10.5152/turkjnephrol.2019.3531

Original Article

Turkish Journal of Nephrology

Assessment of Hemoglobin Stability in Chronic Hemodialysis Patients Receiving Erythropoietin Therapy and the Effect of Hemoglobin Stability on Risk of Cardiovascular Disease

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Abstract

Objective: Anemia is one of the most important factors that decrease the quality of life in patients with end-stage renal desease receiving hemodialysis treatment. In these patients, Erythropoietin stimulating agents (ESAs) are used in the treatment of anemia. Although the target hemoglobin (Hb) value in chronic renal failure is 11-12 gr/dL, it is suggested that hemoglobin values fluctuate between normal, high and low values in the great majority, leading to cardiovascular structural changes which increase mortality. In this study, we investigated the effect of anemia and hemoglobin fluctuations on mortality rate and the risk of cardiovascular disease in chronic hemodialysis patients who received ESA thearapy.
Materials and Methods: Hemoglobin values for 12 months of 181 patients were examined. The target Hb level was 11-12 gr/dL interval and the patients were divided into 6 groups according to the hemoglobin values; persistently low, low-normal, target, normal-high, low-high and persistently high. According to the variability in hemoglobin level, groups were compared in terms of demographic, laboratory characteristics, treatment, risk of cardiovascular disease, hospitalization and death frequency and causes.
Result: The total of 181 patients were classified according to Hb levels; 22 (12.2%) patients were persistently-low, 72 (39.8%) were low-normal, 10 (5.5%) were normal-high and 77 (42.5%) patients were low-high Hb group. During the 12 month fallow up, there were no patients in target and high Hb group. The groups were similar in terms of the presence of comorbid diseases such as diabetes, hypertension, coronary artery disease and other demographic characteristics, and there was no difference between groups in terms of cardiovascular disease development. ESA doses and blood transfusion counts and mortality rates were significantly higher in the persistently-low hemoglobin group compared to the other groups.
Conclusion: In our study, high rate of anemia and hemoglobin fluctuations were shown in chronic hemodialysis patients and anemia was associated with mortality. However, the possible association of these variables with cardiovascular diseases was not observed. Further studies are needed in the larger hemodialysis patient group to investigate the relationship between hemoglobin fluctuation and mortality and cardiovascular risk.
Keywords: Hemodialysis, anemia, hemoglobin variability, cardiovascular disease

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Received: 30.08.2018 **Accepted:** 22.10.2018

Presented in: This study was presented at the 32nd National Congress of Nephrology, 21-25 October 2015, Antalya, Turkey.

Cite this article as: Ulaş Güncan M, Güncan S, Torun D. Assessment of Hemoglobin Stability in Chronic Hemodialysis Patients Receiving Erythropoietin Therapy and the Effect of Hemoglobin Stability on Risk of Cardiovascular Disease. Turk J Nephrol 2019; 28(4): 275-9.

INTRODUCTION

Anemia is one of the most important factors that decrease the quality of life in patients with chronic renal failure (CRF) undergoing hemodialysis (HD) (1). The prevalence of anemia in patients with CRF is quite high, and anemia is an independent risk factor for the development of cardiovascular disease (CVD) (2, 3). The major cause of anemia in patients with CRF is decreased renal erythropoietin production. Erythropoiesis-stimulating agents (ESAs) are used to treat anemia in these patients. It has been shown that the need for blood transfusion, transfusion-related infection, allosensitization, decreased risk of hemosiderosis, increased quality of life, and exercise capacity of patients are seen with ESA treatment (4, 5). The National Kidney

Foundation-Kidney Dialysis Outcome Quality Initiation guideline recommends the target hemoglobin (Hb) levels to be maintained in the range of 11-12 g/dL in patients with CRF (6).

Anemia plays an important role in the development of left ventricular hypertrophy and heart failure in CRF. There was a strong correlation between left ventricular hypertrophy and morbidity and mortality in patients with CRF. By correcting anemia and normalization of Hb value by giving ESA treatment, the development of left ventricular hypertrophy and left ventricular dilatation can be prevented (7).

In clinical practice, Hb values in patients with CRF exceed the target range and transition between low and high values, which is defined as Hb fluctuation (8). Fluctuations in Hb level, as well as low Hb, in CRF are important with respect to morbidity and mortality. Recent studies have shown that Hb fluctuation is associated with cardiovascular events and increases cardiovascular mortality (9-11).

The aim of the present study was to investigate Hb levels and Hb fluctuations and the effect of these factors on mortality and CVD risk in patients with chronic HD using ESA.

MATERIALS AND METHODS

The study was approved by the ethical committee of Baskent University Clinical Research Ethics Committee (KA15/64, dated 03/10/2015). Data of 319 patients undergoing dialysis between 01/01/2014 and 12/31/2014 in Baskent University Adana Research and Application Center were examined. Patients who were excluded from the follow-up due to changes in the province during the study, who had a blood disease other than renal anemia, and who had a malignant disease were excluded from the study. A total of 181 patients over the age of 18 years who had undergone chronic HD from arteriovenous (AV) fistula for at least 3 months 3 times/week were included in the study. Age, sex, HD age, body mass index (BMI, kg/m^2), etiology, presence of concomitant diseases (diabetes mellitus (DM), hypertension (HT), and CVD), and history of antihypertensive use of angiotensin-converting enzyme inhibitor (ACEI)-angiotensin-receptor blocker (ARB) were recorded from the patient files.

One hundred eight-one patients were divided into six groups according to Hb levels and fluctuations during 12 months. The groups were given ESA treatment according to the Health Implementation Communiqué (HIC) applied in our country throughout the process. In all groups, patients received ESA treatment as long as their Hb level was <12 g/dL, and when it was >12 g/dL, the treatment was discontinued. The Hb variability subsets of the patients are shown in Figure 1.

Group 1: Group with Hb levels continuously <11 g/dL (continuously low: CL)
Group 2: Group whose Hb level is occasionally between 11 and 12 g/dL and sometimes <11 g/dL (low-normal (LN))

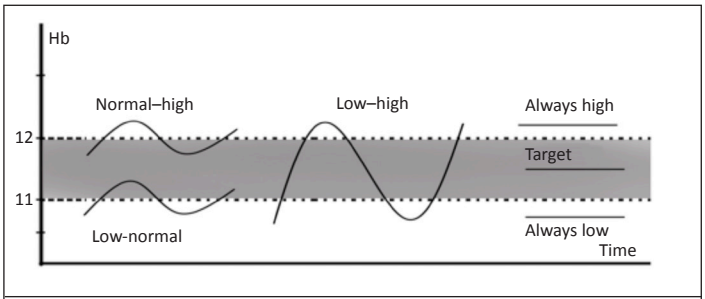

Figure 1. Hb variability subsets.

Group 3: Group with Hb level between 11 and 12 g/dL (target)
Group 4: Group whose Hb level is occasionally between 11 and 12 g/dL and sometimes >12 g/dL (normal-high (NH))
Group 5: Group showing wide variable Hb level (low-high (LH))
Group 6: Group whose Hb level is continuously >12 g/dL (continuously high: CH)

The groups were compared according to the variability in Hb levels with respect to demographic characteristics, laboratory characteristics, treatments, risks of CVD, hospitalization and mortality rates, and causes. Informed consent is not necessary due to the retrospective nature of this study.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 17.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the data. Chi-square test or Fisher's test statistics were used for the comparison of categorical variables. In the comparison of continuous measurements between the groups, the distributions were controlled. One-way Analysis of Variance (ANOVA) was used for variables that provided the parametric distribution prerequisite assumption, and Kruskal-Wallis test was used for variables that did not provide the parametric distribution prerequisite assumption. The correlation between the variables was determined by the Spearman's correlation coefficient.

RESULTS

The average age of the 181 patients included in the study was 56.4 years. The study included 56.9% male and 43.1% female patients. The average HD time was 70.9 months. The mean Kt/V was 1.46, and the mean BMI was 24.2 kg/m^2. The underlying cause of CRF was DM in 37%, HT in 27.6%, glomerulonephritis in 6.6%, polycystic kidney disease in 3.3%, chronic pyelonephritis in 11.1%, and unknown in 14% of the patients. When the accompanying diseases were examined, DM was present in 38.7%, HT in 70.2%, and coronary artery disease in 31.5%. 26.7% of patients with HT and 18.8% of all patients were using ACEI-ARB. The demographic characteristics of the patients mentioned above and the comparison between the groups are shown in Table 1.

When 181 patients were classified according to their 12-month average Hb levels, 22 (12.2%) were in the continuously low Hb group, 72 (39.8%) were in the low-normal Hb group, 10 (5.5%)

Table 1. The demographic characteristics of the patients and the comparison between the groups.

	All patients	CL n=22	LN n=72	NH n=10	LH n=77	p
Age (year)	56.4	53.7±18.5	57.8±15.1	58.1±12.7	55.5±13.9	0.622
Gender (M/F)	103/78	9/13	41/31	5/5	48/29	0.332
HD age (month)	70.9	75.8±48.6	61.3±46.8	83.1±70.4	77.0±54.4	0.236
BMI (kg/m^2)	24.2	21.8±3.4	24.9±6.3	25.1±5.2	24.1±5.1	0.123
CKD etiology						
DM (%)	37	36.4	38.9	30	28	0.476
HT (%)	27.6	31.8	31.9	20	23.4	
Glomerulonephritis (%)	6.6	4.5	2.8	0	9.1	
Chronic pyelonephritis (%)	14.4	10.2	11.4	11.8	13.6	
PCKD (%)	3.3	3.5	2.5	8.2	11.6	
Unknown (%)	11.1	13.6	12.5	30	14.3	
Comorbid disease						
DM presence (%)	36.4	40.3	40	37.7	0.983	
HT presence (%)	54.5	76.4	60	70.1	0.222	
CVD presence (%)	22.7	29.2	30	36.4	0.61	
ACEI–ARB use (%)	18.8	22.7	22.2	10	15.6	0.614
Kt/V	1.46	1.67	1.51	1.54	1.52	0.111

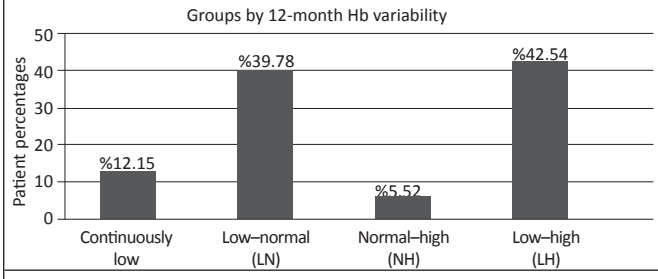

Figure 2. Patient distribution according to the 12-month Hb variability.

were in the normal-high Hb group, and 77 (42.5%) were in the low-high Hb group. The distribution of the groups is shown in Figure 2. During the 12-month follow-up period, there was no patient in the group with continuous target Hb value and continuously high value.

While the number of females was higher in the CL group, the number of males was higher in the LH group, but no statistically significant difference was observed when the four groups were compared. Although the BMI was lower in the CL group than in the other groups, no statistically significant difference was detected. Among the four groups, there was no statistically significant difference with respect to age, HD age (duration of the HD treatment), etiology of renal disease, and comorbid diseases, such as DM, HT, and CVD. Similarly, there was no significant difference with respect to ACEI-ARB use between patients with HT within the groups. There was no difference between the groups with respect to the number of patients with diabetes, the number of patients with HT, and the number of patients with CAD. 26.7% of patients with HT were using ACEI-ARB as antihypertensives, and there was no significant difference between the groups with respect to ACEI-ARB use. There was no significant difference between the groups with respect to dialysis adequacy (Kt/V).

During the study period, 69 (38.1%) out of 181 patients were hospitalized. The reasons of hospitalization were CVD (25.4%), infection (23.9%), surgical reasons (14.1%), hypervolemia (12.7%), AV fistula dysfunction (11.3%), gastrointestinal bleeding (4.2%), renal transplant preparation (2.8%), and other causes (5.6%).

Eighteen (10%) patients died during the study period. Eleven (55.6%) patients died from CVD, 5 (33.3%) patients from infection, 1 (5.6%) patient from ileus, and 1 (5.6%) patient from alveolar hemorrhage due to a traffic accident. The mortality rate was found to be significantly higher in the CL group than in the other groups ($p<0.05$).

In the 12-month retrospective study, 34 (18.8%) patients had a history of cardiac events (myocardial infarction (MI), coronary artery by-pass graft (CABG) frequency, and cardiovascular death). However, while the history of cardiac events in the CL group (MI:

Table 2. The average ESA doses of the groups.

	Minimum dose (IU/week)	Maximum dose (IU/week)	Median (IU/week)	p
Continuously low	2000	8000	6750	0.005
Low-normal	2000	7000	5916	
Normal-high	2000	2000	2000	
Low-high	2000	5000	4416	

13.6%, CABG: 4.5%, and CV death: 13.6%) was more frequent than that in the other groups, there was no statistically significant difference.

During the study, the number of blood transfusions in the CL group was found to be significantly higher than that in the other groups (p=0.004). When the 12-month laboratory data of the groups were evaluated, ferritin and parathyroid hormone (PTH) levels were higher, and transferrin saturation (TSAT) value was lower in the CL group than in the other groups; however, there was no statistically significant difference between the four groups in the follow-up.

The average dose of erythropoietin was 6222±1637 IU/hf per patient. The maximum ESA dose was 12,000 IU/week, and the minimum ESA dose was 2000 IU/week. The ESA dose in the continuously low Hb group was significantly higher than that in the other groups (p<0.05). The average ESA doses of the groups are shown in Table 2. Although the ESA dose was higher in the CL group, when the parameters affecting the ESA non-responsiveness in this group (ferritin, TSAT, C-reactive protein, Ca, P, CaxP, PTH, frequency of hospitalization, frequency of comorbid disease, and ACEI-RAS use) were evaluated, no statistically significant difference was detected between the groups. The NH group had statistically significant lower average ESA doses than the other groups (p<0.05).

One hundred and forth two (78%) patients received intravenous iron treatment during any period within the 12-month period and 39 (22%) patients did not receive this treatment. At any period of the 12-month period, 55% of the patients received active vitamin D treatment, with 30% of which were as calcitriol and the remaining 25% were as paricalcitol replacement. There was no statistically significant difference between the groups with iron, vitamin D, phosphorus binding, and cinacalcet treatments.

DISCUSSION

Low Hb and fluctuations in the Hb levels are associated with morbidity and mortality in CRF-related anemia (12-14). The main objective in the treatment of anemia and the use of ESA is to achieve stabilization in the target Hb range and to minimize fluctuation. According to the HIC applied in our country, to start ESA treatment, the Hb value should be <10 g/dL, TSAT ≥20%, and/or ferritin ≥100 µg/L. The initial dose is continued until the Hb value reaches 11 g/dl, the maintenance dose is given between 11 and 12 g/dL, and treatment is discontinued when the Hb value is >12 g/dL (15). It is very difficult to maintain Hb stability in such a narrow range. There are many studies showing that very few patients with CRF remain within the target Hb range. In a study conducted on 152,846 patients with HD, Ebben et al. reported that although the target range of Hb was kept higher in the 6-month period (11-12.5 g/dL), only 6.5% of the patients remained within the target range, and approximately 90% of the patients fluctuated with respect to the Hb level (14). In our study, we did not observe any patients whose Hb values remained within the target range for 12 months, but the rate of patients who remained at the target values for 6 months was 3.9%, and the results were similar to the literature.

Girbertson et al. divided their 159,720 patients with HD into Hb categories by the method we used in our study and investigated the relationship between Hb fluctuation and mortality. They showed that Hb fluctuation did not increase the mortality rate, but the low Hb level and the time elapsed with low Hb levels increased the mortality rate (16). Similarly, in our study, the mortality rate was found to be significantly higher in the patient group whose Hb level was continuously low than in the other groups. However, no statistically significant relationship was found between Hb fluctuation and mortality rate increase.

There are many studies in the literature indicating that low levels of Hb in patients with HD increase hospitalization. In the study by Ishani et al. on 54,328 patients with HD, it was emphasized that the hospitalization rate increased when the Hb value decreased under the target value (11 g/dL). However, in our study, no statistically significant difference was observed between the Hb groups with respect to hospitalization (17). This discrepancy with the literature can be explained by the limited number of patients and the limitation in the duration of patient follow-up.

In the study by McMahon et al. (18), it was mentioned that the decrease of Hb <11 g/dL increased cardiac output; thus, it was reported to be associated with left ventricular hypertrophy and dilatation. Left ventricular hypertrophy is known to be an independent risk factor for mortality in patients with CRF. Recent studies have shown that Hb fluctuation is associated with cardiovascular events (9-11). In one study, 1 g/dL change in Hb level could cause a 33% increase in mortality when other multiple variables were taken into consideration, and this situation was interpreted as Hb fluctuation being independently associated with high mortality. It has been suggested that the transient ischemic condition caused by Hb fluctuation may cause structural changes, such as left ventricular hypotrophy on the myocardium. There is evidence that the Hb fluctuation may also affect the autonomic nervous system and in patients with sickle cell anemia with similar Hb fluctuations, autonomic dysfunction may increase mortality (12). In our study, no statistically significant relationship was found between the group showing Hb fluctuation and CVD. Similarly, although

the incidence of CVD was higher in the CL group, there was no statistically significant difference compared with the other groups.

In the study by Tessitore et al., it was mentioned that high ESA requirement may be an indicator of mortality (19). In our study, in accordance with the literature, we found that the mortality rate was high in the continuously low Hb group where ESA requirement was high.

There are some limitations in our study. Because the study is single centered, the number of patients is low, and the follow-up period is 1 year, which leads to limitation with respect to the follow-up of the progression. Since there was no patient with the target Hb level, it was not possible to compare normal Hb levels with those deviating from this value. Another limiting factor is the lack of physician initiative and individual patient evaluation due to the HIC.

CONCLUSION

In our study, high rates of anemia and Hb fluctuation were shown in patients with chronic HD. The mortality rate was found to be significantly higher in patients with continuously low Hb levels than in the other groups, but there was no statistically significant increase in the development of CVD. In addition, no statistically significant effect of Hb fluctuation on death rate increase and on the development of CVD is observed, and we think that this relationship can be more clearly demonstrated by prospective researches thatinvolve more patients.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of Baskent University in 2015.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.T., M.U.G.; Design - M.U.G., S.G.; Supervision -D.T.; Resource - S.G., M.U.G.; Materials - M.U.G.,S.G.; Data Collection and/or Processing - D.T., M.U.G.; Analysis and/or Interpretation - S.G., M.U.G.; Literature Search - D.T., M.U.G.; Writing - M.U.G., S.G.; Critical Reviews - D.T., M.U.G.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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