conclusions:* Leukopenia in form of neutropenia or lymphocytopenia may occur as a side effect of i.v. iron therapy, however, its clinical significance appears to be limited. (www.actabiomedica.it)

Key words: Intravenous iron therapy, neutrophils, lymphocytes, iron deficiency anemia, infections.

Introduction

Iron deficiency (ID) is the most common cause of anemia world-wide, and it accounts for the most common nutritional deficiency. Iron deficiency anemia (IDA) particularly affects females in the child-bearing age and children at the pre-school age. Causes of iron deficiency include nutritional deficiency, excessive loss of blood (menorrhagia, bleeding disorders, bleeding from any source), parasitic infestations (like hookworm, schistosomiasis), malnutrition (mainly in developing countries) and malabsorption syndromes. The signs and symptoms can be linked to impaired oxygen delivery to the tissues causing fatigue, exertional dyspnea, light-headedness and pallor, or linked to iron deficiency like pica, ice craving, beeturia and restless leg syndrome (1,2). IDA has been linked to impaired mental and motor development in children (3), preterm birth, heart failure and may predispose to infection and increase mortality rates in

peri-operative settings (4,5). In one large study, IDA was found to account for 8.8% of total disability from all conditions (1).

Early diagnosis of IDA is vital to treat early and avoid complications. Treating the cause of IDA and iron replacement are the mainstay of the management. Correction of iron deficiency anaemia with oral iron is limited by gastrointestinal absorption and is particularly ineffective in the setting of coexisting acute or chronic medical conditions. Supported by laboratory results, intravenous iron therapy has an established role in the treatment of iron deficiency anaemia, when oral preparations are ineffective or cannot be used. Intravenous iron therapy is currently in wide use because of the advantage of overcoming gastric intolerance and constipation that occur with oral iron and the advantage of rapid replacement of iron (6,7).

Leukopenia, neutropenia or lymphocytopenia; as a side effect of iron therapy, has only been reported as sporadic cases in the literature and its clinical significance in relation to infection has not been studied (8). Leukopenia can be defined as low count of circulating white blood cells (WBC) which can be at the expense of neutrophils, lymphocytes, or both. Leukopenia comes from various causes and usually needs holistic approach. However, in a meta-analysis of randomized clinical trials, i.v. iron therapy was associated with a significant increase in risk of infection (relative risk 1.33; 95% confidence interval 1.10 to 1.64) compared with oral or without iron supplementation (9).

The aims of present study was to measure the prevalence of leukopenia, neutropenia or lymphocytopenia, as a side effect of IV iron therapy in a large cohort of females with IDA and find out any association between leukocyte count and occurrence of infection.

Patients and Methods

We retrospectively reviewed the electronic medical records of patients attending to the Haematology Clinic of Hamad Medical Corporation (HMC), Doha (Qatar), for IDA and treated with intravenous iron therapy for over 2 years (from January 2017 to January 2019).

1.567 adult females (mean age: 29.5 years, range: 14-48 years) with IDA who received i.v. iron therapy were included in the study. Anemia due to other causes and conditions (including other medications) that may alter white blood cell counts (WBCs) were excluded. Age, ethnicity, body mass index (BMI), complete blood count and iron studies data were collected using electronic health records (Cerner) before and after treatment with i.v. iron therapy. Each patient received from 500 to 2.000 mg of Ferinject® (ferric carboxymaltose). A cumulative iron dose of 500 mg was given to patients with body weight < 35 kg and for patients with body weight more than or equal 35 kg and less than 70 kg, with Hb level less than 10 g/dL, the total dose did not exceed 1.500 mg and for those with Hb level more than or equal 10 g/dL the total dose did not exceed 1.000 mg. For patients with body weight above or equal 70 kg, with Hb level less than 10 g/dL, a total dose of 2.000 mg /dL was given while for those with a Hb level more than or equal 10 g /dL a total dose of 1.500 mg was not exceeded.

Data about concomitant infection at the time of IDA, during or after i.v. iron therapy, the use of antibiotics and infection site related complications were collected.

Leukopenia was defined as WBCs count less than 4.000/μL, neutropenia was defined as absolute neutrophil count (ANC) less than 1.500/μL and lymphocytopenia as lymphocytes count less than 1.000/μL.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Paired t test was used to compare data for patients before versus after IV therapy when the data were normally distributed, and Mann-Whitney test was used when the data were not normally distributed. Significance was accepted when P value was < 0.05.

Results

After 8 weeks of i.v. iron therapy for IDA, Hb and serum ferritin concentrations significantly increased from 8.8 to 11.4 g/dL and from 22 to 159 μg/L,

respectively (P: < 0.01). On the other hand, platelet and ANC counts decreased significantly after i.v. iron therapy (Table 1) .

After iron therapy, 30 patients (1.9 %; mean age: 32.6 years) out of 1.567 patients with IDA, developed leukopenia,15 patients (0.95%) developed neutropenia and 12 patients (0.76 %) had lymphocytopenia. All had normal values before treatment.

Table 2 illustrates the lab data of the 30 patients who had significant leukopenia after i.v. iron therapy. Their Hb, and serum ferritin levels improved significantly (P: <0.01), but their platelets count decreased.

Table 3 shows the lab data of the 30 patients who had significant lymphocytopenia after i.v. iron therapy. Their Hb, ANC count and serum ferritin level improved significantly (P: <0.01), but their platelets count decreased.

Only 2 patients with neutropenia (6.6%) had infection during the period of iron therapy. One had upper respiratory tract infection and the other had urinary tract infection. The latter was treated with antibiotics. No other patients had recorded infection.

The regression study analysis showed a significant correlation between total serum iron level and Hb and MCV (P: < 0.05). No correlation was observed between total serum iron level and ANC or lymphocyte count (Table 4).

Table 1. Blood parameters in 1.567 females (mean age: 29.5 years, range: 14-48 years) with IDA before and after 8 weeks of iron therapy given i.v.

Variables	WBC	Hb	MCV	pltS	ANC	Lymph	Fe	TSAT	TIBC	TRF	SF
BEFORE iron i.V . therapy	10^9 /L	g/dl	**fL**	10^9 /L	10^9 /L	10^9 /L	µmol/L	%	µg/dL	µmol/L	µg/L
mean	**4.7***	**8.8**	**67.9**	**304.2**	**2.5***	**1.5**	**10.4**	**19.6**	**70.8***	**13.5***	**22.0**
SD	**0.78**	**1.5**	**10.1**	**63.8**	**0.9**	**0.4**	**17.5**	**26.9**	**22.2**	**30.8**	**65.2**
After iron i.V. therapy											
Mean	**3.5**	**11.4***	**79***	**257.6***	**1.67**	**1.4**	**12.0**	**32.7***	**45.1**	**6.8**	**159***
SD	**0.2**	**1.4**	**7.5**	**66.6**	**0.4**	**0.3**	**3.9**	**20.2**	**21.8**	**8.9**	**70.0**

Abbreviations: **WBC:** White Blood Cell Count; **Hb**: Hemoglobin; **MCV:** Mean Corpuscular Volume; **PLTs:** Platelets count; **ANC:** Absolute Neutrophil Count; **Lymph:** Lymphocytes; **Fe:** Total Iron; **TSAT:** transferrin saturation**;TIBC:** Total Iron Binding Capacity**; TRF:** Transferrin**; SF:** Serum ferritin; * **P value** : <0.05 after vs before iron therapy given i.v.

Table 2. Blood parameters in 30 females (mean age: 32.6 years) with IDA who developed neutropenia after i.v. iron therapy

Variables	WBC	Hb	MCV	pltS	ANC	Lymph	Fe	TSAT	TIBC	TRF	SF
Units	10^9 /L	g/dl	**fL**	10^9 /L	10^9 /L	10^9 /L	µmol/L	%	µg/dL	µmol/L	µg/L
BEFORE iron i.V . therapy											
	5.1*	**9.5**	**69**	**339***	**2.4***	**1.9**	**7.2**	**16.1**	**76.5***	**3.2**	**20.3**
	1.3	**1.3**	**12**	**98.7**	**1.1**	**0.4**	**7.0**	**20.4**	**9.0**	**0.5**	**38.7**
After iron i.V. therapy											
	3.7	**11.8***	**81.9***	**295.9**	**1.2**	**1.9**	**14.9***	**29.5***	**58.7**	**6.0***	**126.8***
	0.5	**1.0**	**8.7**	**66.2**	**0.2**	**0.5**	**5.8**	**12.6**	**9.8**	**8.9**	**47.6**

Abbreviations: **WBC:** White Blood Cell Count; **Hb**: Hemoglobin; **MCV:** Mean Corpuscular Volume ;**PLTs:** Platelets count; **ANC:** Absolute Neutrophil Count; **Lymph:** Lymphocytes; **Fe:** Total Iron; **TSAT:** transferrin saturation**;TIBC:** Total Iron Binding Capacity**; TRF:** Transferrin**; SF:** Serum ferritin; * **P value :** <0.05 after vs before iron therapy given i.v.

Table 3. Blood parameters in 30 females with IDA who developed lymphocytopenia after iron therapy given i.v.

Variables	WBC	Hb	MCV	PLTs	ANC	Lymph
Units	10^9 /L	g/dl	fl	10^9 /L	10^9 /L	10^9 /L
Before IRON I.V. therapy						
Mean	**5.25**	**9.48**	**74.31**	**310.4***	**3.05**	**1.7***
SD	**1.28**	**1.85**	**8.35**	**90.37**	**1.17**	**0.41**
After IRON I.V. therapy						
Mean	**7.22**	**11.5***	**80.2***	**223.75**	**6.14***	**0.65**
SD	**4.08**	**1.50**	**5.77**	**61.41**	**3.93**	**0.19**

Abbreviations: **WBC:** White Blood Cell Count; **Hb**: Hemoglobin; **MCV:** Mean Corpuscular Volume ; **PLTs:** Platelets count; **ANC:** Absolute Neutrophil Count; ; **Lymph:** Lymphocytes; * **P value :** <0.05 after vs before iron therapy given i.v.

Discussion

Leukocytopenia is defined as low count of circulating WBCs. This can be caused by low neutrophils count, low lymphocytes count, other WBCs components or combined. Neutropenia can be primary idiopathic or secondary to many conditions including viral infections, hematological diseases, thyroid disorders, drug related or autoimmune diseases (10). Lymphopenia has a broad variety of causes, most importantly are viral infections, hematological disorders and corticosteroids therapy (11,12). Iron deficiency has been proposed to be infrequently associated with neutropenia and lymphopenia when other causes are ruled out (13-15).

Although parenteral iron replacement has a relatively high safety profile, previous case reports suggested a link between iron therapy and impaired production of cell lineages including thrombocytes and leukocytes. The burden of leukopenia/neutropenia/lymphopenia as a consequent of iron therapy has not been well addressed in the literature. One review of 11 case reports and a case series described that thrombocytopenia can be induced by iron replacement (ferrous sulphate) (16). The authors explained their finding based on several effects of iron on the primary hematopoietic cells and stromal cell lines, such as influence on common progenitors, effects on cytokines, and thrombopoietic effect of erythropoietin, which is directly affected by iron levels (16).

Brito-Babapulle et al. (17) reported a case of fatal bone marrow suppression linked to ferric carboxymaltose therapy in a patient with IDA. That case started as amegakaryocytic thrombocytopenia and erythroid cell aplasia which was followed by a drop in neutrophils count. Another case report described the occurrence of neutropenia in a man after oral iron therapy that was transient and improved 1 month after stopping iron tablets (18).

In our study the incidence of leukopenia, neutropenia and lymphopenia associated with parental iron therapy was 1.9%, 0.95%, and 0.76%, respectively, in a large cohort of females treated with intravenous iron for IDA.

Table 4. Correlation between different variables

	WBC	Hb	MCV	PLTs	ANC	Lymph	Total iron level
WBC	**1.00**						
Hb	**0.09**	**1.00**					
MCV	**0.01**	**0.59**	**1.00**				
Platelets	**0.08**	**-0.24**	**-0.33**	**1.00**			
ANC	**0.93**	**0.03**	**0.00**	**0.01**	**1.00**		
Lymphocytes	**0.13**	**0.09**	**0.01**	**0.16**	**-0.17**	**1.00**	
Total iron level	**0.26**	**0.32***	**0.31***	**-0.14**	**0.20**	**-0.04**	**1.00**

Abbreviations: **WBC:** White Blood Cell Count; **Hb**: Hemoglobin; **MCV:** Mean Corpuscular Volume ; **PLTs:** Platelets count; **ANC:** Absolute Neutrophil Count; **Lymph:** Lymphocytes; **Fe:** Total Iron; * **P value :** <0.05.

Iron is required for the oxidative response of neutrophils to allow the production of reactive oxygen species (ROS). However, neutrophil function may be severely altered in conditions of iron overload, as observed in chronically transfused patients. Therefore, a tight regulation of neutrophil iron homeostasis seems to be critical for avoiding iron toxicity.

In animal models, it was found that iron-dependent increase of hepatic hepcidin resulted in neutrophil intracellular iron trapping and consecutive defects in oxidative burst activity. Moreover, systemic iron overload has been correlated with a surprising neutrophil priming and resulted in a more powerful oxidative burst (19).

Excessive iron may impair haematopoiesis, although the mechanism of this deleterious effect is not entirely known. In vitro tests showed that commonly available intravenous iron formulations have differing capacities to saturate transferrin directly: iron gluconate > iron sucrose > iron dextran. Intravenous iron treatment produces oxidative stress, as demonstrated by increases in plasma levels of lipid peroxidation products (malondialdehyde), at a point that is much earlier than the time to peak concentration of catalytically active iron, suggesting a direct effect of iron sucrose on oxidative stress (16).

In animal models, iron overload was found to have a negative impact on the hematopoietic system through the accumulation of ROS and its effect on adhesion molecules and cytokine production. It was suggested that ferrous ammonium sulfate can mediate cell apoptosis and cause growth arrest in immature cells (17). One study found that ferrous ammonium sulphate (FeAS), induced growth arrest and apoptosis in immature hematopoietic cells, which was mediated via ROS activation of Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) pathways (17).

Free iron has been shown to potentiate bacterial growth in vitro. In addition, it has been postulated that intravenous iron might promote infection thought its immune activating effect. It has been shown that iron sucrose can induce phenotypical and functional monocytic alterations and have a higher potential to modulate monocyte differentiation to macrophages and mature dendritic cells than more stable preparations (18,19).

In our large cohort of patients with IDA and those with leukopenia, there was no significant association with infections, with only 2 infections reported in 1.567 females who received i.v. iron therapy. Clinical evidence on the association between i.v. iron therapy and infection however has been inconclusive and conflicting. In support to our findings, no increase in infection observed with i.v. iron therapy in patients undergoing dialysis or in patients after surgery or in a mouse model of critical care anaemia (8). Another meta-analysis concluded that there was no increased risk of infections with the use of i.v. iron (20).

On the other hand, a systematic review and meta-analysis of randomized clinical trials suggested an increased risk of infection (relative risk 1.33, 95% confidence interval 1.10 to 1.64) compared with oral or no iron supplementation. However, these findings were subjected to bias as infection was not a predefined endpoint in many of the trials and patients had renal disorders. They could also not detect a dose–response association between iron and risk of infection (8). In addition, Agarwal et al. (21) undertook a randomized clinical trial (RCT) that assigned no dialysis-dependent chronic kidney disease (NDD-CKD) patients with IDA to either oral iron (69 patients) or i.v. iron sucrose (67 patients). They found an increase in serious adverse events (SAEs) because of infections in patients receiving i.v. iron versus those in the oral iron group (the adjusted RR ratio was 2.12, p: < 0.006) (21).

This discrepancy between these studies might be explained by the variability of free iron concentrations associated with different i.v. iron preparations (8). Given the ongoing uncertainty regarding the risk of infection, identifying and incorporating recent data to evaluate the safety data for i.v. iron on the risk of infection across all clinical settings is of paramount importance. A better understanding of the characterisation of infection in patients receiving i.v. iron therapy will help inform the design of subsequent trials in particular groups of patients (e.g, critically ill, emergency surgery) in whom the risk of infection is of clinical concern.

Conclusion

Leukopenia in the form of neutropenia or lymphocytopenia may infrequently occur as a side effect

of i.v. iron therapy, However, its clinical significance appeared to be limited. RCT trials are still required and should include well defined infection endpoints. Intravenous iron preparations that produce low circulating free iron are preferable (22).

Ethics approval: Ethical approval for the study was obtained from the institutional review board (IRB) at the Medical Research Center (MRC), Hamad Medical Corporation, Doha, Qatar (MRC-01-20-142).

Competing interests: The authors declare that they have no competing interests.

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