JESNT

The Journal of Egyptian Society of Nephrology & Transplantation

Comparing high-dose and low-dose intravenous iron therapy in hemodialysis patients in Benha city, Egypt

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Background
Since the introduction of erythropoiesis-stimulating agents for the management of anemia in patients with chronic kidney disease (CKD), intravenous (i.v.) iron has been universally used, especially with hemodialysis (HD) patients, as their average daily losses of iron typically exceed the oral absorption of iron. The maintenance i.v. iron regimens vary widely between countries and even among HD centers of the same country.
Aim
The aim of this study was to find out if high-dose i.v. iron will be superior to low-dose i.v. iron for treating anemia in HD patients.
Patients and methods
This study was carried out at HD units of Benha University Hospitals and Benha Teaching Hospital from March 2019 till September 2019. It was carried out on 100 patients with CKD stage V on HD, who were subdivided into two groups.
Group ?: 50 patients with CKD stage V on HD who were eligible for low-dose i.v. iron therapy.
Group Π: 50 patients with CKD stage V on HD who were eligible for high-dose i.v. iron therapy.
Results
There was an improvement of hemoglobin, serum ferritin, and transferrin saturation after treatment with low-dose and high-dose iron therapy. However, the high-dose iron therapy was associated with a high statistically significant improvement compared with low-dose iron therapy.
Conclusion
High-dose i.v. iron was superior to low-dose i.v. iron for treating anemia in HD patients.

Keywords:
anemia, hemodialysis, high-dose iron, low-dose iron

Introduction

Independent of erythropoiesis-stimulating agent (ESA) use, there is a strong evidence that hemodialysis (HD) patients are at high risk for cardiovascular events, and patients complicated with heart failure (HF) show improvements in their symptoms and left ventricular systolic function with intravenous (i.v.) iron repletion [1]. On the contrary, there are concerns about the potential safety of high doses of i.v. iron. The Normal Hematocrit Cardiac Trial was halted prematurely because the analysis confirmed that the higher hematocrit (normalization of hematocrit, i.e. 42%) was associated with an ~30% increase in the risk of death or nonfatal myocardial infarction [2]. Moreover, the Correction of Hemoglobin and Outcomes in Renal Insufficiency trial supported an association between higher ESA doses and the primary composite endpoint of death, HF, hospitalization, stroke, or myocardial infarction [3].

These concerns were thought to be owing to the potential for increased oxidative stress owing to hydroxyl radical generation observed in some studies, which could exacerbate cardiovascular toxicity. Similarly, there is laboratory evidence that i.v. iron can enhance bacterial proliferation and reduce neutrophil killing functions, increasing the risk of infection [4,5]. Observational data on cardiovascular outcomes and infection associated with high-dose i.v. iron use are still conflicting and confusing [6].

This study was designed to compare the effects of a high-dose i.v. iron regimen and low-dose i.v. iron regimen among HD patients.

Patients and methods
Patients
This study is a randomized clinical trial and was carried out at HD units of Benha University Hospitals andBenha Teaching Hospital from March 2019 till September 2019. Ethical approval was obtained by the medical ethical committee of benha faculty of medicine and written knowledgeable consent with taken from registered patients, with chronic kidney disease (CKD) stage V on HD were divided into two groups:

(1) Group ? included 50 patients with CKD stage V on HD who were eligible for the low-dose i.v. iron therapy.
(2) Group Π included 50 patients with CKD stage V on HD who were eligible for the high-dose i.v. iron therapy.

Inclusion criteria
The following were the inclusion criteria:

(1) Age more than 18 years.
(2) Patients established on a chronic HD program for end-stage renal failure.
(3) Ferritin less than 400 µg/l.
(4) Transferrin saturation (TSAT) less than 30%.
(5) On ESA therapy.

Exclusion criteria
The following were the exclusion criteria:

(1) C-reactive protein greater than 50 mg/l.
(2) Active infection.
(3) Current active malignancy (i.e. progressive untreated cancer or current treatment with cytotoxic chemotherapy).
(4) Known HIV, active hepatitis B (i.e. hepatitis B virus DNA positive), or active hepatitis C (i.e. hepatitis B virus RNA is positive).
(5) Chronic liver disease and/or screening alanine aminotransferase or aspartate transaminase more than triple normal values.
(6) Advanced HF (i.e. NYHA class IV).
(7) Pregnancy or breastfeeding.
(8) History of acquired iron overload.
(9) Previous severe hypersensitivity reactions to i.v. iron sucrose.

Methods
In both treatment arms, patients were on a calculated dose of short-acting ESA therapy according to their body weight, which was continued throughout the study period. Monthly iron doses were determined following monthly assessments of serum ferritin and TSAT. Iron (if not withheld) was administered during the first HD sessions in the week following the monthly assessment of the iron indices.

All iron was going to be administered as an i.v. infusion of diluted iron sucrose. Patients assigned to the high-dose i.v. iron arm received a loading dose of i.v. iron sucrose 200 mg during each of the three dialysis sessions at the start of the study, and during each of the first two dialysis sessions of the week following the monthly blood tests for all subsequent months (i.e. 400 mg per month). If monthly testing demonstrated ferritin greater than 700 µg/l and/or TSAT greater than or equal to 40%, i.v. iron was withheld for the month.

Patients randomized to the reactive, low-dose i.v. iron arm received iron based on a prespecified dosing schema, which permitted the administration of iron only if patients were deemed 'iron deficient' as assessed by serum ferritin levels and TSAT. If monthly testing showed ferritin greater than 200 µg/l and TSAT greater than 20%, ferritin greater than 700 µg/l, or TSAT greater than or equal to 40%, iron was not be administered that month. Provided that TSAT was less than 40%, patients with ferritin less than 100 µg/l received iron sucrose 200 mg during the first two dialysis sessions of the week; if ferritin was 100–200 µg/l, it was administered only during the first dialysis session of the week. Patients with ferritin levels 201–700 µg/l and TSAT less than or equal to 20% received i.v. iron sucrose 100 mg during the first dialysis session of the week.

Statistical analysis
Analysis of data was done using Statistical Program for the Social Sciences version 20 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were described in the form of mean and SD. Qualitative variables were described as number and percentage. To compare parametric quantitative variables between two groups, Student's *t*-test was performed. Qualitative variables were compared using χ^2-test or Fisher's exact test when frequencies were below five. Pearson's correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, a *P* value less than 0.05 is considered significant

Results
The mean age of group I was 60.1±11.2 years, whereas the mean age of group II range was 59.9±10.5 years, and this was not statistically significant.

Males represented 60%, whereas females represented 40% of patients in group I. In group II, males were 56% and females were 44%, but this difference was not statistically significant.

Overall, 32% of group I and 28% of group IⅩ patients had diabetes, 48% of group I and 44% of group IⅩ patients had hypertension, 16% of group I and group IⅩ patients had atrial fibrillation (AF), 8% of group I and 4% of group IⅩ patients had prior stroke, and 24% of group I and 20% of group IⅩ patients had hyperlipidemia.

Descriptive data

Table 1 shows that there is no statistically significant difference between the studied groups regarding age.

Table 2 shows that there is no statistically significant difference between the studied groups regarding sex distribution.

Table 3 shows that 32% of group I and 28% of group IⅩ patients had diabetes, 48% of group I and 44% of group IⅩ had hypertension, 16% of group I and group IⅩ had AF, 8% of group I and 4% of group IⅩ had prior stroke and 24% of group I and 20% of group IⅩ had hyperlipidemia.

Serum iron (µg/dl), total iron-binding capacity (µg/dl), serum ferritin (ng/ml), and TSAT percentage were assessed. There was a high significant improvement of hemoglobin, serum ferritin, and TSAT after treatment with high-dose iron therapy (Table 4

There was a highly significant difference between high-dose and low-dose iron therapy regarding hemoglobin and iron profile after treatment (Table 4).

There was no significant difference between the studied groups regarding complications during iron therapy (Fig. 1 and Tables 5–8). This table shows that there is no significant difference between the two studied groups regarding complications.

There was more vascular thrombosis in high-dose group more than low-dose group, but it was statistically insignificant, and hospitalization was equal in both groups.

Discussion

Anemia, a common complication of end-stage renal disease, is associated with elevated morbidity, mortality, and health care costs. A primary cause of anemia in end-stage renal disease is iron deficiency, particularly among patients requiring HD [7].

I.v. iron is an effective way to supplement iron and optimize erythropoiesis. Existing randomized controlled trials showed that supplementing ESA therapy with i.v. iron increases hemoglobin production and lowers ESA requirement. Consequently, co-administration of ESAs and i.v. iron has become the primary management strategy for anemia in HD patients [8].

Bailie and colleagues reported that the percentage of i.v. iron use rose from 1999 to 2011 in most countries and varied widely by country; in Japan, it was 36%, but among the other countries, the use ranged from 70% in Australia–New Zealand to 90% in Belgium [9,10].

Reduced ESA use afforded by higher doses of iron may reduce the risk of cardiovascular events observed in the

Table 1 Age of studied groups

Age (months)	group I (n=50)	group II (n=50)	t test	P value
Mean±SD	60.1±11.2	59.9±10.5	0.065	0.948
Range	42–78	43–75		

P value is significant if <0.05.

Table 2 Sex distribution of studied groups

Sex	Group I (n=50) [n (%)]	Group II (n=50) [n (%)]	χ^2	P value
Male	30 (60.0)	28 (56.0)	0.082	0.774
Female	20 (40.0)	22 (44.0)		

Table 3 Associated diseases of the studied groups

Associated diseases	Group I (n=50) [n (%)]	Group II (n=50) [n (%)]
Diabetes	16 (32.0)	14 (28.0)
Hypertension	24 (48.0)	22(44.0)
AF	8(16.0)	8 (16.0)
Prior stroke	4 (8.0)	2(4.0)
Hyperlipidemia	12 (24.0)	10 (20.0)

Table 4 Comparison between groups before treatment as regarding iron profile and hemoglobin

	Group I (n=50)	Group II (n=50)	Statistical test	
			t test	P value
Hemoglobin (g/dl)				
Mean±SD	8.6±1.4	8.5±1.2	0.271	0.787
Range	7.2–10.2	7.2–10.7		
Serum ferritin (ng/ml)				
Mean±SD	200.9±30.8	201.1±32.1	0.022	0.982
Range	100–400	100–400		
Transferrin saturation				
Mean±SD	20.9±5.1	21.2±5.9	0.192	0.848
Range	15–30	15–30		

Figure 1
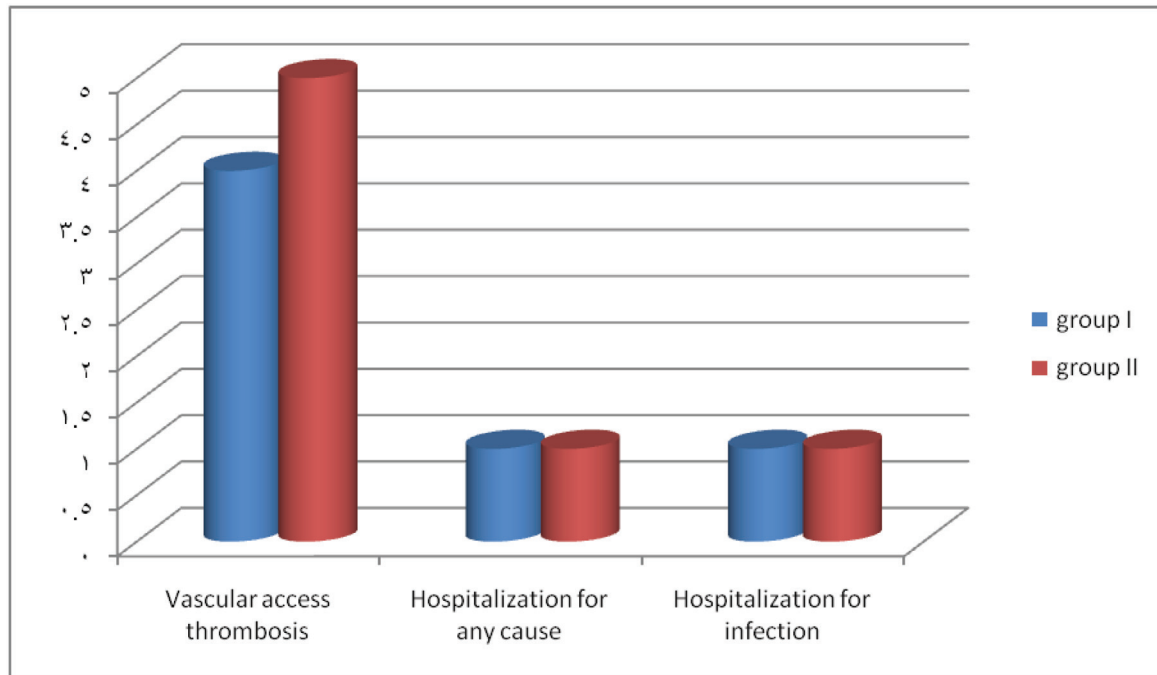
Comparison between the studied groups as regard complications during iron therapy.

Table 5 Comparison between hemoglobin and iron profile before and after treatment in group I

	Before (*n*=50)	After (*n*=50)	Statistical test	
			Paired *t* test	*P* value
Hemoglobin (g/dl)				
Mean±SD	8.6±1.4	11.4±1.1	7.86	<0.001 (HS)
Range	7.2–10.2	10.2–14		
Serum ferritin (ng/ml)				
Mean±SD	200.9±30.8	680.1±10.8	73.4	<0.001 (HS)
Range	100–400	665–700		
Transferrin saturation				
Mean±SD	20.9±5.1	32.1±2.1	10.15	<0.001 (HS)
Range	15–30	30–35		

HS, highly significant.

Table 6 Comparison between hemoglobin and iron profile before and after treatment in group II

	Before (*n*=50)	After (*n*=50)	Statistical test	
			Paired *t*-test	*P* value
Hemoglobin (g/dl)				
Mean±SD	8.5±1.2	12.9±0.9	14.6	<0.001 (HS)
Range	7.2–10.7	11–14.5		
Serum ferritin (ng/ml)				
Mean±SD	201.1±32.1	695.1±8.6	74.32	<0.001 (HS)
Range	100–400	685–700		
Transferrin saturation				
Mean±SD	21.2±5.9	34.2±2.0	10.43	<0.001 (HS)
Range	15–30	32–35		

HS, highly significant.

aforementioned trials. Independent of ESA use, dialysis patients are at high risk for cardiovascular events, and there is also strong evidence in patients with HF, documenting improvements in symptoms and in left ventricular systolic function with i.v. iron repletion [8,11].

Table 7 Comparison between hemoglobin and iron profile in both groups after treatment

	Group I (n=50)	Group II (n=50)	Statistical test	
			t test	P value
Hemoglobin (g/dl)				
Mean±SD	11.4±1.1	12.9±0.9	5.27	<0.001 (HS)
Range	10.2–14	11–14.5		
Serum ferritin (ng/ml)				
Mean±SD	680.1±10.8	695.1±8.6	5.43	<0.001 (HS)
Range	665–700	685–700		
Transferrin saturation				
Mean±SD	32.1±2.1	34.2±2.0	3.62	<0.001 (HS)
Range	30–35	32–35		

HS, highly significant.

Table 8 Complications of therapy among the studied groups

Complications	Group I (n=50) [n (%)]	Group II (n=50) [n (%)]	χ^2	P value
Vascular access thrombosis	4 (8.0)	5 (10.0)		0.983
Hospitalization for any cause	1 (2.0)	1 (2.0)	0.034	
Hospitalization for infection	1 (2.0)	1 (2.0)		

There are concerns about the potential safety of high doses of i.v. iron. These have been reviewed extensively and were the focus of a trail, Kidney Disease: Improving Global Outcomes Controversies Conference on Iron Management. These concerns include the potential for increased oxidative stress owing to hydroxyl radical generation observed in some studies, which could exacerbate cardiovascular toxicity. Similarly, there is laboratory evidence that i.v. iron can enhance bacterial proliferation and reduce neutrophil killing of bacteria, generating concerns about an increased risk of infection [9,12].

A recent meta-analysis of randomized controlled trials comparing high-dose versus low-dose i.v. iron in patients undergoing HD generated only seven studies worthy of inclusion, and all of these had limitations regarding sample size and duration of follow-up [11,13]

Thus, there has been a need for a scientifically designed, adequately powered, randomized controlled trial with sufficient duration of follow-up.

To fulfill this need, our study was designed to compare the effects of a high-dose i.v. iron regimen and low-dose i.v. iron regimen among HD patients. Our study was conducted in HD unit of Benha University Hospital and Benha Teaching Hospital. The duration of study was 6 months.

In our study, we found that there was no statistically significant difference between the studied groups regarding age and sex distribution, and this was concordant with Szczech et al. [3] who reported that there was no statistically significant difference between the studied groups regarding age and sex distribution.

Our study showed that 32% of group I and 28% of group II patients had diabetes, 48% of group I and 44% of group II patients had hypertension, 16% of group I and group II patients had AF, 8% of group I and 4% of group II patients had prior stroke, and 24% of group I and 20% of group II patients had hyperlipidemia. These findings were similar to the findings of Macdougall and colleagues who reported that ∼8% of the randomized population had a history of atrial fibrillation and one-quarter were diagnosed with hyperlipidemia. Nearly two-thirds of participants (63%) denied any history of cigarette smoking. As would be expected for a dialysis population, 73% of the cohort had hypertension. At baseline, 44% of patients had diabetes.

In our study, we found that there is no significant difference between the studied groups before treatment regarding iron profile and hemoglobin, as mean hemoglobin before treatment was 8.6 g/dl in group ? and 8.5 g/dl in group II, and this was concordant with of Szczech et al. [3] who reported that hemoglobin levels at baseline and at 3 weeks (before which subjects all received the same ESA dose) were similar between groups.

In our study, there was a highly significant improvement of hemoglobin, serum ferritin, and TSAT after treatment with low-dose iron and high-dose iron therapy, but it was more improvement in high-dose group, and it was statistically significant.

Our results are supported by a study by Toblli *et al.* [14] as they reported that at the end of the study (6 months), significant increases in the levels of hemoglobin and ferritin were observed in patients receiving high iron dose ($P<0.01$) in comparison with baseline and the control group [13] and added that absolute values and changes were similar to those observed in the original study of 40 patients.

In our study, nine patients were complicated with vascular thrombosis and four patients were hospitalized, but this was statistically insignificant between the two studied groups regarding vascular access thrombosis, hospitalization for any cause, or hospitalization for infection.

Several studies conducted by Pollak *et al.* [15] and Galic *et al.* [16] found that high serum ferritin (typically defined as >500 or 1000 ng/ml or, equivalently, µg/l) was associated with higher incidence of bacterial infection or infection-related mortality. The incidence of bacterial infection ranged from 0.34 to 0.59 infections per patient-year (in studies evaluating the rate of infection) and 0.93–61.9% (in studies evaluating the proportion with infection) in the higher serum ferritin groups, 0.09–0.18 infections per patient-year and 0–37% in the lower serum ferritin groups [17]. This could be explained by the small number of patients included in the study, and we only record the occurrence infection not the rate or proportion of infection per year, as the study duration was 6 months.

A number of reasons can explain discrepancies among studies. The main one is the big confounder of treatment indications: the sicker the patient, the more likely iron therapy is needed. Many observational studies were not longitudinal and tested the exposure to i.v. iron for a short period of time. Considering that i.v. iron is not regarded as toxic, it is unlikely that a 6-month exposure can cause significant harm on adverse end points. In this context, it is likely that patient comorbidities mostly drive the indication to i.v. iron treatment and doses and then affect patient outcome. The presence of indication bias is shown by the fact that at facility levels, iron use is associated with poor survival only in those using i.v. iron inappropriately in the patients with high hematocrit levels [18].

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