Original Article

Impact of Erythropoietin on Anemia in End-Stage Renal Disease Patients on Hemodialysis

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Abstract

Background: End-stage kidney disease occurs when the estimated glomerular filtration rate is not more than 15 mL/min/1.73 m^2 or when the patient requires long-term renal replacement therapy regardless of estimated glomerular filtration rate. Anemia is observed as a frequent comorbid complication of chronic kidney disease (CKD). Erythropoietin (EPO) deficiency is the crucial cause of CKD-anemia development. **Objectives:** The aim of study was to determine the impact of EPO on anemia in end-stage renal disease patients on hemodialysis (HD). **Materials and Methods:** This study was a cross-sectional study. A total of 80 patients (42 men and 38women) at end-stage renal disease planned for HD program at Al-Hakeem general hospital in Al-Najaf city/Iraq in period between November 2020 and February 2021. Many information and analyses were taken such as age, sex, cause of end stage, blood urea, serum creatinine and albumin, hemoglobin, dose of EPO, blood pressure, and body weight. **Results:** The results of study showed that, the level of hemoglobin (g/dL) significantly increased from (8.24 ± 1.77) to (9.57 ± 1.35) after treatment with EPO (P value < 0.05), whereas the levels of blood urea (mg/dL), albumin (g/L) significantly decreased from (218.51 ± 74.47) to (145.76 ± 42.47) and from (40.65 ± 6.35) to (36.56 ± 6.03) respectively, after treatment with EPO (P value < 0.05). ADditionally, there are no significant differences in serum creatinine (mg/dL) and blood pressure after treatment with EPO. **Conclusion:** EPO has a positive role on renal function and in treating anemia in end-stage renal disease patients on HD.

Keywords: Anemia, chronic kidney disease, erythropoietin, hemoglobin (g/dl)

Introduction

Chronic kidney disease (CKD) is an international health problem that characterized by an ongoing deterioration of kidney function with a progressive kidney failure due to uremic toxicity and the complications that arise from it.[1] It recorded as a devastating condition that is reaching epidemic levels due to increasing the prevalence of its related underlying risk factors[2] where 8%–16% of the global population were affected.[3] The worldwide burden is still rising with unfortunately limited public awareness.[4] The recorded global prevalence increasing with the aging of populations as well as increases the risk of morbidity and mortality.[5] In Iraq, CKD is ranked among the five most life threatening disease conditions, where about 7000 death because of renal failure were recorded in 2015 according to the statistics of Iraqi Ministry of Health.[6]

CKD is defined as a presence of persistent kidney damage when the estimated glomerular filtration rate (eGFR) not as much of 60 mL/min/1.73 m^2 or abnormally elevated serum creatinine for three months or more, regardless the cause.[7,8] CKD was classified either depending on eGFR or albuminuria threshold.[9] Six categories were included (G1, G2, G3a, G3b, G4, and G5) but three categories were included (A1–A3) according to eGFR and albuminuria, respectively.[7] End-stage kidney disease occurs when the eGFR is not more than 15 mL/min/1.73 m^2 or when the patient requires long-term renal replacement therapy (RRT) regardless of eGFR.[10] Consequently, there is an emergent

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need for RRT with dialysis or transplantation.[7] The incidence of RRT depends on the incidence and prevalence of fundamental causes of end-stage renal disease (ESRD), early diagnosis of CKD and the available measures to slow progression to ESRD.[11] About 4.902 to 7.083 million patient with ESRD are needing RRT either by dialysis or transplant,[12] where hemodialysis (HD) is the main used type of dialysis that represents a lifeline for patients with kidney failure who without a kidney transplant could not survive.[13]

Several complications were documented in CKD patients especially in those with ESRD including: cardiovascular (CV)[14] that mainly resulted from resistant hypertension.[15] The CV complications represent the most common cause of death for ESRD patients on dialysis, a 10%–20% of those deaths were associated to an acute myocardial infarction.[16]

Anemia is observed as a frequent comorbid complication of CKD that associated with a substantial burden because of decreased patient health-related quality of life and increased healthcare resource utilization. According to the available data, anemia is associated with a poor patient outcome, increased risk of both CKD progression, and CV events in addition to all-cause mortality.[7,17] Erythropoietin (EPO) deficiency is the crucial cause of CKD-anemia development,[18] whereas EPO are lower than expected in patients with renal failure and the deficiency becomes absolute in ESRD.[19]

The current and traditional standard of CKD-anemia care includes: oral or IV iron supplements, erythropoiesis-stimulating agents (ESAs), and blood transfusion; however, hypoxia-inducible factors are investigational.[20,21] Epoetin, darbepoetin, and methoxy polyethylene glycol-epoetin β are examples of ESAs and are recombinant versions of EPO produced pharmacologically and used.[22] They have an important role in the correction of anemia, reducing transfusion requirements with its related complications, increasing exercise capacity, as well as improve quality of life.[23] Although long acting ESAs have more patient preferences with better compliance, several studies recommend using short acting agents in management of renal anemia to lower the risk of both mortality as well as resistance to ESAs among patients with CKD.[24,25] Higher doses of ESAs are not preferred especially in those with in adequate response or resistance to the optimal therapeutic schedule of ESAs because a higher doses use is associated with increasing morbidity and mortality in addition to presents a pressing clinical challenge doses, mainly for patients on RRT specially dialysis.[26]

Materials and Methods

Materials

Epoetin Zeta injection 4000 IU/IE (Retacrit Injection, Wiesbaden-Germany), human kits of urea, creatinine, phosphorus, protein, albumin, and hemoglobin (Human, Wiesbaden-Germany).

Patients collection and study design

This was a cross-sectional study. A total of eighty patients (42 men and 38 women) with chronic renal failure at end-stage renal disease put on HD program at Al-Hakeem general hospital in Al-Najaf city, Iraq in period between November 2020 and February 2021 were enrolled in this study. Patients age ranged between 20 and 75 old years. Patients were diagnosed with CKD based on estimated GFR according to: Cockcroft-Gault equation and Modification of Diet in Renal Disease study equation. Each patient was admitted to the hospital followed by this information and analysis: Patient's name, age, sex, cause of end stage, duration of dialysis, no. of sessions, adequacy of dialysis (KTV), blood urea, serum creatinine, s. albumin, comorbidity unless, hemoglobin (Hb), dose of EPO, blood pressure (BP), body weight, hepatitis B, C, use of angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blockers (ARBS) and use of iron. Further information about the patient case notes and medication records were written and used in our data collection of each patient. All the patients included in this study were given questionnaires and duly signed, written informed consent was obtained. A blood samples were taken from each patient included in this study via peripheral vein before the session of dialysis procedure (S1) and then post the session of dialysis procedure (S2) to use for assay serum urea, creatinine, albumin, and hemoglobin.

Statistical analysis

All data of the 80 patients were analyzed by using the statistical package for social sciences software (SPSS) (version 25 IBM SPSS, Inc., Chicago, Illinois, USA) and Microsoft Excel 2019. Normally distributed numerical variables were compared between two groups by Paired *t*-test, all data expressed as (mean ± SD) standard deviation. Nominal variables were presented as frequency and percentages (%) were compared between studied categories by non-parametric Chi-square test. Correlation coefficient analysis was completed with Pearson's Eta square. Significance of differences was detected at $P < 0.05$.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 83 on October 30, 2020 to get this approval.

Results

All patients demographic characteristics: age, gender, body weight, cause of end-stage renal disease, duration of

dialysis, no. of session, adequacy of dialysis (KTV), blood urea, serum creatinine, s. albumin, comorbidity unless, Hb, dose of EPO, BP, hepatitis B and C, use of ACEI, ARBS and, use of iron were studied. Some without statistically significant differences such as age, gender, duration of dialysis, no. of sessions and other with statistically significant differences between the patient before and after treatment with EPO such as cause of end-stage renal disease, comorbidity unless, hepatitis B and C, and use of ACEI [Table 1].

The effect of treatment with erythropoietin on biochemical parameters in patients with renal diseases

In the present study, the level of HB (g/dL) significantly increased from (8.24 ± 1.77) to (9.57 ± 1.35), after treatment with EPO (*P* value equal to 0.0001) (*P* > 0.05). The levels of blood urea (mg/dL), albumin (g/L) significantly decreased from (218.51 ± 74.47) to (145.76 ± 42.47) and from (40.65 ± 6.35) to (36.56 ± 6.03) respectively, after treatment with EPO (*P* value equal to 0.0001) (*P* < 0.05). There are no significant differences in serum creatinine (mg/dL), systolic blood pressure (SBP), and diastolic blood pressure (DBP) after treatment with EPO [Table 2].

Logistic regression for determined the dependent factor that effected with before and after treatment of erythropoietin

In the present study, the dependent factors data were expressed as odds ratios (OR), 95% confidence intervals (CI) and *P* value that effected with treatment of EPO are expressed in Table 3.

Multivariate (GLM) test for estimated of the main effects of dependent variable after treatment of erythropoietin

In the present study, the main effect of study parameters after treatment of EPO were expressed in Table 4.

Table 1: Demographic data of categories in patients with renal diseases

Variables	Categories	Statistics values *n* = 80 patients	Chi-square	*P* value
Body weight (kg) mean ± SD		68.32 ± 15.12		
KTV mean ± SD		1.04 ± 0.20		
Age (year) mean ± SD		46.56 ± 14.62		
Age distribution	20–29 *n* (%)	12 (15.0%)	5.125	0.275
	30–39 *n* (%)	14 (17.5%)		
	40–49 *n* (%)	18 (22.5%)		
	50–59 *n* (%)	13 (16.3%)		
	≥60 *n* (%)	23 (28.8%)		
	20–29 *n* (%)	12 (15.0%)		
Gender	Male *n* (%)	42 (52.5%)	0.200	0.655
	Female *n* (%)	38 (47.5%)		
Cause of end-stage RD	HTN *n* (%)	25 (31.25%)	17.250	0.045*
	DM *n* (%)	11 (13.8%)		
	HTN + DM *n* (%)	5 (6.3%)		
	Bleeding *n* (%)	9 (11.3%)		
	Renal stone *n* (%)	9 (11.3%)		
	Renal atrophy *n* (%)	2 (2.5%)		
	Nephrotic syndrome *n* (%)	7 (8.8%)		
	UTI *n* (%)	4 (5.0%)		
	Other and unknown *n* (%)	8 (10.0%)		
Comorbidity unless	DM *n* (%)	3 (3.8%)	79.9	0.0001*
	DM & HTN *n* (%)	13 (16.25%)		
	HTN *n* (%)	25 (31.25%)		
	Non *n* (%)	42 (52.5%)		
Duration of dialysis	3 h *n* (%)	34 (42.5%)	1.80	0.180
	4 h *n* (%)	46 (57.5%)		
No. of session	2 times *n* (%)	36 (45.0%)	0.80	0.371
	3 times *n* (%)	44 (55.0%)		
Hepatitis B, C	Non *n* (%)	67 (83.8%)	36.45	0.0001*
	Yes (C) *n* (%)	13 (16.3%)		
ACEI	Yes *n* (%)	11 (13.8%)	42.05	0.0001*
	No *n* (%)	69 (86.3%)		

SD = standard deviation, KTV = adequacy of dialysis, HTN = hypertension, DM = diabetes, RD = renal disease, UTI = urinary tract infection, ACEI = angiotensin converting enzyme inhibitors

*Significant differences at *P* value < 0.05

Table 2: The effect of treatment with erythropoietin dose on bio-chemical parameters in patients with renal diseases

Biochemical parameters	Mean ± SD		Paired *T* test	*P*-value
	Before erythropoietin	After erythropoietin		
Blood urea (mg/dL)	218.51 ± 74.47	145.76 ± 42.47	11.322	0.0001 *
Serum creatinine (mg/dL)	8.47 ± 2.02	8.24 ± 2.20	1.128	0.263
Albumin (g/L)	40.65 ± 6.35	36.56 ± 6.03	4.416	0.0001 *
HB (g/dL)	8.24 ± 1.77	9.57 ± 1.35	–8.979	0.0001 *
SBP (mmHg)	142.93 ± 29.64	148.89 ± 33.02	–1.823	0.072
DBP (mmHg)	85.83 ± 24.86	82.99 ± 16.66	1.058	0.293

SBP = systolic blood pressure, DBP = diastolic blood pressure, ns = non-significant

*Significant differences at *P* value < 0.05

Table 3: Logistic regression for determined the dependent factor that effected with before and after treatment of erythropoietin

		P value	OR	95% CI for OR	
				Lower	Upper
Step a 1 After/before	Cause of end-stage RD	0.199	1.115	0.944	1.317
	Comorbidity unless	0.168	0.797	0.577	1.100
	Duration of dialysis	0.123	2.136	0.814	5.605
	No. of session	0.567	0.759	0.296	1.950
	ACEI	0.749	1.269	0.294	5.471
	Blood urea	0.0001*	0.970	0.958	0.981
	Serum creatinine	0.426	1.088	0.884	1.340
	Albumin	0.007*	0.912	0.852	0.975
	HB	0.0001*	1.951	1.507	2.526
	SBP (mmHg)	0.050*	1.017	1.000	1.035
	DBP (mmHg)	0.489	0.991	0.967	1.016

ACEI = angiotensin converting enzyme inhibitors, OR = odds ratios, 95% CI = confidence intervals

[a]Variable(s) entered on step 1: Cause of end-stage RD, comorbidity unless, duration of dialysis, no. of sections, ACEI, blood urea, serum creatinine, albumin, HB, SBP, DBP

*Significant differences at *P* value < 0.05

Table 4: Multivariate (GLM) test for estimated of the main effects of dependent variable after treatment of erythropoietin

Tests of between-subjects effects							
Dependent variable		Blood urea	Serum creatinine	Albumin	HB	SBP	DBP
Gender	*P*-value	0.109	0.614	0.655	0.014*	0.461	0.901
	Partial eta squared	0.034	0.003	0.003	0.079	0.007	0.000
Age groups	*P* value	0.096	0.176	0.302	0.916	0.002*	0.018*
	Partial eta squared	0.037	0.025	0.014	0.000	0.121	0.073
Cause of end-stage RD	*P* value	0.244	0.219	0.324	0.021*	0.014*	0.057
	Partial eta squared	0.018	0.020	0.013	0.069	0.079	0.048
Comorbidity unless	*P* value	0.636	1.000	0.463	0.024*	0.208	0.006*
	Partial eta squared	0.003	0.000	0.007	0.067	0.021	0.099
Duration of dialysis	*P* value	0.393	0.023	0.002	0.825	0.403	0.747
	Partial eta squared	0.010	0.068	0.123	0.001	0.009	0.001
No. of session	*P* value	0.491	0.947	0.546	0.004*	0.669	0.057
	Partial eta squared	0.006	0.000	0.005	0.105	0.002	0.048

GLM = multivariate of general linear model, RD = renal disease

*Significant differences at *P* value < 0.05

Tests of between subjects effects

In the present study, some factors have the significant role on hemoglobin concentration without effect of these factors with other parameters as shown in Table 5. All factors have significant effect on hemoglobin concentration after treatment with EPO (*P* value < 0.05) and the higher value of partial eta squared represents the factor with larger effect.

Table 5: Tests of between subjects effects

Tests of between-subjects effects			
Source	**Dependent variable**	***P*-value**	**Partial eta squared**
HB after	Gender	0.0001*	0.885
	Age groups	0.0001*	0.806
	Cause of end-stage RD	0.0001*	0.716
	Comorbidity unless	0.0001*	0.812
	Duration of dialysis	0.0001*	0.882
	No. of session	0.0001*	0.894
	Hepatitis BC	0.001*	0.142
	ACEI	0.001*	0.140

ACEI = angiotensin converting enzyme inhibitors, RD = renal disease
*Significant differences at P value < 0.05

Discussion

In the current study, epoetin zeta is used. It is one of the clinically approved ESAs for correction of renal anemia in ESRD patients with or without dialysis, both hemo or peritoneal dialysis[27] with comparable safety and efficacy profile with other ESAs.[28,29]

This study showed that the male patients formed the larger proportion (52.5%), than female patients (47.5%), and this result was consistent with many studies that found most patients of kidney disease were men other than women.[30,31]

Also, the results of the current study showed that there was a significant improvement of hematological status on patients receiving the treatment with EPO-Z. This increment of Hb level was attributed to ESAs ability to ameliorate bone marrow functions that suppressed due to renal impairment either directly by acting on erythroid progenitor cells inhibiting their apoptosis[32] or indirectly by its anti-inflammatory property,[33] where inflammation was recognized to worsen anemia as well as lower renal response or even increase resistance to EPO therapy.[34,35] As a result, the depressing of inflammatory response by diminishing the harmful effects of inflammatory cytokines on EPO production, iron metabolism and erythrogenesis can improve Hb level.

Additionally, this study showed a positive effect on renal function, where the results showed significant reduction of urea level after treatment with epoetin. This reno-protective effects could be attributed to lowering renal cell apoptosis as well as improving their survival in addition to improving renal oxygen transport via increasing Hb level.[36]

Furthermore, this study exhibited non-significant increase of SBP. This increase could be explained by increasing both vascular smooth muscle contractility as well as blood viscosity.[37] Comparable results also recognized up on using other types of ESA.[38]

Conclusion

EPO has an positive role in treating anemia in end-stage renal disease patients on HD. It can cause a significantly increase in the level of hemoglobin HB and significantly decreased in the levels of blood urea and albumin.

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Conflicts of interest
There are no conflicts of interest.

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