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Long-Term Intravenous Iron Therapy and Morbidity in Hemodialysis Patients

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ABSTRACT

Objectives: *The aim of this study was to describe long-term intravenous iron therapy-associated morbidity in hemodialysis patients from a single Hemodialysis Center.*

Materials and methods: *We conducted an observational retrospective cohort study from 01 January to 31 December 2015. Two hundred and twenty prevalent patients on maintenance hemodialysis therapy for at least 12 months (mean age 53±13 years, 56% males, median hemodialysis vintage 5 (1-26) years) were included. Diabetic nephropathy as primary kidney disease, pregnancy and incomplete data records regarding study aims were exclusion criteria. We compared the frequency, duration and causes of hospitalizations in iron sucrose-treated versus gender and age-matched iron non-treated patients. Differences between groups were assessed using Chi-square and Kruskal-Wallis H tests. A* p *value <0.05 was considered statistically significant.*

Results: *From the entire cohort, 68% were iron-treated. One in five patients were treated with higher doses (400 mg monthly), and lower doses were used (100-200 mg monthly) in 80% of patients. There were no differences regarding the rates of admission between the two groups (56/100 patient-years in the iron sucrose-treated* vs. *50/100 patient-years in the iron-untreated group,* p*=0.1). Still, the hospitalization rate significantly increased with the administered iron dose (0.4* vs. *0.7* vs. *0.8/100 patient-years for 100 mg* vs. *200 mg* vs. *400 mg monthly, respectively, p=0.006). Hospitalization rates due to infectious and cardiovascular diseases were similar for both groups (12/100 patient-years vs 5.7/100 patient-years, p=0.3 and 11.3/100 patient-years* vs. *4.3/100 patient-years,* p*=0.2, respectively).*

Conclusions: *Higher doses of intravenous iron sucrose appear to be associated with an elevated risk of hospitalization. Nonetheless, long-term intravenous iron therapy seems to have a limited influence in terms of specific cause of morbidity in non-diabetic hemodialysis patients.*

Keywords: intravenous iron therapy, anemia, hemodialysis, morbidity.

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INTRODUCTION

Anemia is highly prevalent in hemodialysis patients and in up to two thirds of them it is uncontrolled, despite use of erythropoietin stimulating agents (ESA) and iron therapy (1).

Altered iron homeostasis is one of the most significant pathogenic mechanism of anemia in CKD. Particularly in hemodialysis patients, absolute iron deficiency results from poor iron absorption (2) and iron losses (in some cases up to 4-5 g annually) (3), favored by bleeding events, blood tests or blood lost in dialysis membranes and lines. Moreover, treatment with ESA supplementary increases the iron needs by an increase in erythropoiesis.

In attempt to correct iron deficiency, improve ESA responsiveness and prevent the adverse reactions of higher ESA doses, intravenous iron is extensively used and commonly high doses are needed. Although with the new generation intravenous iron formulation the acute adverse reactions are notably reduced, long-term effects are still questionable. Experimental data seems to support the association of iron therapy with the risk of infection (4), nephrotoxicity (5) and cardiovascular risk mediated by the oxidative stress (6). Still, data from observational studies on humans regarding effects of iron therapy on morbidity and mortality are conflicting.

Therefore, in this study we aimed to describe the impact of long-term intravenous iron therapy on the clinical outcome (the frequency, duration and causes of hospitalizations) of hemodialysis patients from a single Hemodialysis Center.

MATERIALS AND METHODS

Study design

This observational retrospective cohort study was conducted at "Dr. Carol Davila" Teaching Hospital of Nephrology, Bucharest, Romania, with the approval of the local Ethics Committee.

Study participants

All patients aged > 18 years who were on maintenance hemodialysis therapy and were admitted in our hospital from 01 January to 31 December 2015 were screened. Those with hemodialysis vintage of at least 12 months were included. Diabetic nephropathy as primary kidney disease (because there were only three cases available in the study period), pregnancy and subjects with incomplete data regarding study aims, were excluded.

For every patient, hemodialysis sessions were performed three times weekly, with duration of 4.5 hours per session, using bicarbonate-based dialysate, standard heparinization and polysulphone/cellulose triacetate dialyzers.

Data sources

Data was recorded from the Electronic Database of our hospital, discharge abstracts (admissions in other hospitals) and hemodialysis patient's files.

Study parameters

1. Demographic and medical characteristics: age, gender, primary kidney disease, hemodialysis vintage.
2. Outcomes measures: number of hospitalizations, total number of days of hospitalization, length of stay *per* admission, main admission diagnoses.
3. Intravenous iron therapy characteristics: monthly dose.

Intravenous iron therapy characteristics were as follows:

- Drug: iron sucrose (Venofer® 20 mg iron/mL, 1 vial = 100 mg)
- Route: infusion diluted with 100 mL 0.9% sodium chloride (1 mg/mL concentration) during the last hour of hemodialysis session *via* the venous line of the extracorporeal circuit.
- Dosage: 100 mg iron sucrose at 1-4 weeks, in order to achieve and maintain the target for renal anemia treatment according to the Romanian Society of Nephrology Guidelines (7).
- Duration: at least 12 months.

Study aims

To describe morbidity in terms of number of hospitalizations, total number of days of hospitalization, length of stay per admission, main admission diagnoses, comparing iron sucrose-treated *vs* iron-untreated groups of hemodialysis patients.

Statistical analysis

All statistical analysis were performed using IBM® SPSS® Version 23 and Microsoft Office Professional Excel®2003.

Normally distributed data were expressed as mean±standard deviation (SD) and non-normally distributed data as median and interquartile range. Categorical variables were described as percentages. Incidence of hospitalizations was calculated as new cases/(population x timeframe).

Differences between groups were assessed using Chi-square and Kruskal-Wallis H tests. A p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the entire cohort

A total of 220 patients with a mean age of 53±13 years were enrolled, with 56% of all subjects being males. The median hemodialysis vintage was 5 (1-26) years.

Two thirds of patients were iron-treated. In almost a half, low doses of 100 mg monthly were used. Only 20% of patients received higher doses (400 mg monthly). Similar percentages of ESA use were noted between groups (Table 1).

Age, gender, primary kidney disease and dialysis vintage distribution were comparable between the two groups (Table 1).

Number of hospital admissions

A total of 119 hospitalizations, with a rate of incidence of 54/100 patient-years, was noted. Eighty-four admissions were recorded in the iron-treated group (56/100 patient-years), in contrast with 35 in the iron-untreated group (50/100 patient-years), $p=0.1$.

No differences were observed regarding the number of hospital admission (no admission, 1, 2 or 3-5 admissions) between the two groups (Figure 1).

Days of hospitalization

The length of stay per admission and the total days of hospitalization was similar, irrespective of iron therapy (Table 2).

Characteristics	Iron-treated group n=150	Iron-untreated group n=70	p
Age, year	53 (27-86)	53 (22-81)	0.8
Male, n (%)	86 (57)	38 (54)	0.7
Primary cause of ESKD (%)			
Glomerular nephropathy	53	59	0.6
TIN	22	26	0.3
Polycystic kidney disease	12	10	0.8
Vascular nephropathy	11	4	0.1
Unknown	3	1	0.5
HD vintage, year	4 (1-24)	6 (1-26)	0.2
Iron therapy, monthly (%)			
100 mg	46		
200 mg	36		
400 mg	18		
ESA therapy n, (%)	102(68)	45(65)	0.6
Data are expressed as median (interquartile range) or percentages. ESKD- end stage kidney disease; HD- hemodialysis; TIN- tubulointerstitial nephropathies; ESA- erythropoiesis stimulating agents.			

TABLE 1. Characteristics of patients according to the presence of iron therapy

TABLE 2. The requirements of hospital admission during the study period

	Iron-treated n=150	Iron-untreated n=70	p
Patients with at least one hospitalization	34%	34%	0.3
Median length of stay per admission (days)	7 (1-92)	6 (1-50)	0.2
Total number of days spent in hospital	401	604	0.1

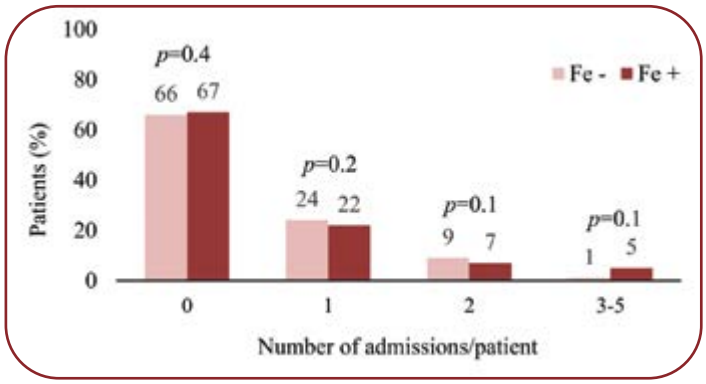

FIGURE 1. Percentages of patients by number of hospital admissions. Fe: iron untreated, Fe+: iron treated

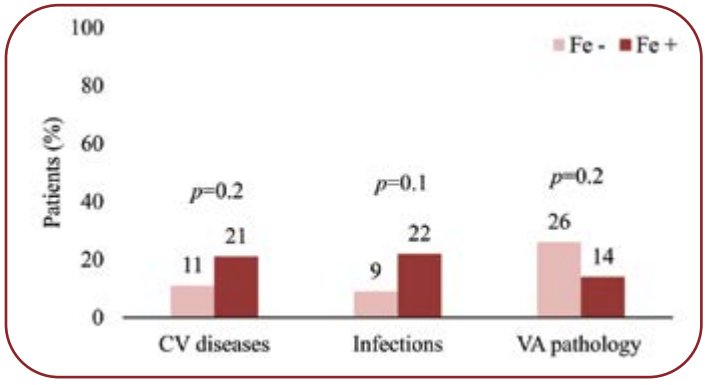

FIGURE 2. Main causes of hospital admission. Fe: iron untreated, Fe+: iron treated, CV: cardiovascular, VA: vascular access

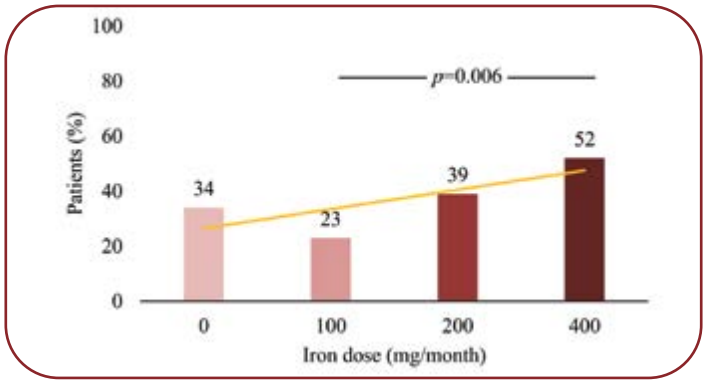

FIGURE 3. Percentage of admitted patients based on the iron dose

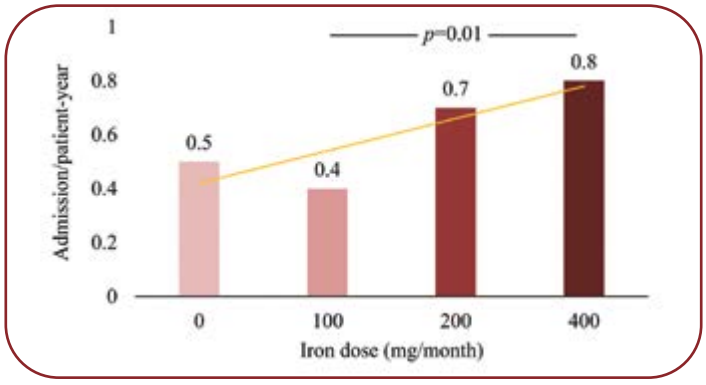

FIGURE 4. Hospitalization rate based on iron dose

Causes of hospital admissions

The most frequent causes for hospital admission in both groups were infections, cardiovascular disease and complication of the vascular access for dialysis (other than infections) (Figure 2).

Hospitalization rates due to infectious and cardiovascular diseases were similar for both groups (12/100 patient-years *vs* 5.7/100 patient-years, $p=0.3$ and 11.3/100 patient-years *vs* 4.3/100 patient-years, $p=0.2$, respectively).

Relationship between iron dosing and hospitalization requirements

The percentage of patients who required at least one hospital admission as well as the hospitalization rate significantly increased with the administered iron dose (Figure 3, Figure 4).

DISCUSSIONS

To date, there are conflicting results regarding long-term effect of intravenous iron therapy in CKD patients (with or without renal replacement therapy). In this observational retrospective cohort study from a single Hemodialysis Center, we found that hospitalization rate significantly increased with the dose of administered iron sucrose.

Anemia is frequent in CKD and its prevalence increases as the kidney function declines. Since alteration in iron homeostasis has a major contribution to renal anemia, iron therapy is frequently needed. In hemodialysis patients, intravenous route is the preferred choice, avoiding additional venous punctures and offering superior efficacy in increasing hemoglobin level (8).

Still, experimental studies suggest that parenteral iron has unfavorable effects. This is because of labile iron that is released to different extents, by different intravenous iron formulations.

Therefore, *in vitro*, iron overload can reduce intracellular killing capacity of polymorphonuclears (PMN) (9). Moreover, when phagocytic functions of PMN isolated from peritoneal dialysis patients were analyzed, *in vitro*, as a response to 300 mg of iron sucrose or placebo, intracellular bactericidal capacity was found to be decreased (10). From the clinical perspective, iron overload was an independent risk factor for bacterial infections in a multicenter prospective study on hemodialysis patients (11). In contrast, data from another prospective study of almost

1000 hemodialysis patients revealed that neither parenteral iron nor iron overload, increased the risk of infection (12). Consistent with that, in our cohort hospitalization rates due to infectious diseases were similar between iron sucrose-treated and iron-untreated patients.

From another perspective, *in vitro*, iron sucrose increased oxidative stress (6), exerted a greater inhibitory effect on endothelial proliferation in comparison with iron dextran (13) and induced apoptosis in cultures of human endothelial cells, in a dose-dependent manner (14). In line with these data, in a recent prospective crossover study on non-dialysis CKD patients we found that a single dose of iron sucrose (200 mg) induced endothelial dysfunction (measured by flow mediated vasodilatation) (15). On the contrary, a safe profile regarding endothelial function was found by Ozkurt et al when administrated repeated doses of 200 mg of iron sucrose (up to 1 000 mg) to 15 hemodialysis patients *vs.* 16 subjects with normal function and iron deficiency (16). However, in a study on 78 hemodialysis patients, higher doses of iron sucrose were associated with elevated cardiac troponin T, which was a prognostic of survival indicator in this group of patients (17). In our patients, either iron sucrose-treated or not, hospitalization rates due to cardiovascular diseases were comparable. Nonetheless, in one of the two recent studies in CKD non-dialysis patients that assessed also long-term safety of intravenous iron (REVOKE), higher cardiovascular serious adverse events resulting in hospitalization were the reason for early termination of the study (18).

Sixty-eight percent of our entire cohort were iron-treated. Lower doses of iron sucrose were mostly used (100-200 mg iron sucrose monthly), with only 20% of them received higher doses (400 mg iron sucrose monthly). There were no differences regarding the rates of admission between the two groups. Still, the hospitalization rate significantly increased with the administered iron dose. In accord with our data, in a large cohort, but with a half of our follow-up period, Feldman et al found no association with the rate of hospitalization when lower *vs.* higher doses of iron were used (19). Moreover, treatment with lower doses (<200 mg monthly) were associated with higher survival chances as compared with larger doses (>455 mg monthly) (20). Conversely, data published from a representative cohort of hemodialysis patients followed up to 23 months indicated that higher cumulative dose of intravenous iron (> 2 100 mg *vs.* 0-900 mg over six months) was not associated with all-cause, cardiovascular or infectious hospitalization (21). Furthermore, results published from the most recent randomized controlled trial (PIVOTAL) in which 2 141 hemodialysis patients were assigned to receive either high-dose iron sucrose (400 mg monthly, unless ferritin > 700 µ/L or transferrin saturation ≥ 40%), or low-dose iron sucrose (0-400 mg monthly) revealed that the proactive fashion of iron therapy reduced cardiovascular events and deaths, and did not increase infections (22).

The limitations of our study consist in its retrospective nature, the relatively small number of patients, and the lack of laboratory data (especially in regard with inflammatory and nutritional status) and information on co-morbidities. Still, it has a follow-up of 12 months. Another strength is that subjects with diabetic nephropathy were excluded, and this could eliminate the burden of cases of diabetes with complications, that are associated with a higher risk of infections and cardiovascular events.

CONCLUSIONS

Long-term intravenous iron therapy seems to have a limited influence on the overall and specific cause morbidity of non-diabetic hemodialysis patients.

However, higher intravenous iron sucrose doses appear to be associated with an elevated risk of hospitalization. Because of conflicting results of studies over the time, even if prescribing lower doses (100-200 mg iron sucrose/month) seems to be a safe approach for anemia treatment in chronic hemodialysis patients, caution is warranted when larger dosage is needed. ❑

Conflicts of interest: none declared.
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