

# Comparison of Hemoglobin Levels Before and After Hemodialysis and Their Effects on Erythropoietin Dosing and Cost

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## Abstract

**Background:** Hemoglobin levels measured after hemodialysis, as compared to hemoglobin levels measured before hemodialysis, are suggested to be a more accurate reflection of the hemoglobin levels between hemodialysis sessions, and to be a better reference point for adjusting erythropoietin dosing.

**Objectives:** The aim of this study was to compare the hemoglobin levels before and after hemodialysis, to calculate the required erythropoietin doses based on these levels, and to develop a model to predict effective erythropoietin dosing.

**Patients and Methods:** In this cross-sectional study, the hemoglobin levels of 52 patients with end-stage renal disease were measured before and after hemodialysis. The required erythropoietin doses and the differences in cost were calculated based on the hemoglobin levels before and after hemodialysis. A model to predict the adjusted erythropoietin dosages based on post-hemodialysis hemoglobin levels was proposed.

**Results:** Hemoglobin levels measured after hemodialysis were significantly higher than the hemoglobin levels before hemodialysis ( $11.1 \pm 1.1$  vs.  $11.9 \pm 1.2$  g/dL,  $P < 0.001$ , 7% increase). The mean required erythropoietin dose based on post-hemodialysis hemoglobin levels was significantly lower than the corresponding erythropoietin dose based on pre-hemodialysis hemoglobin levels ( $10947 \pm 6820$  vs.  $12047 \pm 7542$  U/week,  $P < 0.001$ , 9% decrease). The cost of erythropoietin was also significantly lower when post-hemodialysis levels were used ( $15.96 \pm 9.85$  vs.  $17.57 \pm 11.00$  dollars/patient/week,  $P < 0.001$ ). This translated into 83.72 dollars/patient/year in cost reduction. The developed model for predicting the required dosage is: Erythropoietin (U/week) =  $43540.8 + (-2734.8) \times$  Post-hemodialysis Hb\* (g/dL). [ $R^2 = 0.221$ ; \* $P < 0.001$ ].

**Conclusions:** Using post-hemodialysis hemoglobin levels as a reference point for erythropoietin dosing can result in significant dose and cost reduction, and can protect hemodialysis patients from hemoconcentration. The prediction of the erythropoietin adjusted dosage based on post-hemodialysis Hb may also help in avoiding overdosage.

**Keywords:** Hemoglobin, Hemodialysis, Erythropoietin, Cost

## 1. Background

Anemia is a common problem in end-stage renal disease (ESRD), and insufficient production of erythropoietin (EPO) by the kidneys is considered to be one of its major causes (1, 2). One routine approach to treating anemia in ESRD is the administration of erythropoiesis-stimulating agents (3, 4); however, the high cost of these drugs necessitates their judicious use (5).

Both hemoconcentration caused by excessive use of erythropoiesis-stimulating agents and anemia are associated with some complications in ESRD patients (3). Anemia, especially with hemoglobin (Hb) levels less than 9 g/dL, can lead to symptoms which negatively affect quality of life, including low energy, fatigue, decreased physi-

cal functioning, and low exercise capacity. Anemia also increases the need for blood transfusions and further possible complications (3, 6). On the other hand, hemoconcentration, especially with Hb > 13 g/dL, is also associated with adverse outcomes, including increased risk for stroke (7, 8), hypertension (9), and vascular access thrombosis (10). Thus, it is vital to maintain Hb levels within a conventional target range (10 - 11.5 g/dL) in ESRD patients by administering the appropriate amounts of EPO (3).

Most of the studies which have contributed to establishing a target Hb level have focused on pre-hemodialysis Hb and hematocrit (Hct) values (3). However, some other research has focused on post-hemodialysis Hb and Hct values, reporting a significant rise in Hb and Hct concentrations following a hemodialysis (HD) session, especially in

the first 24 hours, which is then followed by a gradual decrease during the rest of the interdialysis period (11-13). In a more recent study, it was found that serum Hb levels measured at 4, 24, and 48 hours after an HD session were still elevated as compared to the pre-hemodialysis Hb level, whereas they did not have a significant difference when compared to the immediate post-hemodialysis Hb concentration (14). These findings suggest that in HD patients, the real Hb and Hct values are closer to the post-hemodialysis concentrations than the pre-hemodialysis levels. Therefore, using post-hemodialysis Hb levels as the reference point for EPO dosage adjustments in HD patients is reasonable, as it can be considered to be an action that results in the reduction of the required EPO dosages and their cost (14). Nevertheless, the amount that an EPO dosage should be decreased and the resulting cost reduction may not be the same in different centers, and thus needs further investigation.

## 2. Objectives

In this study, the pre-hemodialysis and post-hemodialysis Hb concentrations of patients on maintenance HD in a dialysis center in Shiraz were measured in order to calculate the decline in EPO dosage prescriptions and the subsequent cost reduction when using post-hemodialysis Hb levels as the reference point. A model was then developed to predict the adjusted EPO dosages according to post-hemodialysis Hb levels.

## 3. Patients and Methods

In this cross-sectional study, 52 patients aged 18 years or older undergoing hemodialysis at an outpatient center at Shiraz University of Medical Sciences were enrolled. The research was reviewed and approved by the ethics committee at Shiraz University of Medical Sciences and was performed in accordance with the declaration of Helsinki. All patients provided their informed written consent before enrollment in the study.

Participants were required to be on maintenance HD for more than three months. They underwent bicarbonate hemodialysis three times weekly with polysulfone membranes (1.8-2 m<sup>2</sup>). The dialysis time for each HD session was 240 minutes for all of the patients. All of the patients also received EPO therapy.

The exclusion criteria consisted of active infection, including hepatitis B, hepatitis C, or human immunodeficiency virus, active hematologic malignancy, and acute illness requiring hospitalization within three weeks prior to enrollment in the study.

Hb and Hct levels were measured before and after the first HD session of the week using an autoanalyzer. The prescribed EPO dosages were determined and the adjusted doses of EPO were calculated using the pre-hemodialysis Hb levels as the reference point. The hypothetically adjusted EPO dosages using the post-hemodialysis Hb levels as the reference point were also calculated. The reductions in EPO dosage for each patient and week were calculated, the cost reduction was estimated, a model was then developed to predict the adjusted EPO dosages based on post-hemodialysis Hb levels. Weight for each patient was measured with the same digital scale both before and after the HD session in three consecutive sessions.

The primary outcome measurement of this study was an absolute change in Hb levels both before and after the HD session. Following a cohort pilot study in which mean pre-hemodialysis and post-hemodialysis Hb concentrations were measured (14), the sample size of 52 patients was used to detect the mean difference of pre-hemodialysis and post-hemodialysis Hb levels with a standard deviation of 1.1 g/dL, type I error of 5%, and precision of 0.3 g/dL.

Statistical analysis was performed using the SPSS version 16 (SPSS Inc., www.ibm.com/software/analytics/spss/products/statistics) statistical software package. Results for the quantitative variables are shown as means and standard deviations, and the results for the categorical variables are shown in terms of frequencies and percentages. The changes in the measured parameters were calculated with a normal distribution before and after the intervention with a paired t-test. The McNemar-Bowker's test was used to calculate the changes in the Hb level categories before and after the HD session in 3 × 3 square tables. In order to predict the adjusted EPO dosage, post-hemodialysis Hb and weight loss after the HD session were entered as covariates in a linear regression model, where EPO dosage was considered as a dependent variable. The stepwise method was used to detect the most influential covariates.  $P < 0.05$  was considered to be statistically significant.

## 4. Results

There were 27 males and 25 females included in the study, with a mean age of  $62 \pm 15$  years (range: 18 to 90 years). The baseline characteristics of the patients are listed in Table 1.

The mean post-hemodialysis Hb level was significantly higher than the mean pre-hemodialysis Hb level ( $11.9 \pm 1.2$  vs.  $11.1 \pm 1.1$  g/dL,  $P < 0.001$ ). The mean intradialytic percent variations (% delta) of the Hb and Hct levels was  $7.0 \pm 6.0\%$  (range: -7 to 20) and  $6.5 \pm 5.6\%$  (range: -6 to 19), respectively. The mean weight loss during HD was  $2.26 \pm 0.89$  kg (range:

**Table 1.** Baseline Characteristics of the Patients

Characteristics	
Age, y	62 ± 15 (range: 18 - 90)
Sex (male), No. (%)	27 (52)
Underlying disease, No. (%)	
Diabetic nephropathy	24 (46.2)
Nephroangiosclerosis	11 (21.2)
Glomerulonephritis	6 (11.5)
Polycystic kidney disease	4 (7.7)
Other	7 (13.5)
Time of dialysis, min	240 ± 0
Kt-V	1.52 ± 0.31
Ultrafiltration, ml/kg/h	8.61 ± 3.16 (range 0 to 14.71)
EPO dose per week, U	12423 ± 7078
EPO dose per Kg and week, U	210 ± 139.58
Type of EPO, No. (%)	
Epoetin $\alpha$	52 (100)
Without EPO	0 (0)

Abbreviations: EPO, erythropoietin.

0 to 4.6 kg) and the mean UF rate in an hour was  $8.61 \pm 3.16$  mL/kg/h (range: 0 to 14.71 mL/kg/h).

According to the KDIGO clinical practice guidelines (3), using the pre-hemodialysis Hb concentrations revealed that 27 patients (51.9%) had adequate Hb levels (10 - 11.5 g/dL), while seven patients (13.5%) had low Hb levels (< 10 g/dL) and 18 patients (34.6%) had high Hb levels (> 11.5g/dL). However, using the post-hemodialysis Hb levels, five out of the seven patients (71%) with low pre-hemodialysis Hb levels had adequate post-hemodialysis Hb concentrations, and 12 out of the 27 patients (44.4%) with pre-hemodialysis Hb concentrations within the KDIGO target had high post-hemodialysis Hb levels (Table 2,  $P = 0.001$ ). Taking into account the patients who received more than 12,000 U/week of EPO, five out of six patients (83%) with low pre-hemodialysis Hb concentrations had post-hemodialysis Hb levels within the KDIGO target, and three out of 10 patients (30%) with adequate pre-hemodialysis Hb levels had high post-hemodialysis Hb concentrations (Table 3,  $P = 0.018$ ).

The hypothetically adjusted EPO dosage was calculated using post-hemodialysis Hb levels as the reference point. If this EPO dosage was used, the mean required EPO units in a week would be significantly lower in comparison to the mean EPO dosage prescribed based on pre-hemodialysis Hb concentrations in routine practice (10947

$\pm 6820$  vs.  $12047 \pm 7542$  U,  $P < 0.001$ , 9% decrease). After adjusting for weight, the prescribed EPO dosage could be reduced by 8.8% if the post-hemodialysis Hb was used as the reference point (EPO dosage according to pre-hemodialysis Hb,  $204 \pm 145$  U/kg/week; EPO dosage according to post-hemodialysis Hb,  $186 \pm 134$  U/kg/week). Finally, using post-hemodialysis Hb as the reference point of EPO dosage calculation results in significant cost reduction:  $17.57 \pm 11.00$  dollars/patient/week for pre-hemodialysis Hb level vs.  $15.96 \pm 9.85$  dollars/patient/week for post-hemodialysis Hb level, respectively ( $P < 0.001$ ) (15). Thus, this course of action could bring about savings of 83.72 dollars/patient/year, and for the 52 patients included in our study, this would result in savings of 4,353 dollars/year. Taking into account the at least 12,500 HD patients in Iran (16), this change in routine practice could lead to a minimum of savings of 1,046,500 dollars/year.

The stepwise regression model showed that only post-hemodialysis Hb levels were significantly related to the adjusted EPO dosages. Thus, the linear regression model to predict the adjusted EPO dosage is as follows: Erythropoietin (U/week) =  $43540.8 + (-2734.8) \times$  Post-hemodialysis Hb\* (g/dL). The adjusted coefficient of determination ( $R^2$ ) was 0.221 (\*post-hemodialysis Hb,  $P < 0.001$ ).

## 5. Discussion

These results confirm that using post-hemodialysis Hb levels as the reference point for EPO dosage calculation causes significant reductions in dosages and cost. Reduction in the prescribed EPO dosages could have beneficial effects on HD patients because of its ability to prevent vulnerability to high Hb and Hct levels and complications during the interdialysis period, and its economic efficiency (14). In addition, a simple model has been developed to estimate the adjusted EPO dosage based on post-hemodialysis Hb so that overdosage of EPO can be prevented.

Vlassopoulos et al. reported a significant rise in Hb and Hct following the HD session, which remained significantly elevated for at least 24 hours (11). Movilli et al. and Bellizzi et al. discussed similar findings in their studies (12, 13). Furthermore, Castillo et al. reported increases of 6.1% and 5.8% in the Hb and Hct values, respectively, after the HD session (14). This result is similar to our findings, which indicate 7% and 6.5% rises in the Hb and Hct levels, respectively.

The normal hematocrit cardiac trial (NHCT), a study consisting of 1,200 HD patients with congestive heart failure or ischemic heart disease randomized into two groups with target Hct ranges of  $42 \pm 3\%$  (the normal Hct group) and  $30 \pm 3\%$ , was prematurely stopped by the data

**Table 2.** Patients Categorized According to Pre-Hemodialysis and Post-Hemodialysis Hemoglobin Levels

Hemoglobin, g/dL	Post-Hemodialysis			Total
	Low (< 10)	Normal (10 - 11.5)	High (> 11.5)	
<b>Pre-hemodialysis</b>				
Low (< 10)	2 (5.3)	5 (10.5)	0 (0)	7 (13.5)
Normal (10 - 11.5)	0 (0)	15 (28.8)	12 (23.1)	27 (51.9)
High (> 11.5)	0 (0)	1 (1.9)	17 (32.7)	18 (34.6)
<b>Total</b>	2 (3.8)	21 (40.4)	29 (55.8)	52 (100)

**Table 3.** Patients Who Received More Than 12,000 U/Week of Erythropoietin Categorized According to Pre-Hemodialysis and Post-Hemodialysis Hemoglobin Levels

Hemoglobin (g/dL)	Post-Hemodialysis			Total
	Low (< 10)	Normal (10 - 11.5)	High (> 11.5)	
<b>Pre-hemodialysis</b>				
Low (< 10)	1 (4.8)	5 (23.8)	0 (0)	6 (28.6)
Normal (10 - 11.5)	0 (0)	7 (33.3)	3 (14.3)	10 (47.6)
High (> 11.5)	0 (0)	0 (0)	5 (23.8)	5 (23.8)
<b>Total</b>	1 (4.8)	12 (57.1)	8 (38.1)	21 (100)

safety monitoring board because of concerns about the increased risk of cardiovascular disease and mortality in the normal Hct group. Three recent randomized controlled trials, the correction of hemoglobin and outcomes in renal insufficiency (CHOIR) (17), the cardiovascular risk reduction by early anemia treatment with epoetin beta (CREATE) (18), and the trial to reduce cardiovascular events with Aranesp therapy (TREAT) (8), showed that achieving a high versus a low Hb target by administering higher EPO doses was associated with an increased risk of myocardial infarction, stroke, and death in chronic kidney disease patients who had not undergone dialysis. In addition, a meta-analysis on anemic chronic kidney disease patients treated with erythropoietin suggested that a higher Hb target increases the risk of all-cause mortality, arteriovenous access thrombosis, and poorly-controlled hypertension (19).

In accordance with the KDIGO guidelines (3), when using post-hemodialysis measurements, most of the patients with low pre-hemodialysis Hb levels had adequate Hb levels, and some of the patients with a pre-hemodialysis Hb level within the KDIGO target also had a high Hb level. These changes are a result of the slow reequilibration process following the HD session (14) and can potentially lead to hemoconcentration in HD patients. Therefore, by using post-hemodialysis values as the reference point for EPO prescription, hemoconcentration-related complications can be reduced, including the increased risk of stroke (7, 8), hypertension (9), vascular access thrombosis (10) and

all-cause mortality (19) in a significant number of HD patients.

In conclusion, using post-hemodialysis Hb levels as the reference point for EPO administration can protect hemodialysis patients from hemoconcentration and can result in significant reductions in EPO dosages (8.8% U/kg/week) and cost (83.72 dollars/patient/year). Also, a simple model was presented to estimate the adjusted EPO dosage based on the post-hemodialysis Hb level to avoid EPO overdosage. The main limitations of this study are the small sample size and its cross-sectional design without follow-up. Future multicenter studies with larger sample sizes and longer follow-up durations are needed to examine the outcomes of using post-hemodialysis Hb levels as the reference point for EPO prescription.

#### Footnotes

**Authors' Contribution:** Study concept and design: Mohammad Mahdi Sagheb, Mohammad Hossein Fallahzadeh; acquisition of data: Mohammad Mahdi Sagheb, Mohammad Amin Fallahzadeh, Alireza Moaref; analysis and interpretation of data: Mohammad Mahdi Sagheb, Mohammad Amin Fallahzadeh, Banafshe Dormanesh; drafting of the manuscript: Mohammad Mahdi Sagheb, Mohammad Amin Fallahzadeh, Mohammad Hossein Fallahzadeh; critical revision of the manuscript for important intellectual content: Alireza Moaref, Banafshe Dormanesh; Statistical

analysis: Mohammad Mahdi Sagheb, Mohammad Amin Fallahzadeh, Alireza Moarefi; administrative, technical, and material support: Mohammad Mahdi Sagheb; study supervision: Mohammad Hossein Fallahzadeh

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