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ORIGINAL ARTICLE

Do Parenteral Iron Therapies Preserve or Deteriorate Kidney Functions? "Iron Carboxy Maltose or Iron Sucrose?"

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SUMMARY

Background: **Treatment of end stage renal disease (ESRD) is based on preserving renal functions. Since renal anemia is frequently detected, we use parenteral iron treatments in patients with chronic kidney disease (CKD). However, there need to be more precise and sufficient studies on the effect of these treatments on the rate of decrease in the glomerular filtration rate (GFR). Therefore, we conducted a study comparing the rates of change in renal function in patients who had used parenteral iron for at least five years.**
Methods: **Our study is a retrospective cohort study, and 180 patients with CKD (86 women, 94 men, mean age: 63.5 ± 11.4 years) who had been followed and treated in nephrology outpatient clinics for at least five years and met the study criteria were included in the study. Patients were divided into three groups for iron therapy: not receiving iron therapy, iron carboxy maltose (ICM), and iron sucrose (IS) parenterally. Each group consisted of 60 people. The first and last creatinine and GFR values were compared for a 5-year follow-up in each group.**
Results: **There was no significant difference between the two groups, those using and those not using iron, regarding creatinine increase and GFR decrease rate. Additionally, no significant difference was detected in the GFR decline rates of patients using ICM and IS.**
Conclusions: **This study reduces the concerns that correcting anemia through parenteral iron therapy in patients with CKD may harm renal function.**
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KEYWORDS

iron therapy, renal anemia, chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD) is a common public health problem on a global scale. The global estimated prevalence of CKD is 13.4% (11.7 - 15.1%), and patients with end-stage kidney disease (ESKD) needing renal replacement therapy is estimated between 4.902 and 7.083 million [1,2].
A wide variety of reasons causes CKD. The leading etiological factors of CKD worldwide include diabetes, hypertension, urological problems, chronic glomerulonephritis, chronic use of anti-inflammatory medication, autoimmune diseases, polycystic kidney disease, Alport

disease, congenital malformations, and prolonged acute renal disease [3-9].

Anemia is a common complication in patients diagnosed with CKD [10]. The leading causes include decreased erythropoietin production, impaired erythropoiesis and iron deficiency, and inability to use existing stores due to reduced kidney function. Additionally, chronic inflammation that occurs in chronic kidney failure also contributes to anemia.

Oral or intravenous iron preparations are preferred for treating chronic anemia in patients with chronic renal failure [11-13].

Preserving renal functions in patients with CKD is of great importance for patients and economically, as it will reduce the need for renal replacement therapies. We wanted to examine the effect of parenteral iron therapy on the progression of kidney disease, that is, intravenous iron treatments' effect on the decline in glomerular filtration rate (GFR) in pre-dialysis patients with chronic kidney disease (CKD).

There are only a limited number of studies on this subject and conflicting results to investigate the effect of intravenous iron treatments on the rate of GFR decline in patients with CKD; we planned this study because it is essential for both anemia management and preservation of kidney functions.

MATERIALS AND METHODS

The data of renal failure patients admitted to the nephrology outpatient clinic and who received parenteral iron therapy were examined. Among the patients who were followed and treated for at least five years between January 2008 and June 2023, 180 patients with CKD, who were between the ages of 20 - 80 years at the time of first admission and who did not receive hemodialysis and met the study criteria (86 women, 94 men, mean age: 63.5 ± 11.4 years), were included in the study.

According to the NKF-DOQI classification, there are five stages of chronic renal failure. Kidney damage and evidence of damage begins below 90 mL/minute, that is, from stage 2. Therefore, patients with GFR < 90 mL/minute were included in this study.

On the other hand, GFR < 15 mL/minute = stage 5 = end-stage renal disease and is divided into pre-dialysis and dialysis stages. We included pre-dialysis patients in the study and excluded dialysis patients.

In the biochemistry laboratory of the hospital where this study was conducted, GFR is automatically calculated by using the CKD-EPI formula according to the creatinine value in patients over the age of 18.

CKD patients are checked periodically, approximately every three months. During these visits, hemoglobin, ferritin, serum iron, and total iron binding capacity are measured. According to the guidelines, the hemoglobin target value is given as 12 - 13 gr/dL. If hgb is < 12 gr/dL and ferritin is < 100 ng/mL or transferrin saturation (TSAT) is found to be < 20%, parenteral iron treatment is recommended for CKD patients, since it corrects anemia quickly and improves quality of life.

Iron treatments are applied to patients when required by the treatment criteria recommended by the guidelines, with the results monitored.

Patients are divided into three groups for receiving iron therapy: not receiving iron therapy, iron carboxy maltose (ICM), or iron sucrose (IS) parenterally. Each group consists of 60 people. The first and last creatinine and GFR values were compared for a 5-year follow-up in each group.

Criteria for inclusion of patients in the study:

1/ being over 20 years old
2/ being under 80 years old
3/ not having cancer, solid or hematological malignancy
4/ having chronic kidney failure
5/ not undergoing hemodialysis
6/ selecting patients of similar age and gender in each group
7/ GFR level should be similar in each group

Criteria for exclusion of patients from the study:

1/ being under the age of 20/being over the age of 80
2/ being on hemodialysis
3/ pregnancy
4/ having GI bleeding or polycystic kidney disease

Our study is a retrospective cohort study. When the sample size was calculated with the calculation formula in the analysis of qualitative data; the standard effect size was determined as 0.6, with a 5% margin of error and 80% power. Therefore, it was deemed sufficient to include n = 60 cases in each group. Patient and patient information were provided from patient files, hospital information management system, and the Medula system of the Ministry of Health.

Mean, standard deviation, median, lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov-Smirnov test. In the analysis of quantitative independent data, ANOVA (Tukey test), independent sample *t*-test, Mann-Whitney U Test, and Kruskal-Wallis test were used, the chi-squared test was used in the analysis of qualitative independent data, and Fischer test was used when chi-squared test conditions were not met. SPSS 28.0 program was used in the analyses.

The study was conducted in full compliance with the principles of the Declaration of Helsinki and the laws and regulations of the country where the research was conducted. The study strictly adhered to the principles outlined in Good Clinical Practice. Patients' names were kept confidential, and individuals' identities were protected from unauthorized parties. Before any changes to the protocol were implemented, approval was obtained from the local ethics committee for any regulations that may affect the safety of patients or the conduct of the study (decision No.: 179, date: 07-07-2023, University of Heath Science, Research and Training Hospital - Ethics Committee).

Table 1. General characteristics of the patients.

		Minimum-maximum	Median	Mean ± standard deviation	Number of patients	Percentage of patients
Age (year)		26.0 - 79.0	66.0	63.5 ± 11.4		
Gender	female				86	47.8
	male				94	52.2
Duration (year)		1.0 - 18.0	5.0	5.8 ± 3.7		
Iron Therapy	(-)				60	33.3
	(+)				120	66.7
Drug	iron carboxy maltose				60	50
	iron sucrose				60	50
Creatinine (mg/dL)						
First measurement		1.0 - 5.1	1.4	1.6 ± 0.5		
Last measurement		1.0 - 6.9	1.6	1.9 ± 0.9		
Glomerular filtration rate (mL/minute/1.73 m^2)						
First calculation		14.3 - 64.7	46.2	44.8 ± 10.7		
Last calculation		9.7 - 80.0	38.2	37.2 ± 13.7		

Table 2. Comparison of patients' creatinine levels.

	Iron therapy (-)				Iron therapy (+)			
	Mean ± standard deviation			Median	Mean ± standard deviation			Median
Creatinine (mg/dL)								
First measurement	1.6	±	0.6	1.4	1.5	±	0.5	1.4
Last measurement	1.8	±	0.7	1.6	2.0	±	1.0	1.7
First/last changes	0.2	±	0.5	0.1	0.5	±	0.9	0.2
Intragroup change probability	<u>0.014</u>				<u>0.000</u>			

Table 3. Comparison of patients' glomerular filtration rate levels.

	Iron therapy (-)				Iron therapy (+)			
	Mean ± standard deviation			Median	Mean ± standard deviation			Median
Glomerular filtration rate (mL/minute/1.73 m^2)								
First calculation	46.0	±	10.7	47.1	44.2	±	10.7	45.1
Last calculation	40.9	±	13.5	42.6	35.3	±	13.5	36.9
First/last changes	-5.1	±	12.7	-3.5	-8.9	±	14.0	-8.1
Intragroup change probability	<u>0.001</u>				<u>0.000</u>			

RESULTS

A total of 180 patients, 86 (47.8%) women and 94 (52.2%) men, were included in the study. The average age of the patients was 63.5 ± 11.4 years. The general characteristics of the patients and the general averages of the investigated parameters are summarized in Table 1.

Table 4. Comparison of iron carboxy maltose and iron sucrose groups by age and gender groups.

		Iron carboxy maltose				Iron sucrose			
		Mean ± standard deviation/ number and percentage of patients			Median	Mean ± standard deviation/ number and percentage of patients			Median
Age (year)		63.8	±	12.0	67.5	64.9	±	10.0	67.0
Gender	female	25		41.7%		40		66.7%	
	male	35		58.3%		20		33.3%	
Treatment duration (year)		6.4	±	4.1	5.0	5.9	±	3.3	5.0

Table 5. Comparison of iron carboxy maltose and iron sucrose groups according to creatinine levels.

	Iron carboxy maltose				Iron sucrose			
	Mean ± standard deviation			Median	Mean ± standard deviation			Median
Creatinine (mg/dL)								
First measurement	1.6	±	0.5	1.5	1.4	±	0.4	1.3
Last measurement	2.1	±	0.8	1.8	1.9	±	1.1	1.5
First/last changes	0.4	±	0.9	0.3	0.5	±	0.9	0.2
Intragroup change probability	0.000				0.000			

Table 6. Comparison of iron carboxy maltose and iron sucrose groups according to glomerular filtration rate levels.

	Iron carboxy maltose				Iron sucrose			
	Mean ± standard deviation			Median	Mean ± standard deviation			Median
Glomerular filtration rate (mL/minute/1.73 m^2)								
First calculation	42.5	±	10.3	44.1	45.8	±	11.0	47.4
Last calculation	34.3	±	13.3	35.0	36.3	±	13.8	37.6
First/last changes	-8.3	±	13.9	-9.0	-9.5	±	14.2	-7.2
Intragroup change probability	0.000				0.000			

According to the five-year follow-up results, the last measured creatinine value in the group that did not receive treatment increased significantly (p = 0.014) compared to the first measurement. In the treatment group, the last measured creatinine value increased significantly (p = 0.0001) compared to the first measurement. The first/last measured creatinine increase rate did not differ significantly (p = 0.053) in the groups receiving/not receiving iron treatment (Table 2).

According to the five-year follow-up results, the last calculated GFR value in the group that did not receive treatment decreased significantly (p = 0.001) compared to the first calculated GFR. In the group receiving treatment, the last calculated GFR value decreased significantly (p = 0.0001) compared to the first calculated GFR. However, the first/last calculated GFR decrease rate did not differ significantly (p = 0.160) in the groups receiving/not receiving iron treatment (Table 3).

Treatment duration did not show a significant difference (p = 0.706) between the iron carboxy maltose and iron sucrose groups. Patients with an average treatment duration of 5 years were evaluated in both groups (Table 4).

According to the five-year follow-up results, the last measured creatinine value in the iron carboxy maltose group showed a significant increase compared to the first measurement (p = 0.0001).

In the iron sucrose group, the last measurement of creatinine value increased significantly compared to the first measurement (p = 0.0001).

There was no significant difference in the first/last mea-

surement of creatinine increase between the iron carboxy maltose and iron sucrose groups (p = 0.871) (Table 5).
According to the five-year follow-up results, the last calculated GFR value in the iron carboxy maltose group showed a significant decrease compared to the first calculated GFR (p = 0.0001).
In the iron sucrose group, the last calculated GFR value decreased significantly compared to the first measured GFR (p = 0.0001).
The first/last calculated GFR decrease did not show a significant difference between the iron carboxy maltose and iron sucrose groups (p = 0.962) (Table 6).

DISCUSSION

Randomized controlled studies have shown that iron treatments, especially parenteral treatments, increase blood values. One of these shows that combining IV iron and low-dose EPO is a rapid and effective method of managing anemia in CKD pre-dialysis patients. It is also stated that parenteral iron therapy enables some patients to reach target Hct levels without using EPO. Likewise, many studies show that IV iron therapy is more effective than oral iron in treating anemia in pre-dialysis CKD patients [14-19].
A randomized, controlled trial of intravenous (IV) iron versus oral iron for the treatment of anemia in pre-dialysis CKD patients found a decrease in GFR from baseline in both treatment groups. This decrease was more significant in the oral iron treatment group [20]. The positive effect of correction of anemia on renal functions explains this situation.
In a study lasting 56 weeks, MacDougall et al. examined the effect of iron carboxy maltose (ICM) or oral iron therapy on renal functions. We found this study to be the closest in the literature to our research. The result shows that ICM or oral iron therapy does not significantly affect renal function. There were no differences between the groups regarding dialysis initiation rates and kidney-related adverse events [21].
In the literature, clinical studies measuring the short- or long-term effects of ICM and IS on the renal function of pre-dialysis CKD cases versus control groups are quite limited. However, studies have not found that ICM and IS have a negative effect on kidney function.
In our study, those who did not receive iron treatment and those who used iron carboxy maltose and iron sucrose for a longer period of time were compared. No significant difference was detected between the groups. The fact that the study was conducted retrospectively, even though it was a cohort, and with a limited number of patients can be considered limiting factors. Prospective studies with a more extensive participation may be more enlightening.

CONCLUSION

We concluded that anemia treatment with iron carboxy maltose and iron sucrose, as well as parenteral iron treatments, is really safe for pre-dialysis CKD patients. We found no difference in the GFR decline rate between iron carboxy maltose and iron sucrose.

Declaration of Interest:
All authors declared that they have no conflict of interest.

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