Original Article

Assessment of Erythropoiesis-Stimulating Agents for Anemia Treatment among Chronic Kidney Disease Patients: A Descriptive, Retrospective Study

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Abstract

Background: Renal anemia is a cause of significant morbidity, and to lesser extent mortality in patients with chronic kidney disease (CKD), the leading causes of anemia in CKD primarily are the lack of erythropoietin (EPO) and iron. Thus, effective management is possible using oral and intravenous (IV) iron preparation and genetically engineered erythropoiesis-stimulating agents such as EPO. This study aimed to assess the effect of EPO in the treatment of anemia among hemodialysis (HD) patients. **Methods:** A descriptive, retrospective hospital-based study was conducted in Elshaheeda Salma Hospital, Khartoum, Sudan. All patients who were anemic or had a history of anemia and undergoing HD during the period (January to June 2018) were recruited. Data were collected using a checklist and analyzed with the Statistical Package for the Social Sciences software. **Results:** A total of 191 anemic patients were included: 60% of them were males, and more than half of the participants were aged between 41 and 65 years. Clinically, the average duration of the dialysis among participants was 7.7 ± 5 years, and 97% of them had two dialysis sessions per week. Patients were used either IV or subcutaneous injection of EPO. 8000 IU/week were the most prescribed (52.2%) EPO dose. Whereas, only 6% and 18% were taking 100 mg IV and 150 mg oral ferrous sulfate, respectively. Furthermore, 70% of them were taking 5 mg folic acid. Moreover, the mean hemoglobin level among the participants at the end of the study was 10 ± 2.1 g/dl. **Conclusion:** EPO was effective in treating renal anemia in HD patients. Among the studied patients, 8000 IU/week was the most frequently used dose. The present study highlights significant low adherence to international guidelines in the management of anemia in patients on HD.

Keywords: Anemia, chronic kidney failure, Elshaheeda Salma hospital, erythropoietin

Introduction

Chronic kidney disease (CKD) is usually asymptomatic, but it is detectable, and its treatment can prevent or delay the progression of CKD and reduce or prevent the development of complications.[1] The most frequent causes of CKD include diabetic nephropathy, hypertension, glomerular nephritides, interstitial nephritis, pyelonephritis, polycystic kidney disease, and obstructive nephropathy.[1] The selection of renal replacement therapy depends on the patient's physical and socio-demographic characteristics. Renal transplantation is the best option because it assures a better quality of life and more prolonged survival, nevertheless due to the scarcity of transplants, peritoneal dialysis, and mainly hemodialysis (HD) are applied in most cases.[2,3] Hemodialysis is a medical procedure to remove the waste products from the blood and to correct the electrolyte imbalance. This is accomplished using a machine and dialyzer and is used to treat both acute and chronic kidney failure.[4,5]

One of the main complications of CKD is the development of anemia, as the kidney secretes erythropoietin (EPO) hormone that plays a vital role in erythropoiesis process.[6] Thus, using different types of recombinant human EPO, including epoetin alfa and Darbepoetin can be administered to

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manage CKD-induced anemia.[7,8] Approximately 5%–10% of patients receiving EPO therapy will show resistance.[9] Causes of hypo-responsiveness to EPO therapy are infection, inflammation, iron deficiency, B12 and folate deficiency, blood loss, hyperparathyroidism, malnutrition, and malignancy.[8,10] Moreover, anemia in CKD can be the leading cause of morbidity and mortality.

In Sudan, there are problems in prescribing and monitoring of treatment of anemia in CKD patients. These problems exacerbate the incidence of anemia leading to many complications of anemia as reduced oxygen utilization, increased cardiac output and left ventricular hypertrophy, increase the progression of CKD, and how much these complications are translated into the adverse outcomes such as impaired quality of life, increased hospitalization, and increased cardiovascular event.[6] Thus, this study was carried to assess the prescribing and monitoring of erythropoiesis-stimulating agents (ESA) for the treatment of anemia among CKD patients.

Methods

Study design and settings

This study was a descriptive, retrospective, cross-sectional, and hospital-based study conducted at Elshaheeda Salma Center for dialysis, Khartoum, Sudan. The present study involved CKD adult patients who were attending during the period of study for HD. The study duration was from January to June 2018.

Inclusion and exclusion criteria

A total coverage sampling technique was used. All patients more than 18 years on HD who were anemic or had a history of anemia were included. While those who were coming to the center for a period of fewer than 6 months from the beginning of the study were excluded from the study. The total number of recruited included patients was 191 patients; all their medical records were also reviewed.

Data collection tools

A data collection sheet was developed based on the guideline for the management of anemia among CKD. It was designed to assess the appropriateness of anemia management in CKD; it contained the following sections: Demographic data, data on dosing of treatments, and questions related to dialysis. A pilot study consisting of 10 initial records was first conducted to check the validity of the data collection sheet.

Statistical analysis

Data were collected and analyzed using the Statistical Package for the Social Sciences program SPSS version 22 (Armonk, NY: IBM Corp). The descriptive statistics were presented in tables. A Chi-square test was used to test the significant association between the readings of different months following EPO treatment. $P < 0.05$ was considered statistically significant.

Ethical consideration

An ethical clearance (FPEC-10-2018) was obtained from the Ethical Committee of the Faculty of Pharmacy, University of Khartoum. Additional approval for checking the medical records was obtained from Elshaheeda Salma Hospital.

Results

As shown in Table 1, 191 participants were recruited in the study; the average age of the participants was 51 ± 15 years, with a minimum age of 22 years and a maximum of 87 years. Sixty percent of them were males and more than half of the participants aged 41–65. The average weight was 59.8 ± 16 kg with a minimum weight of 27 kg and a maximum of 107 kg, with 13% their weight was more than 80 kg. About half of the participants were living in Khartoum. Clinically, the average duration of the dialysis among participants was 7.7 ± 5 years, with a minimum of 8 months and a maximum of 22 years. About one-third of the participants were on dialysis for more than 10 years, and 97% of them had two dialysis sessions per week [Table 1].

More than half of the participants were used either intravenous (IV) or subcutaneous (SC) injection of EPO. 43% and 11% of the patients measured their hemoglobin and iron within 1–3 months [Table 2]. Moreover, more than half the participants were taking 8000 IU of ESA therapy per week, and only 10% were taking 12000 IU while ESA therapy was not prescribed for about 12% of the participants. Regarding ferrous

Table 1: Sociodemographic and clinical characteristics of the participants (n=191)

Variable	Frequency (%)
Gender	
Male	114 (59.7)
Female	77 (40.3)
Age (years)	
20-40	47 (24.6)
41-65	109 (57.1)
>65	35 (18.3)
Weight (kg)	
20-50	57 (29.8)
51-80	108 (56.5)
>80	26 (13.6)
Residence	
Omdurman	39 (20.4)
Bahri	41 (21.5)
Khartoum	94 (49.2)
Others	17 (8.9)
Economic state	
Moderate	50 (26.2)
Poor	141 (73.8)
Duration of the disease (years)	
<2	29 (15.2)
2-10	92 (48.2)
>10	70 (36.6)
Number of dialysis	
Once/week	1 (0.5)
Twice/week	186 (97.4)
Three/week	4 (2.1)

sulfate, 82.5% of the participants were not taking ferrous sulfate IV, whereas 55.4% of them were not taking the oral form. 6% were taking 100 mg ferrous sulfate IV, whereas 18% were taking 150 mg oral ferrous sulfate. Furthermore, 70% were taking folic acid 5 mg, and about 55% of them were not taking oral Vitamin B12 [Table 2]. The average hemoglobin, ferritin, and TSAT levels throughout the 6 months (January to June) are shown in Table 3, the mean hemoglobin level among the participants was 10.9 ± 2.3, and in the 6th month, it was 10 ± 2.1. Regarding TSAT, no one was doing the test in the 1st month, and the average level of TSAT was fluctuating between 28.1 ± 21.7 in February and 50.7 ± 42.2 in April, whereas the average level of ferritin was fluctuating between 456.8 ± 321.5 in May and 833.2 ± 478 in April.

Table 2: Treatment and monitoring of anemia among the studied population (*n*=191)

Variable	Frequency (%)
Route of erythropoietin administration	
IV	23 (12)
SC	63 (33)
IV + SC	105 (55)
Interval of Hb monitoring	
1-3 months	82 (42.9)
More than 3 months	109 (57.1)
Interval of iron monitoring	
1-3 months	21 (11)
More than 3 months	170 (89)
Hypo-responsiveness	
Yes	2 (1)
No	189 (99)
Erythropoietin dose (IU/week)	
4000	71 (37.2)
8000	100 (52.4)
12,000	20 (10.4)
Ferrous IV dose (mg/week)	
Not prescribed	157 (82.5)
100	3 (1.6)
100	12 (6.3)
200	13 (6.8)
300	4 (2.2)
400	2 (1.1)
Ferrous oral dose (mg/day)	
Not prescribed	107 (56)
150	34 (17.8)
350	50 (26.2)
Folic acid oral dose (mg/day)	
Not prescribed	16 (8.4)
5	134 (70.2)
6	41 (21.5)
Vitamin B12 oral dose (mcg/day)	
Not prescribed	103 (53.9)
7.5	34 (17.8)
10	40 (20.9)
17.5	14 (7.3)

IV: Intravenous, SC: Subcutaneous, Hb: Hemoglobin

When Pearson's correlation test was performed to determine the associations between the doses of EPO and hemoglobin level throughout 6 months, we found that EPO doses that were administered to the participants were associated with a significant decrease in the Hb level in February (R = 0.178, P = 0.014) and April (R = 0.150, P = 0.038). The results were statistically insignificant for the rest of the months.

Discussion

In this study, 48.2% of the participants receiving HD for 2–10 years, followed by 36.6% receiving HD for more than 10 years and 15.2% for <2 years either twice/weekly (97.4%), (2.1%) thrice/week and (0.5%) once/week. This result was consistent with a study that was done in Saudi Arabia.[11] On the other hand, the economic state of most patients was poor (73.8%), and 26.2 were a moderate state, due to this result, most of the patients did not do the routine laboratory investigation as recommended by doctors.

In the current study, we found that the hyporesponsiveness to EPO represents 1% of all patients. There were two patients who were hyporesponsive one was due to inflammation, and the other was due to hyperparathyroidism, this result was not found only in this study only; a study was done in Saudi Arabia the authors reported that CKD itself is a central cause of hyporesponsiveness of ESA due to inflammation condition that stimulates hepcidin release from the liver leading to iron deficiency.[11] Furthermore, another study showed that hyperparathyroidism was one of the most causes of hyporesponse to EPO.[12] Furthermore, another report found that inflammation was the major cause of hyporesponse.[13]

The monitoring of anemia did not follow international guidelines as no patient was measured his hemoglobin monthly as recommended by the KIDIGO guidelines.[6] Most patients (56.5%) measured their hemoglobin at a time interval of more than 3 months, and only (43.5%) were measured at the time interval of 1–3 months, and they were followed NICE

Table 3: The average levels of the hemoglobin, serum transferrin saturation, and ferritin throughout the 6 months

Lab investigations	Month (mean±SD)					
	January	February	March	April	May	June
Hb (g/dL)	10.9±2.3	11.5±1.8	11.2±1.8	11±2.1	11.1±2.1	10±2.1
TSAT (ng/ml)	25.4±19.6	28.1±21.7	34.7±25.7	50.7±42.2	31.4±20	42.7±212
Ferritin (ng/ml)	467.4±229.5	690.2±374	556.8±367.1	833.2±478.5	456.8±321.5	831±428.3

SD: Standard deviation, Hb: Hemoglobin, TSAT: Serum transferrin saturation

guidelines according to their recommendation.[6] Furthermore, monitoring of iron by measuring ferritin and transferrin saturation did not follow the guideline, as 89% measuring their iron in time interval more than recommended by guideline, and only 11% followed guidelines as they measure their iron at the time interval recommended by the guideline. There were few patients measuring their ferritin and TSAT in each month of study as these tests are too expensive. The patients were used both IV and oral routes of iron administration, which is not recommended by the guideline. The present study that was done in India showed the same result,[14] but differed from a study done in Saudi Arabia and Lebanon, in which patients were using an IV route, which is the preferable route by the guideline.[11,15]

Data on folic acid and Vitamin B12 doses were collected, and serum folate and serum B12 were done for only three patients during the study, so they were excluded from the analysis. Patients did not do these laboratory investigations because they are very expensive. All patients used oral Vitamin B12, and only one patient used the IV route. At this point, the prescriber adhered to the guidelines, and these tests were written to patients as recommended, but due to their poor economic state, patients did not do these investigations.

EPO was given according to hemoglobin measure, which matches with the guideline.[16] In Elshaheeda Salma, higher doses of EPO were prescribed to patients with lower hemoglobin levels; this result was also found in a study done in Lebanon. The types of EPO used in our study were epoetin Alfa and epoetin beta. In a study that was done in India and Lebanon, patients have used epoetin alfa, epoetin beta, and darbepoetin alfa.[11,14]

The route of administration of EPO in this study for 55% of patients was by either IV or SC route at the end of dialysis session. These are preferable routes of administration regarding EPO by the guidelines followed by 33% by SC only and the rest 12% by IV only. This result was inconsistent with the results of the study done in Saudi Arabia, which showed that the administration route for all patients was IV,[11] and studies in Lebanon showed that EPO were administered to all patients by SC route.[17]

Hemoglobin level is the most specific parameter used to establish the presence and severity of anemia in HD patients.[18] Among all months, April showed a high frequency of monitoring hemoglobin because the center did the test, and other months showed low frequency in monitoring hemoglobin, thus assessing target hemoglobin (10–12 g/dl) if it complies with guidelines being difficult because the sample is not representative.

Conclusion

All recruited patients were received EPO to manage renal anemia, 8000 IU/week were the most frequently used dose. Some of patients were further received ferrous sulfate and folic acid to treat anemia. Furthermore, the present study revealed significant low adherence to the international guidelines in the management of anemia in patients on HD.

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Conflicts of interest

There are no conflicts of interest.

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