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ORIGINAL ARTICLE

Erythropoietin impact on serum ferritin levels in dialysis-dependent chronic kidney disease patients receiving iron therapy.

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ABSTRACT… Objective: To assess the effect of Erythropoietin on serum ferritin levels in dialysis-dependent Chronic Kidney Disease patients receiving iron therapy. **Study Design:** Observational study. **Setting:** Dialysis Unit of the Nephrology Department, Khyber Teaching Hospital, Peshawar. **Period:** September 2023 to March 2024. **Methods:** The study included adults aged 18 years and older who were diagnosed with chronic kidney disease (CKD) stages 3 to 5, undergoing dialysis, and receiving iron therapy with and without Erythropoietin. Patients with recent infections or acute renal failure were excluded from the study. Data analysis was conducted using SPSS software, where quantitative variables were reported as mean and standard deviation. Categorical variables were compared using the Chi-square test, with statistical significance defined as a p-value of less than 0.05. **Results:** The mean age of the 329 patients in this study was 41.28 years, with a standard deviation of 12.67. Among the participants, 54.1% were male and 45.9% were female. Of the total, 319 patients (97%) were receiving hemodialysis, while 10 patients (3%) were on peritoneal dialysis. Out of the 329 patients, 204 (62%) were undergoing erythropoietin therapy. Findings indicate that patients receiving erythropoietin had significantly higher serum ferritin levels, with a p-value of less than 0.05. Additionally, among erythropoietin users, 31.37% had hemoglobin levels below 7 g/dL, 55.4% had levels between 7 and 10 g/dL, and 13.2% had hemoglobin levels ranging from 10 to 14 g/dL. **Conclusion:** Our study concludes that approximately 62% of dialysis-dependent chronic kidney disease patients were receiving erythropoietin, and these patients exhibited higher hemoglobin and serum ferritin levels compared to those who were not taking the medication.

Key words: Dialysis, Serum Ferritin Levels, Erythropoietin, Chronic Kidney Disease.

INTRODUCTION

Chronic Kidney Disease (CKD), as defined by the National Kidney Foundation in the United States, is characterized by kidney damage evident from abnormal urinalysis or structural changes, alongside a glomerular filtration rate (GFR) of less than 60 mL/min persisting for over three months.[1] This classification divides CKD into five stages, from renal disease with preserved GFR to end-stage kidney failure. Anemia is a notable comorbidity in CKD, defined by hemoglobin levels below 13.0 g/dL in adult males and post-menopausal women, and below 12.0 g/dL in pre-menopausal women. This condition significantly increases morbidity and mortality as kidney failure progresses.[2,3]

Iron deficiency is a contributing factor to anemia, with hepcidin playing a crucial role.[4-6] Patients undergoing dialysis experience increased iron losses, leading to a common occurrence of iron deficiency among CKD patients who are treated with erythropoiesis-stimulating agents (ESAs). This deficiency is a significant factor contributing to the hypo-responsiveness of ESA therapy.[7,8] Iron therapy, whether used alone or in conjunction with ESAs, is crucial for managing anemia related to CKD. In this context, absolute iron deficiency is defined as serum ferritin levels below 100 ng/mL (or below 200 ng/mL for hemodialysis patients) and/or transferrin saturation levels under 20%. “Functional” or “relative iron deficiency” occurs when the demand for iron exceeds the supply, even in the presence of adequate iron stores.

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Intravenous iron is an effective treatment for functional iron deficiency anemia.[9]

In summary, the relationship between CKD stages and anemia is closely intertwined. Iron deficiency, driven by hepcidin, significantly contributes to the development of anemia, especially in dialysis patients and those receiving ESA therapy. The complexities of iron therapy highlight the importance of personalized management strategies for CKD patients to address anemia and enhance their quality of life. ESA therapy was introduced to the market in 1989, resulting in increased hemoglobin levels among dialysis patients. A study published in the same year observed a swift decline in serum ferritin levels soon after initiating ESA therapy, which was associated with heightened red blood cell production and increased iron utilization.[10]

Iron therapy is commonly prescribed for dialysis patients to address iron deficiency, a prevalent issue in this population due to blood loss during dialysis and decreased intestinal absorption. Serum ferritin serves as an indicator of the body's iron stores. This study aims to evaluate serum ferritin levels in dialysis patients receiving iron therapy, both with and without erythropoietin treatment, to examine the impact of erythropoietin on iron utilization and storage.

METHODS

This observational cross-sectional study was carried out in the Dialysis Unit of the Nephrology Department at Khyber Teaching Hospital, Peshawar, from September 2023 to March 2024, following approval from the Institutional Review and Ethics Board vide letter reference no 554/DME/KMC on 11.09.2023. A non-probability sampling technique was employed, and the sample size of 329 was calculated using OpenEPI Software, based on a proportion of 69%, a 95% confidence interval, and a 5% margin of error.

The study included patients aged 18 years and older who were diagnosed with chronic kidney disease (CKD) stages 3 to 5, undergoing dialysis, and receiving iron therapy with and without Erythropoietin. Those who were taking Erythropoietin were receiving 25-50 IU per kg twice weekly of Beta Erythropoietin. Serum ferritin levels were measured using the Electrochemiluminescence (ECLIA) method. Blood samples were collected in gel tubes and analyzed using the Cobas 601 device. Patients with recent infections or acute renal failure were excluded from the study.

The data analysis was conducted using SPSS version 21. Quantitative variables were assessed using mean and standard deviation, while qualitative variables were described through frequencies and percentages. The categorical variables were stratified using the Chi-square test, with statistical significance defined as a p-value of less than 0.05.

RESULTS

The study involved 329 patients, with a mean age of 41.28±12.67 years, comprising 54.1% males and 45.9% females. The majority of patients, 319 (97%), were receiving hemodialysis, while 10 patients (3%) were undergoing peritoneal dialysis. Dialysis duration varied among patients where 13.4% had been on dialysis for 6 months, 14.3% for 6 months to 1 year, 29.8% for 1-2 years, 14.6% for 2-3 years, and 28% for more than 3 years. Additional demographic information is provided in Table-I.

Regarding erythropoietin therapy, 204 patients (62%) were receiving it, while 125 patients (38%) were not, as shown in Figure-1. Figure-2 compares hemoglobin levels between the two groups. It demonstrates that there was no significant difference in hemoglobin levels between 7-10 g/dL; however, the erythropoietin-treated group had a higher proportion of patients with hemoglobin levels in the 10-14 g/dL range. This suggests that erythropoietin therapy is associated with improved hemoglobin levels in CKD patients, highlighting its effectiveness.

Table-II demonstrates a significant association between erythropoietin therapy and ferritin levels (P-value < 0.05), indicating that erythropoietin significantly increased serum ferritin levels, the storage form of iron. This finding underscores the

effectiveness of erythropoietin in managing CKD patients.

Variables	Frequency (%)
Gender	
Male	178 (54.1)
Female	151 (45.9)
Dialysis Type	
Hemodialysis	319 (97)
Peritoneal	10 (3)
Diagnosis leading to CKD	
HTN	210 (63.8)
DM	63 (19.1)
HTN+DM	45 (13.7)
Drugs	11 (3.3)
Duration of Dialysis	
<6 Months	44 (13.4)
6 Months to 1 Year	47 (14.3)
1 to 2 Years	98 (29.8)
2 to 3 Years	48 (14.6)
More than 3 Years	92 (28)
Erythropoietin therapy received	
Yes	204 (62)
No	125 (38)

Table-I. Demographic features of study participants

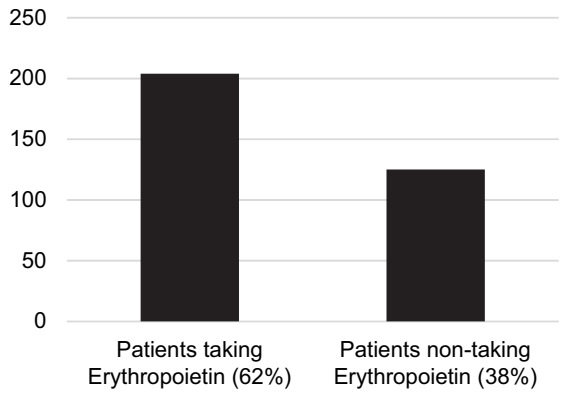

Figure-1. Erythropoietin therapy use in patient population

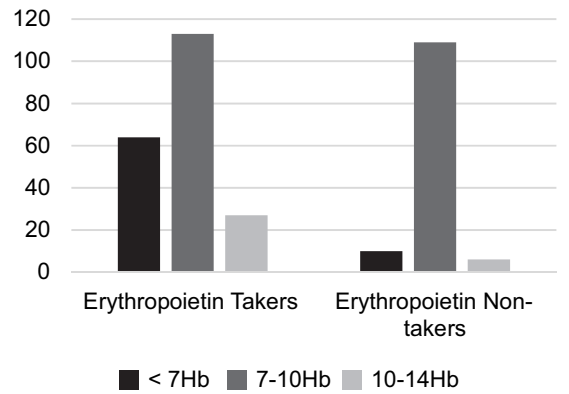

Figure-2. Hemoglobin levels in erythropoietin users and non-users

Erythropoietin Therapy Received	Serum Ferritin Levels		Total	P-Value
	<100 ng/mL	100-500 ng/mL		
Yes	11	193	204	<0.001
No	35	90	125	
Total	46	283	329	

Table-II. Association between erythropoietin therapy and serum ferritin levels

DISCUSSION

Chronic kidney disease (CKD) is a progressive condition that often leads to complications such as anemia, which is commonly managed through Erythropoietin therapy. However, its impact on iron metabolism, specifically serum ferritin levels, remains a topic of ongoing research. The present study highlights the effectiveness of erythropoietin in improving both hemoglobin (Hb) and ferritin levels in dialysis-dependent CKD patients. Of the 329 patients included in the study, 204 (62%) received erythropoietin therapy, while 125 (38%) did not. Among those receiving erythropoietin, there was a higher proportion of patients with hemoglobin levels in the 10-14 g/dL range. These findings further support the benefits of erythropoietin therapy in CKD patients.

This study demonstrated that the use of erythropoietin did not lead to a decrease in serum ferritin levels, a finding that is strongly supported by a study conducted in the United States.[11] Comparing hemoglobin levels between the two groups, there was no significant difference in Hb levels between 7-10 g/dL. Our results may be attributed to the inconsistent use of erythropoietin, as many patients struggle with adherence due to the medication's high cost. Additionally, improper dosing may contribute to this outcome, as there is an inverse relationship between erythropoietin dosage and serum ferritin levels, a trend observed in earlier studies conducted when ESA medications were first introduced.[10] Furthermore, the duration of dialysis may also influence serum ferritin levels. Longer dialysis duration correlates with higher ferritin levels. In contrast to our findings, a smaller study reported a rapid decline in serum ferritin shortly after initiating ESA treatment, attributed to increased red blood cell

production and iron utilization.[11]

In this study, 31.37% of patients on erythropoietin therapy had hemoglobin levels below 7 g/dL. It could be due to many reasons including ESA hyporesponsiveness, which is defined as a failure to show an increase in hemoglobin concentration from baseline after one month of treatment with the appropriate weight-based dosing.[12] Key factors contributing to ESA hyporesponsiveness include absolute or functional iron deficiency, inflammation[13], and uremia, with hepcidin playing a critical role in this process.[14,15] Other contributing factors include mineral bone disease related to chronic kidney disease (CKD) and non-iron malnutrition.[16,17] There is ongoing debate about the optimal treatment strategy for managing ESA hyporesponsiveness. The emergence of hypoxia-inducing factor (HIF) stabilizers offers new perspectives and potential approaches for addressing this challenge.[18,19]

In this study, a large proportion of patients had hemoglobin (Hb) levels between 7 and 10 g/dL in both ESA users and non-users. This suggests that nephrologists may not only target lower Hb levels in ESA-treated patients but also allow Hb to decrease further before starting ESA therapy. Similar trends were observed in a study of Swedish chronic kidney disease patients conducted between 2008 and 2013.[20] However, another study found that hemoglobin levels declined over time for both ESA-treated and untreated patients, suggesting that after hemoglobin target thresholds were lowered, patients began receiving ESAs at lower hemoglobin levels.[21]

We acknowledge that the observational design of this study, along with our reliance on aggregated data, restricts our ability to establish causal relationships between changes in intravenous iron or ESA dosage and serum ferritin levels. However, a strength of this design is its ability to capture real-world variations in dialysis practices. We suggest that future research should focus on ensuring strict patient compliance and appropriate dosing of ESAs to better assess the effects of erythropoietin on serum ferritin and hemoglobin levels.

CONCLUSION

Our findings show that erythropoietin notably increases serum ferritin levels, which indicate improved iron stores and are associated with higher hemoglobin levels, particularly in patients with more favorable outcomes. Despite some variability in the hemoglobin levels observed, a notable proportion of erythropoietin users achieved levels in the 10-14 g/dL range, further highlighting the therapy's potential in improving anemia management in CKD patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Arsalan Khan	Data analysis, Manuscript write-up.	
3	Muhammad Saleh Faisal	Data analysis, Editing final draft.	
4	Ahmad Zeb Khan	Study design, Statistical analysis.	
5	Muhammad Najumusaqib	Critical review.	
6	Kashif Ur Rehman Khalil	Data interpretation, Bibliography.	