Renal anemia refractory to erythropoietin

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Background
Anemia is a common feature of chronic kidney disease and is associated with poor outcomes. Renal anemia has a multifactorial etiology, and the major cause is decreased production of erythropoietin (EPO). The standard of care for the treatment of the renal anemia is EPO for achieving target of hemoglobin levels (11gm /dl), but some causes lead to inadequate response to EPO.

Aim
The study aimed to determine the frequency and various factors contributing to the etiology of renal anemia refractory to EPO in patients with end-stage renal disease (ESRD) on hemodialysis (HD).

Patients and methods
A descriptive longitudinal study was performed. The study was carried out on 30 patients with ESRD on HD selected randomly and received EPO drug at the Nephrology Unit and Outpatient Clinic at the Department of Internal Medicine of Assiut University Hospital. The data were obtained from full medical history and clinical examination, such as general data concerning patients (age, sex, comorbidities, and used medications), which were recorded directly from the patients or from their hospital files, laboratory investigations, and follow-up of patients for 4 months, with complete blood count examination every month.

Results
The study found that of 30 studied patients, 23 (76.7%) had partial response to reach the targeted hemoglobin level and seven (23.3%) had complete response to reach the targeted hemoglobin level of 11 g/dl. The 23 patients who had partial response had poor nutrition, iron-deficiency anemia (IDA), inadequate dialysis, arteriovenous fistula and chest infections, drugs containing aluminum, acute blood loss, hypocalcemia, hyperphosphatemia, and hyperparathyroidism. These may be possible risk factors of renal anemia refractory to EPO.

Conclusions
Anemia is a common complication of uremia and a major contributor to morbidity and mortality in HD patients. The availability of recombinant human EPO has led to almost complete disappearance of severe anemia in HD patients; however, despite an increase in its use and average dose, a substantial percentage of patients still fail to achieve the Hb targets recommended by the international guidelines. Anemia refractory to EPO is common in HD patients (76.6%), which may be owing to several factors such as bad nutrition, IDA, inadequate dialysis, arteriovenous fistula and chest infection, aluminum-containing drugs, hypocalcemia, hyperphosphatemia, and hyperparathyroidism.

Recommendations
The study recommends to monitor serum levels of iron, calcium, phosphate, and parathyroid hormone at the start, with follow-up by complete blood count monthly, as well as treatment of the possible causes, that is, iron for IDA, antibiotic for infections, calcium therapy for hypocalcemia, and management of hyperphosphatemia and secondary hyperparathyroidism, during treatment of renal anemia by erythropoietin (EPO) drug to responded to it. Moreover, the study recommends performing more studies on a larger number of patients with ESRD having renal anemia for more demonstration of the possible causes of this condition.

Keywords:
chronic kidney disease, erythropoietin, hemodialysis

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Introduction

Chronic kidney disease (CKD) is considered a public health problem worldwide with high incidence and prevalence rates [1].

Anemia is a common feature of CKD and is associated with poor outcomes. It has increased prevalence, affecting nearly all patients with stage 5 CKD. Anemia in CKD is normocytic, normochromic, and hypoproliferative [2].

The etiology of anemia in CKD is multifactorial, but the major cause is decreased production of EPO as renal function declines. Iron deficiency and blood loss also contribute [3].

EPO therapy has become the standard of care for the treatment of the anemia of CKD [4].

The starting dose of EPO is 50 units/kg (3000–4000 units/dose) once or twice a week, and darbepoetin is started at 0.45 μg/kg and can be administered every 2–4 weeks.

These agents can be given intravenously or subcutaneously. Iron stores should be repleted with oral or parenteral iron before the initiation of an ESA [5].

Aim

This study aimed for the following:

(1) Determination of the frequency of renal anemia refractory to EPO in hemodialysis (HD) patients.
(2) To identify various factors contributing to the etiology of renal anemia in EPO-resistant patients.

Patients and methods

The study was approved and monitored by the Medical Ethics Committee, Assiut Faculty of Medicine, IRB no: 17100366.

The investigators explained the steps and value of the research to all eligible participants. Those who agreed to be included in the study provided fully informed verbal consent.

Patients

(1) The present study is a descriptive and analytical longitudinal one, performed in the period between October 2018 and February 2019.
(2) A total of 30 patients with end-stage renal disease (ESRD) on HD were selected randomly and received EPO drug at Nephrology Unit and Outpatient Clinic of the Department of Internal Medicine of Assiut University Hospital.
(3) All patients were adult Egyptians.

Inclusion criteria

The following were the inclusion criteria:

(1) New patients with ESRD on HD not receiving EPO therapy before.
(2) Patients older than or equal to 18 years old.

Exclusion criteria

The following were the exclusion criteria:

(1) All patient with ESRD on regular HD who receiving EPO therapy.
(2) Patients younger than 18 years old.

Methods

All patient were subjected to the following:

(1) Full medical history and clinical examination.

The general data concerning patients (age, sex, comorbidities, and used medications) were recorded directly from the patients or from their hospital files.

(2) Laboratory investigations at the start of study included the following:
    (a) Complete blood count, including reticulocytes.
    (b) C-reactive protein.
    (c) Erythrocyte sedimentation rate.
    (d)Parathyroid hormone (PTH).

Intact parathyroid hormone (iPTH) was measured by chemiluminescence immunoassay, with reference range of 10–93 pg/ml.

    (e) Serum Ca++.
    (f) Serum phosphate.
    (g) Serum iron.
    (h) Serum ferritin.

(3) Follow-up of patients for 4 months with complete blood count every month.

The number of patients who respond to EPO and who failed to respond to EPO (100 IU/kg/week – SC) whit target Hb 11 g/dl. calculated and searching for the possible underling cause of anemia refractory to EPO the end of study period at the fourth month.

Ethical considerations

(1) The research was approved by Ethics and Research Committees in Assiut University Hospital, with IRB no: 17100366.
(2) Informed written consent was obtained from each patient who participated in the study.
(3) Confidentiality was maintained during all stages of the assessment.
(4) Statement describing the research procedure was given to the participants.
(5) We assured that the results of the research were only for scientific purpose and were not to be used for any other aims.

Statistical analysis

The obtained data were reviewed, prepared for computer entry, coded, analyzed, and tabulated. The data were tested for normality using the Kolmogorov–Smirnov

test and for homogeneity variances before further statistical analysis. Categorical variables were described by number and percentage, whereas continuous variables were described by mean and SD. χ^2-test used to compare between categorical variables, whereas comparison between continuous variables was done by *t*-test. A two-tailed *P* less than 0.05 was considered statistically significant. All analyses were performed with the IBM SPSS 20.0 software (statistical Package for the Social Sciences), academic institutions. United States (http://www.spss.com).

Results

A total of 30 patients with ESRD with renal anemia on HD were included (14 males and 16 females) and received EPO. These patients were classified into two groups:

(1) Group A (partial response) was formed of 23 patients with renal anemia who responded to EPO but did not reach the target level of hemoglobin (11 g/dl.).
(2) Group B (complete response) was formed of seven patients with renal anemia who responded to EPO and reached the target hemoglobin level (11 g/dl.).

Fig. 1 shows the follow-up hemoglobin level among both groups of 30 studied patients, at the start of studied groups before EPO therapy, first month, second month, and third month of hemoglobin level.

Table 1 shows the hemoglobin levels in 30 studied patients before and after EPO therapy in the follow-up period. Renal anemic patients were further subdivided into three subcategories based on the severity of anemia:

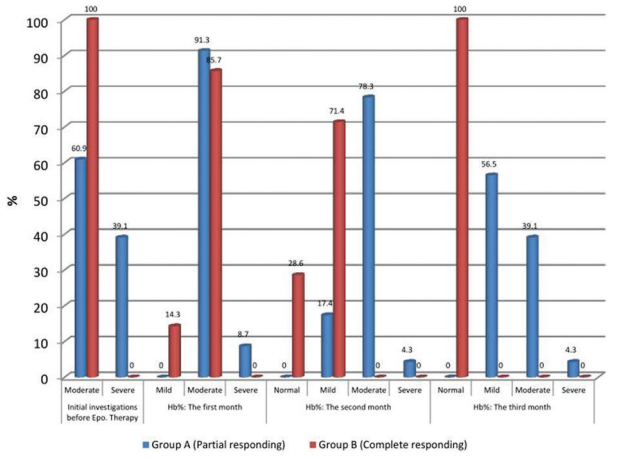
(1) Mild anemia: 10.0–10.9 g/dl.
(2) Moderate anemia: 7.0–9.9 g/dl.
(3) Severe anemia: less than 7.0 g/dl [5].

At the start of study, before the use of the EPO therapy, 21 (70%) patients had moderate anemia and nine (30) had severe anemia, whereas after first month of treatment, one (3.3%) had mild anemia, 27 (90%) had moderate anemia, and two (6.7%) had severe anemia. At the second month of treatment, two (6.7%) had normal Hb, nine (30%) had mild anemia, 18 (60%) had moderate anemia, and one (3.3%) had severe anemia.

After the third month of treatment, the hemoglobin level among studies patients significantly improved than the start of study, where seven (23.3%) had normal Hb, 13 (43.3%) had mild anemia, nine (30%) had moderate anemia, and one (3.3%) had severe anemia.

Table 2 shows that there was a statistically significant higher level of phosphorus in group A (partial

Figure 1



Hemoglobin level and follow-up of both studied groups.

Table 1 Hemoglobin levels in the 30 studied patients

Hemoglobin levels	Normal Hb% [*n* (%)]	Mild [*n* (%)]	Moderate [*n* (%)]	Severe [*n* (%)]
Initial investigations before EPO therapy	0	0	21 (70.0)	9 (30.0)
Hb%: the first month	0	1 (3.3)	27 (90.0)	2 (6.7)
Hb%: the second month	2 (6.7)	9 (30.0)	18 (60.0)	1 (3.3)
Hb%: the third month	7 (23.3)	13 (43.3)	9 (30.0)	1 (3.3)

Hb, hemoglobin.

Table 2 Laboratory data before erythropoietin therapy in both groups

Variables	Mean±SD (range)		*P*
	Group A: partial responding (*n*=23)	Group B: complete responding (*n*=7)	
PTH	481.91±235.45 (150-960)	349.86±186.79 (180-616)	0.187
ESR	18.61±10.24 (7-50)	17.86±12.54 (10-45)	0.873
CRP	6.78±10.12 (0-24)	12.34±12.03 (0-24)	0.233
Serum Ca+	7.51±1.1 (5.4-10.5)	7.96±1.22 (5.9-9)	0.368
Serum phosphorus	5.4±1.03 (4-8)	4.24±0.78 (3.1-5.1)	0.010
Serum ferritin	172.04±79.21 (50-400)	184.14±87.14 (89-300)	0.732

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PTH, parathyroid hormone.

responded), with mean ± SD (range) of 5.4 ± 1.03 (4–8), than group B (completely responded), with *P* value of 0.010.

There was no significant statistical difference between both groups regarding calcium level, parathyroid hormone, erythrocyte sedimentation rate, C-reactive protein, iron, and ferritin level, with *P* value of greater than 0.05.

Fig. 1 shows follow-up hemoglobin levels among both groups. At the start, before EPO therapy, there was a statistically significant higher level of hemoglobin in the group B than group A, with *P* value of 0.048.

There was a statistically significant higher level of hemoglobin in group B compared with group A on the second month and third month, with *P* value of 0.001. On the first month, hemoglobin level was not statistically significant between both groups, where *P* value was greater than 0.05.

Table 3 shows the follow-up hematocrit (Hct) values among the 30 studied patients in the first, second, and third month, where there was a statistically significant higher level of Hct in the group B compared with the group A, with *P* values of 0.040, 0.011, and 0.001, respectively.

However, there was no statistically significant difference between both groups regarding Hct value in the initial investigations before EPO therapy, where *P* value was greater than 0.05.

Figs. 2 and 3 show the correlation between Hb% and RBCs in the study group A, where there was a significant positive moderate correlation with RBC value ($r = 0.743$, $P < 0.000$).

Table 4 shows the possible risk factors of group A (patients with ESRD on HD who partially responded to EPO). Overall, 20 (87.0%), 17 (73.9%), and 11 (47.8%) patients had hypocalcemia, hyperparathyroidism, and hyperphosphatemia, respectively. However, low food intake (bad nutrition) was presented in 14 (60.9%), and four (17.4%) patients had iron-deficiency anemia (IDA). The number of patients who had inadequate dialysis was three (13%). Of the studied patients, four (17.4%) patients, two (8.7%) patients, five (21.7%) patients, and one (3.3%) patient had arteriovenous fistula (AVF) and chest infection, aluminum used as antacid, and acute blood loss, respectively (Fig. 3).

Discussion

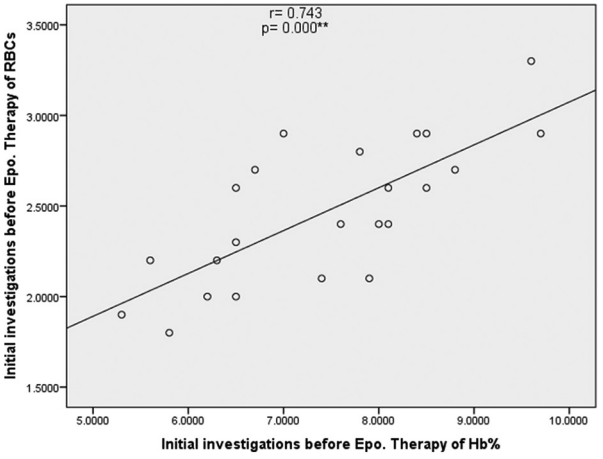
Anemia is a common complication in HD patients, mainly owing to the insufficient production of EPO by the failing kidney [6].

There is, however, a marked variability in the response to the EPO therapy, and 5–10% of the patients develop resistance to rhEPO therapy [2].

The present study tried to detect the frequency and the possible risk factors of renal anemia refractory to EPO in patients with ESRD, as this topic is underestimated in many studies that give greater concern to those on HD.

Our results showed that among patients with ESRD on HD who had anemia, 23.1% completely responded to EPO therapy, whereas 76.9% showed partial response for hemoglobin level to reach the target levels. This agrees with a study by Gouva *et al.* [7], who initiated rHuEPO therapy in patients with CKD with mild-to-moderate anemia, which was corrected to subnormal levels over a period of 6 months.

Figure 2



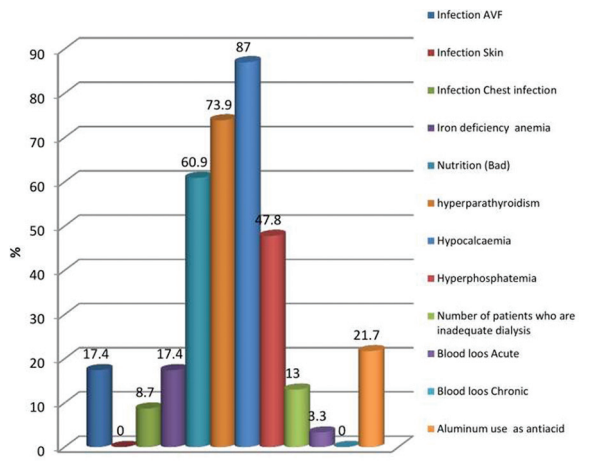
Correlation between hemoglobin % and red blood cells in group A.

Table 3 Hematocrit value and follow-up among both groups

Hct%	Mean±SD (range)		*P*
	Group A: partial responding (*n*=23)	Group B: complete responding (*n*=7)	
Initial investigations before EPO therapy	28.47±3.9 (18-33)	28.3±4.9 (25-38)	0.925
Hct: the first month	28±4.5 (20-38)	32±3.5 (29-37)	0.040
Hct: the second month	31.1±6.6 (20-45)	38.6±5.6 (30-46)	0.011
Hct: the third month	31.4±4.6 (20-39)	39.6±6.3 (31-51)	0.001

EPO, erythropoietin; Hct, hematocrit.

Figure 3



Frequency of possible risk factors in group A (partially responded to erythropoietin).

Table 4 Frequency of possible risk factors from erythropoietin resistance in group A (partial responding) patients with end-stage renal disease on hemodialysis

Possible risk factors	Group A: partial responding (*n*=23) [*n* (%)]
Infection	
AVF	4 (17.4)
Skin	0
Chest infection	2 (8.7)
Iron-deficiency anemia	4 (17.4)
Nutrition (bad)	14 (60.9)
hyperparathyroidism	17 (73.9)
Hypocalcemia	20 (87.0)
Hyperphosphatemia	11 (47.8)
Number of patients who had inadequate dialysis	3 (13)
Blood loss	
Acute	1 (3.3)
Chronic	0
Aluminum use as antacid	5 (21.7)

AVF, arteriovenous fistula.

Our study demonstrated in group A (partially responded) that there was a significant negative correlation between low hemoglobin and high level of PTH (~481.91 ± 235.45 pg/ml), which agrees with Rao *et al.* [8], who reported that those with anemia did not respond to EPO therapy, with mean levels of PTH at ~800 ± 248 pg/ml, which explains why the high PTH level associated with low hemoglobin level. It is suggested that excessive amounts of PTH interferes with normal erythropoiesis by downregulating the EPO receptors on erythroid progenitor cells in the bone marrow [9].

Erythropoiesis is highly dependent upon iron availability. Infections and inflammations cause an increase of production of hepcidin by liver, which has intrinsic antimicrobial activity, and its expression increases in response to inflammatory stimuli. These inflammatory cytokines may result in inefficient macrophage iron release and subnormal intestinal iron absorption. Many studies have shown a correlation between inflammation, elevated circulating cytokines, and anemia in patients [10]. Our study demonstrated in group A (partially responded) that four (17.4%) and two (8.7%) patients had AVF and chest infection with low hemoglobin level, respectively; however, the relation of these values was insignificant, so studies on a large number of patients with infections are needed to confirm these results.

Lastly, the results of this study revealed that the 23 patients who partially responded had low-nutrition food intake (bad nutrition), IDA, inadequate dialysis, AVF and chest infection, aluminum-containing drugs, acute blood loss, hypocalcemia, hyperphosphatemia, and hyperparathyroidism, which may be the possible risk factors of renal anemia refractory to EPO.

Conclusion

Our study concluded that availability of recombinant human EPO has led to almost complete disappearance of severe anemia in HD patients; however, despite an increase in its use and average dose, a substantial percentage of patients still fail to achieve the Hb targets.

Anemia refractory to EPO is common in HD patients (76.6%), which may be owing to several factors. Parenteral iron supplement and treatment of hyperparathyroidism may have good roles in improving the refectory anemia of renal disease in patients with ESRD on HD.

Recommendations

Regarding the results of the current study, we recommend monitoring and monthly follow-up of complete blood count in patients with ESRD and serum levels of iron, calcium, phosphate, and PTH for early detection and management of refectory renal anemia, and we recommend to correct all factors contributing toward resistant anemia to EPO, such as increased PTH, infections, IDA, and inadequate dialysis to improve outcomes in patients with ESRD. More studies should be done on a larger numbers of patients with ESRD having renal anemia for more demonstration of the possible causes of this condition.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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