Anemia Evaluation and Erythropoietin Dose Requirement Among Hemodialysis Patients

A Multicenter Study

Mohsen Nafar,[1,2] Shiva Samavat,[1,2] Alireza Khoshdel,[3] Behrang Alipour-Abedi[2,4]

[1]Department of Nephrology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Public Health, School of Medicine, AJA University of Medical Sciences, Tehran, Iran
[4]Iranian Society of Nephrology, Tehran, Iran

Keywords. anemia, erythropoietin, end-stage renal disease, hemodialysis, hemoglobin

Original Paper

Introduction. Both anemia and high doses of erythropoietin have been associated with increased mortality among dialysis patients. This study was conducted to evaluate the effective dose of erythropoiesis-stimulating agents.

Materials and Methods. This multicenter nationwide cross-sectional study assessed adult patients on hemodialysis for at least 3 months from 80 hemodialysis centers in Iran. Demographic data, erythropoietin dose, and laboratory data were collected.

Results. A total of 7009 prevalent hemodialysis patients were enrolled. Fifty-five percent of the patients had their hemoglobin levels within the target values. In those with a hemoglobin level of 8 g/dL to 10 g/dL, an erythropoietin dose of 10000 IU/wk to 12000 IU/wk led to a significant increase in hemoglobin level. A mean erythropoietin dose of 7700 IU/wk was effective in maintaining the target hemoglobin of 10 g/dL to 12 g/dL during a 3-month follow-up period. Improvement in hemoglobin level was associated with male sex, diabetes mellitus, and hemodialysis adequacy, and its deterioration with lower parathyroid hormone, calcium-phosphorus product, and creatinine levels; malnutrition; transfusion; and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers ($R^2 = 29.1\%$, $P < .001$). A dosage of 66.5 IU/kg/wk led to 1 g/dL increase in hemoglobin in anemic patients.

Conclusions. Data suggested that an estimated erythropoietin dose of 66.5 IU/kg/wk for each 1 g/dL hemoglobin level below the target could be used as a guide for prescription. A dosage of about 8000 IU/wk could help maintaining hemoglobin within the target. A longitudinal study is needed to estimate the required erythropoietin dose.

IJKD 2017;11:56-65
www.ijkd.org

INTRODUCTION

Anemia is a frequent complication in patients with chronic kidney disease, as about three-quarter of patients with end-stage renal disease have been reported to be anemic.[1] It occurs mostly due to reduced production of erythropoietin by renal parenchymal cells. The erythropoiesis-stimulating agents (ESAs) are the main players in anemia management in hemodialysis patients. A wide variety of factors have been reported to influence the optimal response to these agents, such as iron deficiency, secondary hyperparathyroidism, dialysis

adequacy, systemic inflammation, malnutrition, and drugs.[2] However, the results of the studies are contradictory and the studied populations were small.[3,4]

On the one hand, low hemoglobin level is associated with increased mortality,[5] and on the other, high doses of ESAs and variable hemoglobin level were associated with increased mortality. A metaregression analysis reported a higher all-cause mortality rate among patients with chronic kidney disease with higher ESA doses (a per erythropoietin alfa-equivalent of a 10000 U per week increment) independent of achieved or targeted hemoglobin.[6] Yet, poor erythropoietin response was associated with decreased survival, which might be the effect of high doses of ESA rather than not achieving the target hemoglobin.[7] Additionally, the increments in erythropoietin dose does not necessarily result in improvement of hemoglobin level. Thus, there is a growing interest by the Kidney Disease Improving Global Outcome (KDIGO) guideline in defining the effective factors and estimating the optimal dose of erythropoietin that can help reaching the hemoglobin target without increasing mortality.[8]

The present study was a cross-sectional study designed to evaluate the current status of anemia among hemodialysis patients, in order to identify the influential factors in erythropoietin responsiveness, and to estimate the dose-response relationship between erythropoietin dose and hemoglobin response. This study was designed to establish the lowest erythropoietin dose with a gradual increase in the hemoglobin concentration toward the target.

MATERIALS AND METHODS

Patients and Data Collection

In a multicenter cross-sectional and prospective study, 7009 point-prevalent hemodialysis patients from 21 provinces of Iran (80 centers) were included. The sample size from each province was proportional to the share of that province from the total hemodialysis patients. A cluster sampling system was designed in order to reach the desired sample size. Patients older than 18 years who were on dialysis for at least 3 months and had no history of hematologic disorders such as thalassemia, sickle cell disease, and hematologic malignancies were included in the study. The Ethics Committee of Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, approved the study protocol. Informed consents were obtained from all participants.

Data collection included demographic characteristics, cause of end-stage renal disease, time on dialysis, history of recent transfusion, and type and dose of erythropoietin (unit per week), type and dose of iron preparation, and other medications (folic acid, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blocker [ARBs], and statins). Three consecutive monthly laboratory records of patients were collected by trained nurses and data were entered to a specifically designed software. Laboratory data collected from patients' chart included anemia (based on hemoglobin level, hematocrit level, and mean corpuscular volume), mineral bone disease (serum calcium, phosphorus, and intact parathyroid hormone [PTH]), iron status (serum iron, total iron binding capacity, and serum ferritin), dialysis prescription (blood flow rate, ultrafiltration rate, time of session, and type of dialysis membrane) and dialysis adequacy (pre- and post-blood urea nitrogen and single-pool Kt/V), malnutrition (serum albumin, total cholesterol, and serum creatinine), and inflammation (C-reactive protein [CRP]).

In order to define the iron status of patients, we used the following criteria: iron adequacy was defined as a serum ferritin level greater than 200 ng/mL and a transferrin saturation (TSAT) level greater than 20%; functional iron deficiency was defined as a ferritin level greater than 200 ng/mL and TSAT less than 20%; and absolute iron deficiency was defined as a ferritin level less than 200 ng/mL and TSAT less than 20%.

Statistical Analysis

Results were presented as mean ± standard deviation for quantitative variables and were summarized as frequencies and percentages for categorical variables. Quantitative and qualitative variables were compared by the *t* test and the chi-square test, respectively. Correlation between the quantitative variables was examined using the Pearson correlation coefficient test. Regression model and multivariable analysis were conducted and the findings were interpreted based on the clinical logics. For the statistical analysis, the SPSS software (Statistical Package for the Social Sciences, version 21.0, SPSS Inc, Chicago, IL, USA) was used. *P* values less than .05 were considered significant.

RESULTS

Baseline Demographic Characteristics

From 80 centers across the country, 7009 prevalent hemodialysis patients enrolled in the study from January 2015 to December 2015. The baseline characteristics and demographic data of the patients are demonstrated in Table 1. The mean age of the patients was 57.2 ± 14.9 years, and 62.3% of them were older than 55 years. Men constituted 58.4% of the patients and the mean age of the men and the women was not significantly different (56.8 ± 15.2 years versus 57.8± 14.4 years, respectively). Dialysis vintage was 40.0 ± 35.2 months, with 37% patients on dialysis for 12 to 36 months. The maximum time on dialysis was 183 months.

Hemoglobin Level and Erythropoietin Dose

The mean hemoglobin level among all the recruited patients was 10.7 ± 1.4 g/dL, with a wide variation across the country, ranging from 10.1 ± 1.4 g/dL to 11.8 ± 1.6 g/dL. Hemoglobin level was not significantly different between the men and the women (10.8 ± 1.4 g/dL versus 10.6 ± 1.3 g/dl, respectively).

Based on the KDIGO guideline, a target hemoglobin was considered as a hemoglobin level of 10 g/dL to 12 g/dL, and 54.5% of prevalent patients were in the target range. The percentage of anemic patients was 28.3%, of whom 3% had a hemoglobin level below 8 g/dL. Finally, 17.2% of the patients had a hemoglobin level above 12 g/dL.

Erythropoietin had been prescribed for 95.5% of the hemodialysis patients. The mean weekly dose of erythropoietin was 8180 ± 5001 IU/wk, with the dose adjusted for body weight of 128.5 ± 82 IU/kg/wk. Fifty-two percent of the patients were treated with weekly doses of 4000 IU to 10000 IU of erythropoietin, while 33.3% of the patients were being treated with doses higher than 10000 IU/wk. The type of erythropoietin provided to patients was as follows: PDpoietin (erythropoietin alpha) in 92.1%, CinnaPoietin (erythropoietin beta) in 4.74%, and Exipoetin (erythropoietin alpha) in 3.2% of the patients.

During the 3-month observation period, while the mean hemoglobin level of the patients did not have a significant change, there was a significant increment in erythropoietin dose from 8127 IU/wk to 8255 IU/wk ($P < .05$; Figure 1). In order to assess the erythropoietin dose and hemoglobin level relationship, we categorized the patients based on their hemoglobin level into 4 groups of less than 8 g/dL, 8 g/dL to 10 g/dL, 10 g/dL to 12 g/dL, and greater than 12 g/dL. Figure 2 demonstrates the hemoglobin trend and erythropoietin dose in these subgroups. As expected, in order to reach the target

Table 1. Baseline Characteristics and Demographic Data*

Characteristic	Value
Number of patients	7009
Mean age, y	57.2 ± 14.9
Male sex, %	58.4
Mean dry weight, kg	65.5 ± 11.5
Mean body mass index, kg/m^2	24.1 ± 3.5
Body mass index, kg/m^2	
< 20	9.4
20 to 25	57.7
26 to 30	25.5
> 30	7.4
Cause of end-stage renal disease	
Diabetes mellitus	36.8
Hypertension	28.7
Glomerulonephritis	6.45
Polycystic kidney disease	3.52
Others	10.58
Unknown	13.95
Mean dialysis vintage, mo	40.0 ± 35.2
< 6	7.0
6 to 12	12.1
13 to 36	37
37 to 60	21.4
> 60	22.5

*Values are mean ± standard deviations and percentages.

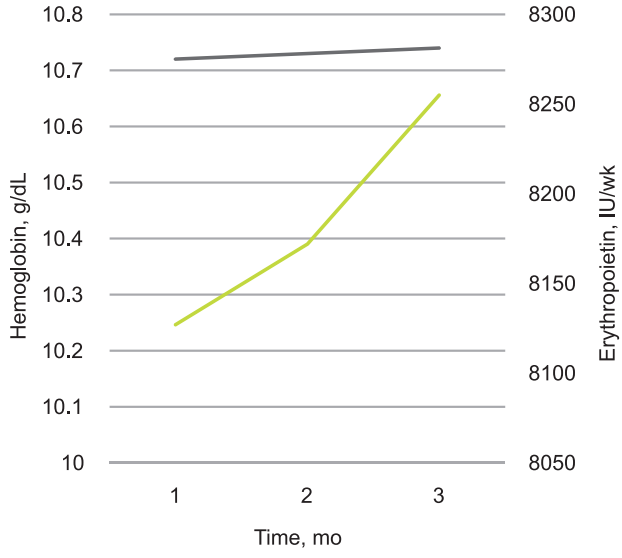

Figure 1. The trend of hemoglobin level and erythropoiesis-stimulating agents during the 3-month observation.

hemoglobin, those with hemoglobin levels less than 8 g/dL received highest doses of erythropoietin and those with hemoglobin levels greater than 12 g/dL received the lowest erythropoietin dose (Figures 2A and 2D). However, in the patients with hemoglobin levels between 8 g/dL and 10 g/dL, the increment in erythropoietin dose during the observation period did not result in improving hemoglobin levels on average (Figure 2B). With the aim of evaluating the most effective dose of erythropoietin in this subgroup, we stratified patients based on erythropoietin dose at initial visit and evaluated the hemoglobin response in these groups. Among these patients, those who started with erythropoietin 10000 IU/wk to 12000 IU/wk had a significant increase in hemoglobin level when compared to lower and higher doses (Figure 3). However, the mean erythropoietin dose of 6000 IU/wk to 8000 IU/wk did not lead to significant increases in hemoglobin levels (Figure 3A), and

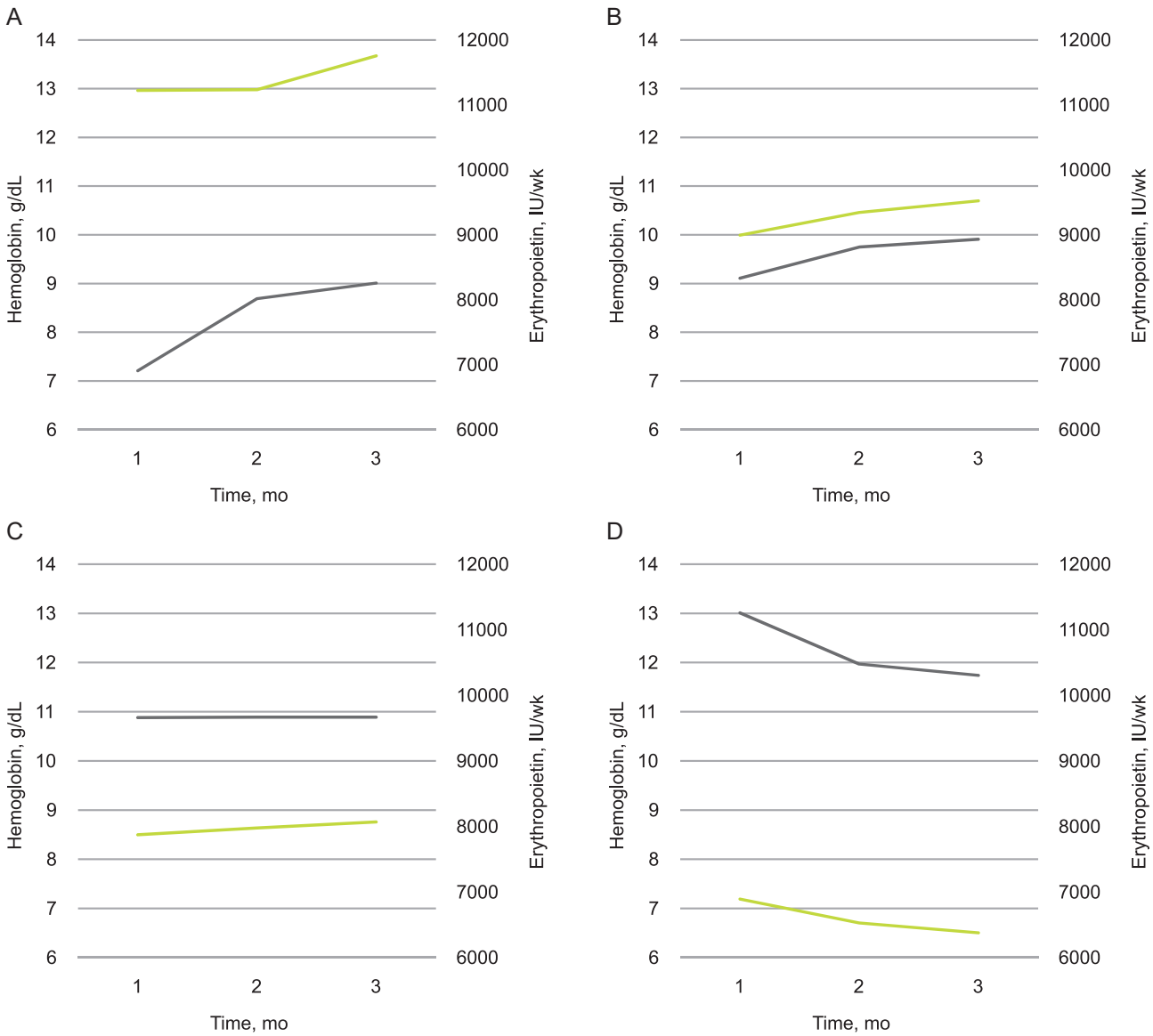

Figure 2. The trend of hemoglobin level and erythropoietin dose in different hemoglobin subgroups. A, Those with a hemoglobin level less than 8 g/dL were treated with a mean erythropoietin dosage of 11 000 IU/wk and a significant increase in hemoglobin with incrementing erythropoietin dose. B, In patients with a hemoglobin level of 8 g/dL to 10 g/dL with a mean erythropoietin dose of 9000 IU/wk, the increase in erythropoietin dose did not lead to significant increase in hemoglobin level. C, In patients with a hemoglobin level of 10 g/dL to 12 g/dL, there was no significant change in hemoglobin level and erythropoietin during the observation period. D, In patients with a hemoglobin level greater than 12 g/dL, a small decrease in erythropoietin dose led to a decrease in hemoglobin into the target range.

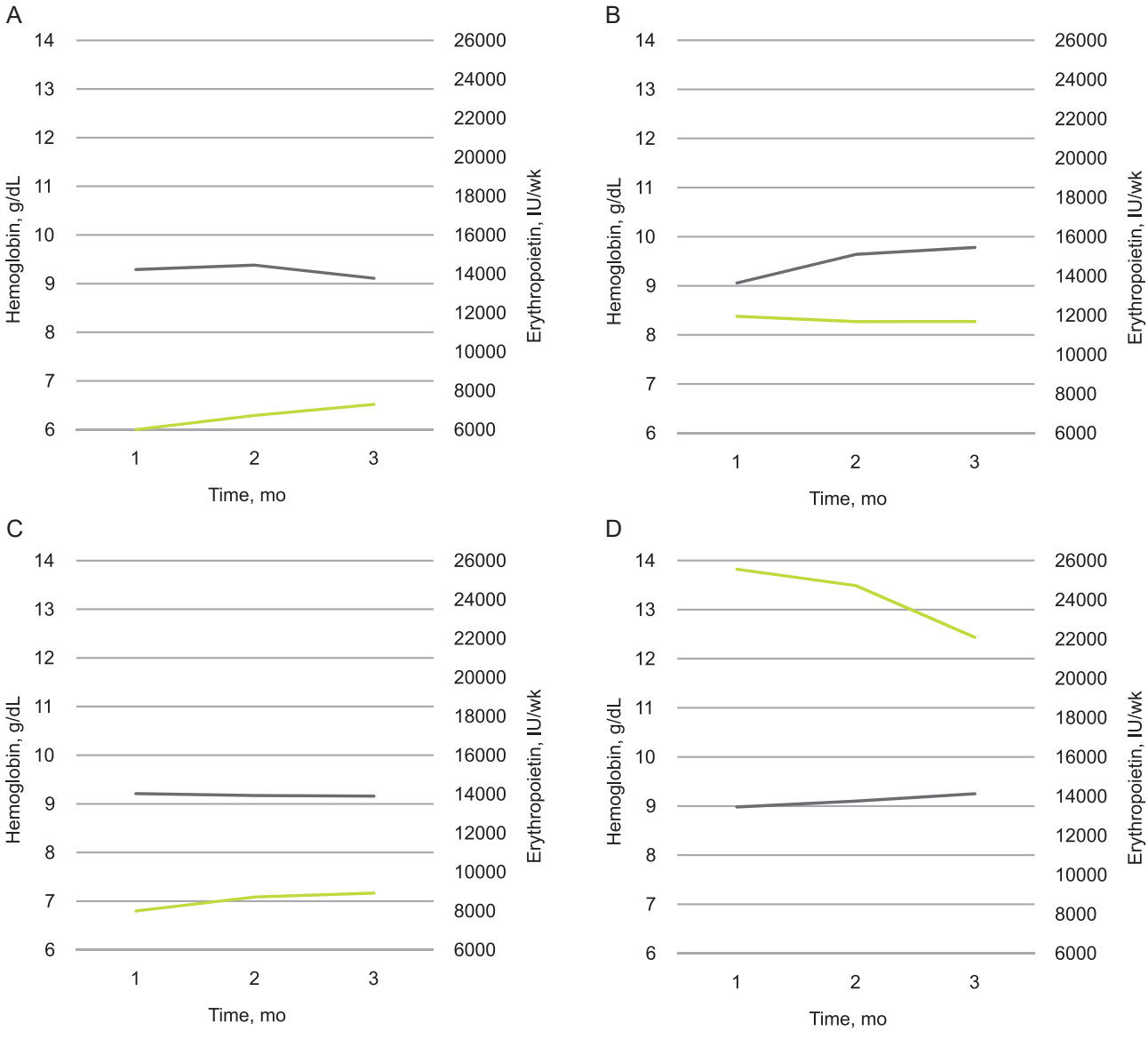

Figure 3. Baseline erythropoietin dose and its effect on hemoglobin level in patients with a hemoglobin level of 8 g/dL to 10 g/dL. A, Treatment with an erythropoietin dose of 6000 IU/wk to 8000 IU/wk did not lead to improvement in hemoglobin level. B, An erythropoietin dose of 8000 IU/wk to 10000 IU/wk also did not result in target hemoglobin level. C, Treatment with an erythropoietin dose of 10000 IU/wk to 12000 IU/wk resulted in a significant increase in hemoglobin level. D, Treatment with an erythropoietin dose larger than 20000 IU/wk did not make a significant change in hemoglobin level.

neither did the mean dose of 8000 IU/wk to 10000 IU/wk (Figure 3B). Doses larger than 20000 IU/wk in this group of patients did not lead to a significant increase in hemoglobin level (Figure 3D). Thus, the optimal dose to improve hemoglobin level in patients with basal hemoglobin between 8 g/dL and 10 g/dL seemed to be between 10000 IU/wk and 12000 IU/wk.

Although an erythropoietin dose of 10000 IU/wk to 12000 IU/wk seemed to be the most effective one in the patients with a hemoglobin level of 8 g/dL to 10 g/dL, 50% of patients in this group received an erythropoietin less than 10000 IU/wk, that pointed out the need for re-evaluation of erythropoietin prescription. (Figure 4). On the other end of hemoglobin range, 37.7% of those with hemoglobin levels greater than 12 g/dL received high doses of ESAs that was not necessary.

Iron Status

Of all of the participants, 59.6% had an adequate iron status, while 24.4% and 16.0% had functional

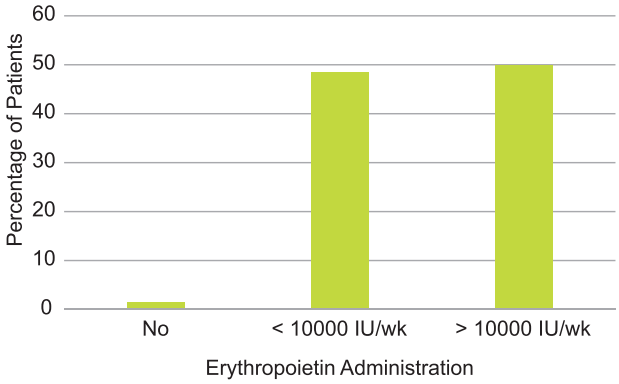

Figure 4. Erythropoietin dose in patients with a hemoglobin level between 8 g/dL and 10 g/dL.

iron deficiency and absolute iron deficiency, respectively. In addition, 31.8% had a TSAT less than 20%, and 33.5% had a serum ferritin less than 200 ng/mL, while 29.5% had a ferritin level greater than 500 ng/mL. Among patients with iron deficiency, 66.6% of the diabetic patients had functional iron deficiency compared to 57.1% in nondiabetic individuals ($P < .001$; odds ratio, 1.28; 95% confidence interval, 1.16 to 1.42).

Dialysis Adequacy

As a dialysis adequacy index, 27.6% of the patients had a single-pool Kt/V greater than 1.4, which was the target as determined by the Kidney Disease Outcomes Quality Initiative. About 42% of the patients had a Kt/V less than 1.2, which was lower than the minimum acceptable delivered single-pooled Kt/V.

Factors Associated With Lower Hemoglobin Level

In order to ascertain factors that might have influence on hemoglobin level, we divided patients into 2 groups based on their hemoglobin level (hemoglobin < 10 g/dL versus ≥ 10 g/dL). The proposed affecting factors that were studied are as followed: sex, age, time on dialysis, history of blood loss, history of diabetes mellitus, history of hypertension, body mass index, dialysis adequacy (single-pool Kt/V), malnutrition, serum albumin, iron status, CRP, intact PTH, erythropoietin dose, iron supplement, and drug history (ACE inhibitors, ARBs, and statins). Malnutrition was defined based on the presence of 3 out of 4 the following criteria: serum creatinine less than 8 mg/dL, triglyceride less than 150 mg/dL, cholesterol less than 150 mg/dL, and serum albumin less than 4 g/dL.

In univariable analysis, younger age, malnutrition, lower serum albumin and ferritin level, positive CRP, and ACE inhibitors or ARBs use were associated with hemoglobin levels lower than 10 g/dL. Surprisingly, diabetes mellitus was significantly less prevalent among patients with a hemoglobin level less than 10 g/dL (Table 2).

In a subgroup analysis among patients with hemoglobin levels less than 8 g/dL who were treated with erythropoietin dose higher than 20000 IU/wk, data demonstrated that 32% of them had ferritin levels less than 500 ng/dL and 23% had functional iron deficiency. Thus, improvement of their iron status and inflammation as the major cause of functional iron deficiency might help reducing the needed erythropoietin dose. Additionally, about 75% of them had a Kt/V less than 1.4 (44.2% with Kt/V < 1.2).

The McNemar-Bowker test revealed that achieving target hemoglobin levels was lower in patients with a PTH level greater than 300 pg/mL (45.3%) when compared to lower PTH groups (about 51%; $P < .001$). However, the patients with higher PTH level were older.

A logistic regression model including the abovementioned factors had 80% accuracy for predicting target hemoglobin achievement ($P < .001$). Achieving target hemoglobin was significantly and directly associated with baseline hemoglobin, male sex, diabetes mellitus, statin use, and erythropoietin dose and inversely with PTH, ACE inhibitor or ARB use, and history of transfusion and intravenous iron dose. In multivariable analysis, improvement in hemoglobin in two consecutive visits was associated significantly and positively with baseline hemoglobin, male sex, diabetes mellitus, and hemodialysis adequacy and negatively with PTH, calcium-phosphorus product, serum creatinine, malnutrition, history of transfusion, and administration of ACE inhibitors or ARB medication ($R^2 = 29.1\%$, $P < .001$), but not independently related to age, iron deficiency and body mass index. However, when diabetes mellitus was removed from the model, iron status converted to a significant factor.

With the aim of estimating the initiating dose of erythropoietin in patients with anemia, we compared anemic patients who achieved target with those who did not. Data suggested that a dose of

Table 2. Factors Associated With Lower Hemoglobin Level

Parameter	Hemoglobin Level		*P*
	< 10 g/dL	≥ 10 g/dL	
Mean age, y	55.7 ± 15.3	57.8 ± 14.7	< .001
Male sex, %	55.9	59.4	<.05
Mean dialysis vintage, mo	38.3 ± 33.9	40.8 ± 35.6	< .05
History of blood loss, %	31.3	32.2	< .001
History of diabetes mellitus, %	33.9	38.0	< .05
History of hypertension, %	32.9	34.7	> .05
Mean body mass index, kg/m^2	24 ± 3.5	24.1 ± 3.5	> .05
Single-pool Kt/V < 1.2, %	44.4	40.9	<.05
Malnutrition, %	47.0	40.0	<.001
Mean serum albumin, g/dL	3.80 ± 0.48	3.90 ± 0.54	< .001
Positive C-reactive protein, %	41.7	38.7	<.05
Intact parathyroid hormone, pg/mL	259.8 ± 274.2	247.0 ± 240.8	> .05
Mean serum ferritin, ng/mL	388 ± 361	411 ± 360	< .001
Absolute iron deficiency, %	15.8	12.9	< .001
Functional iron deficiency, %	40.5	36.7	< .001
Adequate iron state, %	43.7	50.3	< .001
Mean erythropoietin dose, IU/wk	10219 ± 5637	7375 ± 4479	< .001
Iron supplement, %	90.3	87.6	< .05
Angiotensin-converting enzyme inhibitor use, %	12.6	9.7	< .001
Angiotensin receptor blocker use, %	31.0	23.2	< .001
Statin use, %	16.7	22.0	< .001

*Values are mean ± standard deviations and percentages.

66.5 U/kg/wk of erythropoietin for each unit deficit in hemoglobin yielded the best positive likelihood ratio, and 59.1 U/kg/wk demonstrated the best negative likelihood ratio for target achievement. Since positive result was of interest, 66.5 IU/Kg/wk for each hemoglobin unit deficit could be used as a rule of thumb in administration of erythropoietin for optimal hemoglobin target.

DISCUSSION

In this cross-sectional study, 7009 prevalent dialysis patients older than 18 years were evaluated. The mean age was 57 years, which demonstrated the fact that dialysis patients are becoming older since in 2006 when the mean age was 52.8 years old.[9] This was also obvious when we compared the percentage of patients older than 65 years old (there was a significant increment from 22% to 34%).[10] The same pattern of aging was reported in the United State Renal Data System (USRDS) annual report.[11] This might be due to the fact that the survival on dialysis improved or the fact that younger patients with end-stage renal disease proceeded to transplantation. The male-female ratio was gradually increased over the past 15 years from 1.24 in 2000 to 1.32 in 2006 and finally to 1.5 in our recent study.[9,10]

With respect to anemia management, mean hemoglobin level was 10.7 ± 1.4 g/dL with 54.5% of patients within the KDIGO target range (10 g/dL to 12 g/dL) and only 3% of patients had hemoglobin levels less than 8 g/dL. When compared with data from 2005, the percentage of severely anemic patients (hemoglobin level below 8 g/dL) declined from 14.8% to 3% and mean hemoglobin level was improved over the past decade (mean hemoglobin level was 10.14 ± 2 g/dL in a study in 2005).[12] In our cohort, 17.2% of patients had hemoglobin levels higher than 12 g/dL, whereas on USRDS report only 13.5% had hemoglobin more than 12 g/dL.[11]

The mean dose of erythropoietin was 102.45 ± 29.10 IU/Kg/wk in 2005, which has been increased to 128.5 ± 82 IU/Kg/wk in our recent study.[12] This increment in erythropoietin dose seemed to result in better anemia target, while at the same time, there was also a decrement in percentage of patients with hemoglobin levels higher than 12 g/dL. These differences might be due to the fact that recently published data were emphasizing on the cardiac side effects of high doses of erythropoietin and that of high hemoglobin levels.

Miskulin and colleagues showed a sharp decrease in erythropoietin dose and at the same period an increase in percentage of patients with hemoglobin levels less than 10 g/dL, and predicted that without individualization of anemia management, the current trend in decreasing erythropoietin dose would lead to emergence of patients with hemoglobin level less than 10 g/dL and immunologic and infectious complications of transfusion.[13]

While the mean monthly dose of erythropoietin was lower in our study than in the USRDS report (8180 ± 5001 U/wk versus 10620 ± 17.9 U/wk), higher percentage of our patients receiving erythropoietin treatment (95.5% versus 80%), which might be due to higher prevalence of anemic patients in our study (28.3% versus 21.5% of patients with hemoglobin levels less than 10 g/dL).[11]

Of our studied patients, 24.41% and 16.03% had functional iron deficiency and absolute iron deficiency, respectively. Functional iron deficiency was more prevalent among diabetic patients, which might be due to systemic inflammation. While mean TSAT was 33.3% and the mean serum ferritin was about 400 ng/mL, a TSAT less than 20% and serum ferritin level less than 200 ng/mL were reported in 31.8% and 33.5% of the hemodialysis patients, respectively. As excessive iron load may induce hepcidin and suppress erythropoiesis,[14] judicious and exact regulation of iron status and serum ferritin seems to be necessary, and defining a robust ferritin level is needed.

Dialysis adequacy as indicated by a Kt/V of 1.2 and greater was achieved in 58% of our patients (with the mean Kt/V of 1.26 ± 0.18). Despite the impressive improvement comparing to previous data of mean Kt/V of 0.97 ± 0.25 in 2005,[15] and 43.3% of patients with a Kt/V higher than 1.2 in a report from 2008 report of Iran,[16] this finding might be affected by smaller body size of Iranian patients and less availability of high-flux dialysis membranes.

Evaluating the erythropoietin dose-response amongst patients with different baseline hemoglobin in our study, we demonstrated that in patients with hemoglobin levels lower than 8 g/dL, the increasing trend of erythropoietin resulted in improvement of hemoglobin level. These patients needed 12000 U/wk in order to increase their hemoglobin level, but only 65% of them received the adequate dose. On the other end of hemoglobin range (hemoglobin levels greater than 12 g/dL), gradual small decrease in erythropoietin dose did not lead to anemia development and patients were still in the target range. Amongst patients with baseline hemoglobin of 8 g/dL to 10 g/dL in our study showed the point that a dose of 10000 U/wk to 12000 U/wk might lead to significant increase in hemoglobin levels toward the target. Doses lower than 10000 U/wk were not sufficient to cause increments in hemoglobin level in this group and doses greater than 20000 U/wk were not able to increase hemoglobin toward target. It seems that further increase in ESA dose cannot correct anemia. In order to evaluate the reason for this nonresponsiveness, we evaluated the iron status and dialysis adequacy of anemic patients with erythropoietin dose more than 20000 U/wk. Serum ferritin was less than 200 ng/mL in 20% of them and less than 500 ng/mL in 32%, and 23% had functional iron deficiency. Single-pool Kt/V was less than 1.2 in more than 44.2% of patients (single-pool Kt/V < 1.4 in about 75%). It seems that better iron profile and dialysis adequacy would lead to better erythropoietin response.

With the assumption of individualization of ESA dosing instead of "one size fit all" method, a study in 2008 suggested the initiating dose of 12000 U/wk to 14000 U/wk to be effective in erythropoietin naive dialysis patients in achieving the target hematocrit of 36%.[17] However, as our study was a cross-sectional, patients were not erythropoietin naive and the follow-up was short (only 3 months), the requisite dose of erythropoietin was lower. Despite these limitations, 10000 U/wk to 12000 U/wk appears to be an appropriate dose after improving iron and dialysis indexes.

In order to maintain the target hemoglobin of 10 g/dL to 12 g/dL, our results suggested an erythropoietin dose of 7700 U/wk could maintain target hemoglobin during the 3-month follow-up. Cotter and colleagues demonstrated the average erythropoietin dose of 7500 U/wk to 15000 U/wk was appropriate to maintain hematocrit in target range of 33% to 36%, which was almost the same as our results. However, these findings are contradictory to the Food and Drug Administration recommendation of utilization of lowest ESA dose with gradual increment to reach the target hemoglobin.[17]

Our results could be used as a guide for policy makers to estimate the ESA requirements, nonetheless these data are not solid as a wide list of factors apart from the baseline hemoglobin level should be considered in order to achieve optimal anemia management. Accordingly, factors associated with low hemoglobin level such as iron status, hyperparathyroidism, dialysis adequacy, inflammation, malnutrition, and drugs like statins, ACE inhibitors, and ARBs should be considered.[2] If these factors are not taking into account, the prerequisite erythropoietin dose would be underestimated and there would be higher rates of hyporesponsiveness.

Our data demonstrated that younger age, female sex, inadequate dialysis, malnutrition, lower albumin level, and a positive CRP as a marker of inflammation were associated with lower hemoglobin level. Furthermore, an intact PTH greater than 300 pg/mL, iron deficiency, and ACE inhibitor or ARB use were more common in patients with a hemoglobin level less than 10 g/dL. These results were consistent with previous studies,[18-20] except for the fact that anemia was less frequent in diabetic patients and older ones. The exact reasons for discrepancies were not detected.

In multivariable analysis, the baseline hemoglobin, male sex, statin use, and diabetes mellitus were positively associated with reaching the target hemoglobin, and factors such as PTH, ACE inhibitors and ARB use, and history of transfusion and iron dose were inversely associated with target hemoglobin achievement. Taking these confounding factors into account, we estimated the initial erythropoietin dose of 66.5 U/kg/wk as an optimal dose in hemodialysis patient, that is for a 70 kg hemodialysis patient with a baseline hemoglobin of 9 g/dL, the initial erythropoietin dose for reaching a hemoglobin level of 11 g/dL is 9310 U/wk (eg, erythropoietin dose = [11 − 9] × 66.5 × 70 U/wk). This finding, if confirmed in ESA-naive patients, would be a guide for treatment and estimating the needed doses of ESA in dialysis centers and could highly prevent unnecessary doses of ESA and its complications.

Our study had several limitations. First, it was a cross-sectional study with a short follow-up period, which made cause-and-effect conclusions less implacable. Second, we were not aware of duration of erythropoietin treatment prior to the study. Recently, studies with the aim of individualizing ESA dosing were conducted utilizing biophysical system dynamics and artificial neural network-based approaches and demonstrated less hemoglobin variability and better achievement of targets.[21,22] Studies with longitudinal design on ESA-naive dialysis patients with recent initiation of dialysis may help to overcome these limitations and provide materials for model predictive control approach.

CONSLUSIONS

Despite significant improvement in anemia management, there is a necessity for nationwide efforts in order to improve iron status and dialysis adequacy. Our results suggest the initial erythropoietin dose of 66.5 U/kg/wk in patients with anemia and a maintenance dose of about 8000 U/wk in patients within the target hemoglobin range of 10 g/dL to 12 g/dL. Further, artificial intelligence studies are needed to improve anemia management and avoid complications hemoglobin variability and high-dose ESA by individualizing ESA dosing instead of a one-size-fits-all protocol-based approach.

ACKNOWLEDGEMENTS

Authors thank Dr Nayeb-Pour and Dr Tabatabaie for their cooperation.

FINANCIAL SUPPORT

The study was supported by a grant from Pooyesh Darou Biopharmaceutical Co.

CONFLICT OF INTEREST

Mohsen Nafar and Behrang Alipour-Abedi have editorial relationship with the *Iranian Journal of Kidney Disease*.

REFERENCES

1. Johnson DW, Pascoe EM, Badve, SV, et al. A Randomized, Placebo-Controlled Trial of Pentoxifylline on Erythropoiesis-Stimulating Agent Hyporesponsiveness in Anemic Patients With CKD: The Handling Erythropoietin Resistance With Oxpentifylline (HERO) Trial. Am J Kidney Dis. 2015; 65:49-57.
2. Johnson DW, Pollock CA, Macdougall IC. Erythropoiesis-stimulating agent hyporesponsiveness. Nephrology. 2007;12:321-30.
3. Panich V1, Rosati A, Bigazzi R, et al. Anaemia and resistance to erythropoiesis-stimulating agents a prognostic factors in haemodialysis patients: results from the RISCAVID study. Nephrol Dial Transplant.

2011;26:2641-8.

4. Ogawa T, Shimizu H, Kyono A, et al. Relationship between responsiveness to erythropoiesis stimulating agent and long-term outcomes in chronic hemodialysis patients: a single-center cohort study. Int Urol Nephrol. 2014;46:151-9
5. Hanafusa N, Nomura T, Hasegawa T, et al. Age and anemia management: relationship of hemoglobin levels with mortality might differ between elderly and nonelderly hemodialysis patients. Nephrol Dial Transplant. 2014;29:2316-26.
6. Koulouridis I, Alfayez M, Trikalinos TA, et al. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. Am J Kidney Dis. 2013;61:44-56.
7. Duong U, Kalantar-Zadeh K, Molnar MZ, et al. Mortality Associated with Dose Response of Erythropoiesis-Stimulating Agents in Hemodialysis versus Peritoneal Dialysis Patients. Am J Nephrol. 2012;35:198-208.
8. Drüeke TB, Parfrey PS. Summary of the KDIGO guideline on anemia and comment: reading between the (guide) line(s). Kidney Int. 2012;82:952-60.
9. Mahdavi-Mazdeh M. Renal Replacement Therapy in Iran. Urol J. 2007;4:66-70
10. Nobakht Haghighi A, Broumand B, D'Amico M, et al. The epidemiology of end-stage renal disease in Iran in an international perspective. Nephrol Dial Transplant. 2002;17:28-32.
11. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2016;67:S139-58.
12. Mahdavi-Mazdeh M, Zamyadi M, Nafar M. Assessment of management and treatment responses in haemodialysis patients from Tehran province, Iran. Nephrol Dial Transplant. 2008;23:288-93.
13. Miskulin DC, Zhou J, Tangri N, et al. Trends in anemia management in US hemodialysis patients 2004–2010. BMC Nephrol. 2013;14:264.
14. Ogawa C, Tsuchiya K, Fumiyoshi Kanda F, et al. Low Levels of Serum Ferritin Lead to Adequate Hemoglobin Levels and Good Survival in Hemodialysis Patients. Am J Nephrol. 2014;40:561-70.
15. Aghighi M, Heidary Rouchi A, Zamyadi M, et al. Dialysis in Iran. Iran J Kidney Dis. 2008;2:11-5.
16. Amini M, Aghighi M, Masoudkabir F, et al. Hemodialysis Adequacy and Treatment in Iranian Patients A National Multicenter Study. Iran J Kidney Dis. 2011;5:103-9.
17. Cotter D, Zhang Y, Thamer M, et al. The effect of epoetin dose on hematocrit. Kidney Int. 2008;73:347-53.
18. Rossert J, Gassmann-Mayer C, Frei D, et al. Prevalence and predictors of epoetin hyporesponsiveness in chronic kidney disease patients. Nephrol Dial Transplant. 2007;22:794-800.
19. de Lurdes Agostinho Cabrita A, Pinho A, Malho A, et al. Risk factors for high erythropoiesis stimulating agent resistance index in pre-dialysis chronic kidney disease patients, stages 4 and 5. Int Urol Nephrol. 2011;43:835-40.
20. Kuwahara M, Mandai S, Kasagi Y, et al. Responsiveness to erythropoiesis-stimulating agents and renal survival in patients with chronic kidney disease. Clin Exp Nephrol. 2015;19:598-605.
21. Gaweda AE, Aronoff GR, Jacobs AA, et al. Individualized Anemia Management Reduces Hemoglobin Variability in Hemodialysis Patients. J Am Soc Nephrol. 2014;25:159-66.
22. Akabua E, Inanc T, Gaweda A, et al. Individualized model discovery: the case of anemia patients. Comput Methods Programs Biomed. 2015;118:23-33.

Correspondence to:
Shiva Samavat, MD
Department of Nephrology, Shahid Labbafinejad Hospital,
Boostan 9th St, Pasdaran Ave, Tehran, Iran
Tel: +98 21 2258 0333
E-mail: samavat@sbmu.ac.ir

Received October 2016
Accepted December 2016