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The Determinants of Hemoglobin Variability in Hemodialysis Patients

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Abstract

Introduction. Factors that have been reported to affect erythropoietin (EPO) responsiveness in hemodialysis (HD) patients include iron deficiency, chronic inflammation, secondary hyperparathyroidism, malnutrition and inadequate HD dose. The aim of the study was to analyze the deteminants of hemoglobin variability in HD patients.
Methods. The study encompassed 526 patients (197 F and 329 M). According to HD vintage at the beginning of the study the patients were divided into two groups: group-1 encompassed 153 patients with HD vintage bellow 24 months, and group-2 encompassed 329 patients with HD vintage over 24 months. Over a period of 21 months after admission the following parameters were analyzed: hemoglobin (Hb), EPO dose, iron dose, HD dose (eKT/V), transferrin saturation (TSAT), C-reactive protein (CRP), ferritin and serum albumin at 3 months and parathyroid hormone (PTH) at 6 months.
Results. The percentage of patients with Hb>=105g/L significantly improved, and the average Hb level significantly increased in both groups over a period of 21 months. The average EPO and iron dose significantly decreased, but TSAT and ferritin levels significantly increased over a period of 21 months. The average eKT/V and s-albumin values significantly increased, but the average CRP and PTH levels significantly decresead over a period of 21 months. In group-1 EPO dose and CRP, but in group-2 EPO dose, ferritin, HD vintage, and iron dose were statistically significant predictors of the Hb level 9 months after admission.
Conclusions. Insufficient EPO therapy, iron deficiency and chronic inflammation were the main factors of inadequate correction of anemia in HD patients before admission.

Keywords: anemia, chronic kidney disease, erythropoietin, hemodialysis, hemoglobin variability, iron dose

Introduction

The anemia of chronic kidney disease (CKD) is a multifactorial disorder that can be managed successfully by erythropoiesis-stimulating agents (ESAs) administration. The required dose of ESAs is quite variable in different CKD patients or in the same patient at different periods of time. Hemoglobin variability is the fluctuation of hemoglobin above or below the target range over time or the extent to which multiple measured hemoglobin values differ from each other within a given time span, whereas the calculated mean of all hemoglobin levels may still remain within the target range [1,2]. Identification of predictors of hyporesponsiveness to ESAs in hemodialysis (HD) patients may help improve anemia management and reduce hemoglobin variability [3].
Iron deficiency is the most common cause of EPO hyporesponsiveness, underscoring the need for treating pre-existing iron deficiency concurrently with ESA therapy [3,4]. ESAs stimulate bone marrow to accelerate the rate of RBC production. If iron stores are inadequate to meet the demands of ESA-activated bone marrow, the patient will not respond adequately to ESAs.
Besides iron deficiency, various comorbidities contribute to anemia and complicate its diagnosis in patients with CKD. Anemia of chronic disease, often associated with acute or chronic infection, inflammation, malignancy, or autoimmune disease, activates cytokines that impair erythropoiesis [5,6]. Inflammation or infection, often combined with malnutrition and atherosclerosis in MIA syndrome, is considered the most common cause of ESA hyporesponsiveness [6]. Hemodialysis, per se, and the adequacy of hemodialysis dose measured by KT/V have been shown to play an important role in improving anemia and reducing the ESA dosage required for anemia correction in HD patients [7,8]. Hyperparathyroidism is usually listed among the possible reasons for impaired response to ESAs in CKD patients. Possible pathogenic links between anemia and parathyroid hormone (PTH)

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include reduced erythropoiesis due to calcitriol deficiency, and direct or indirect effects of PTH on erythropoietin release, red blood cell production, survival, and loss [9].
The aim of the study was to determine the prevalence of HD patients with anemia and to analyze the determinants of hemoglobin variability in HD patients.

Materials and methods

The multicenter observational retrospective study encompassed 526 patients (197 F and 329 M) with the average age of 60.98±12.94 years and the average HD vintage of 71.28±69.05 months. According to HD vintage at the beginning of the study the patients were divided into two groups: group-1 (G1) encompassed 153 patients with HD vintage bellow or equal at 24 months and group-2 (G2) encompassed 329 patients with HD vintage over 24 months. Patients' dialysis charts were retrospectively examined to obtain data regarding the erythropoietin (EPO) dose (IU/kg/week) and iron (Fe) dose (i.v. mg/month) in the observed time period. In accordance with ERBP and KDIGO guidelines [10,11] and Health Insurance Fund of Macedonia guidelines for anemia treatment in HD patients the following targets were sustained: hemoglobin 10.5-12.5 g/dl; TSAT: lower limit 20%, target range 30-50%, and serum ferritin: lower limit 100 ng/ml, target range 200-500 ng/ml. Hemoglobin levels were classified as low (<105 g/L), within target (105-125 g/L), or high (>125 g/L). To assess the frequency and the size of the fluctuations in hemoglobin levels over time, we defined six subgroups of patients on the basis of their overall pattern of fluctuation during the first 9 months after admission: consistently low (all 9 months with Hb<105 g/L), consistently within the target range (all 9 months with Hb=105-125 g/L), consistently high (all 9 months with Hb>125 g/L), low-amplitude fluctuation with low Hb levels (LAL- all 9 months with Hb<105 g/L or Hb=105-125 g/L), low-amplitude fluctuation with high Hb levels (LAH- all 9 months with Hb=105-125 g/L or Hb>125 g/L), and high-amplitude fluctuation (HA- within 9 months period with Hb<105 g/L, Hb=105-125 g/L and Hb>125 g/L).
The following laboratory parameters were monitored over the period of 21 months after admission: hemoglobin (Hb-g/L), hemodialysis dose (eKT/V), transferrin saturation (TSAT- %), C-reactive protein (CRP-mg/L), ferritin (ng/ml) and serum albumin (g/L) at 3 months and parathyroid hormone (PTH-pg/ml) at 6 months prior to the mid-week hemodialysis session in the first week of the month. All laboratory values were measured by automated and standardized methods. The continuous variables are presented as the mean values with standard deviation, but categorical variables are presented as percentage. For statistical analysis chi-square test, combined analysis of variance for repeated measures and multivariate regression analysis were performed by the statistical software package SPSS, version 11.5 for Windows.

Results

The prevalent primary renal disease according to the EDTA registry codes in patients were: hypertensive nephropathy in 27.3% of patients, diabetes mellitus type 1 and 2 in 15.5%, glomerulonephitis with no histology in 11%, and Autosomal Dominant/Recessive Polycystic Kidney Disease in 9.1%. Distribution of monthly hemoglobin levels in both groups of patients over the period of 21 months are shown in Figure 1 and 2. The percentages of patients with Hb levels over 105 g/L significantly improved over the period of 21 months in both groups. Nearly 87% of patients in group-1 and 84% in group-2 showed some pattern of Hb level fluctuation during the 9-month study period, as shown in Figure 3. Patients who were classified in the low, target range, and high subgroup in both groups of patients (overall 12.8% in group-1 and 15.66% in group-2) remained stable within their original Hb level ranges during the 9-month study period. Patients who were classified in the

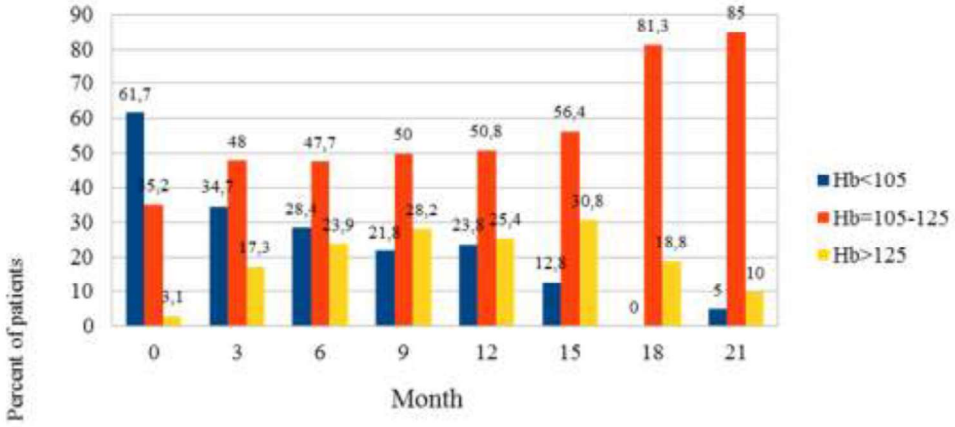

Fig. 1. Distribhution of monthly hemoglobin levels in group-1 of patients

their Hb levels crossed one of the boundaries at 105 or 125 g/L during the 9-month period. Patients who were classified in the HA subgroup showed large fluctuations in their Hb levels, such that they crossed both the upper and the lower boundaries of target range. This was the most common pattern of Hb level fluctuation over time in group-1 (44.48% of patients), with levels falling below or rising above the target range (105-125 g/L) during the 9-month period.

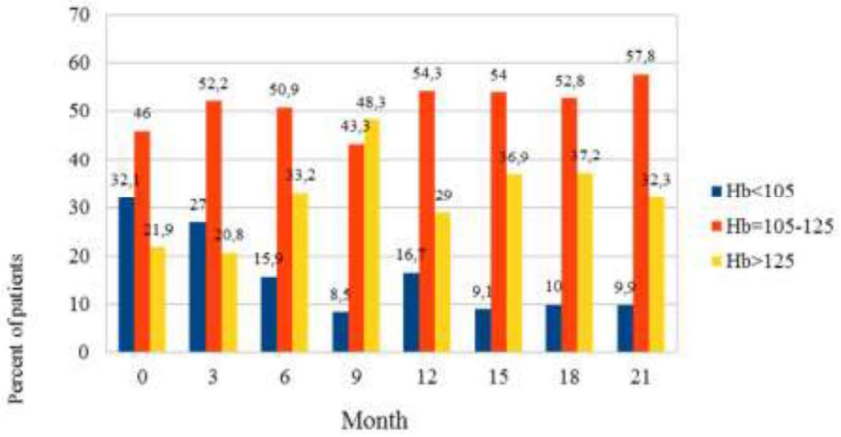

Fig. 2. Distribution of monthly hemoglobin levels in group-2 of patients

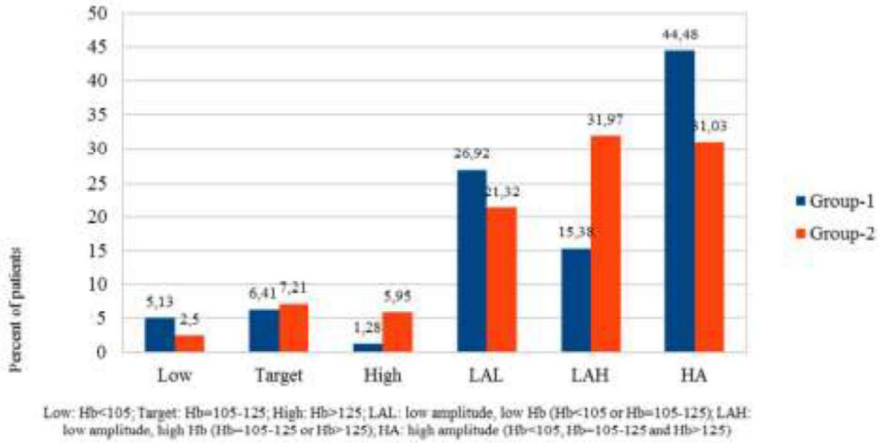

Fig. 3. Patterns of fluctuations in Hb levels during a 9-month period after admission

The average Hb level significantly increased over the period of 21 months in both groups and there was a significant difference in hemoglobin increase between the two groups (Table 1). EPO dose significantly decreased in both groups over the period of 21 months and there was no significant difference in EPO dose decrease between two groups (Table 1). Iron dose significantly decreased over the period of 21 months in both groups and there was a significant difference in iron dose decrease between the two groups (Table 1). The average TSAT and ferritin levels significantly increased over the period of 21 months in both groups and there was a significant difference in TSAT increase, but no in ferritin increase between the two groups (Table 1). The average eKT/V significantly increased over the period of 21 months in both groups and there was a significant difference in eKT/V increase between the two groups (Table 1). The average albumin value significantly increased over the period of 21 months in both groups and there was no significant difference in albumin increase between the two groups (Table 1). The average CRP significantly decresead over the period of 21 months in both groups and there was a significant difference in CRP decrease between the two groups (Table 1). The average PTH significantly decresead over the period of 21 months in both groups and there was no significant difference in PTH decrease between the two groups (Table 1).

In group-1 EPO dose and CRP, but in group-2 EPO dose, ferritin, HD vintage and iron dose were statistically significant predictors of the Hb level 9 months after admission by the model of multivariate regression analysis (Table 2).

Table 1. Mean values of anemia-related factors in both groups of patients over the period of 21 months

Month		0	3	6	9	12	15	18	21	Wilks` Lambda Sig.[a]
Hb (g/L)	G1	98.4±16.4	111.5±15.6	113.0±18.2	115.7±15.8	114.3±17.1	118.2±12.2	119.3±7.3	117.0±8.0	0.736
	G2	111.8±17.0	113.3±15.6	119.5±14.9	124.1±15.2	118.3±15.3	121.4±13.5	121.4±13.8	120.9±13.7	p<0.001
Sig. between groups		p<0.001	n.s.	p=0.001	p<0.001	n.s.	n.s.	n.s.	n.s.	p<0.001
TSAT (%)	G1	25.4±11.0	27.9±13.7	32.3±15.9	36.9±19.1	36.6±16.7	32.8±15.9	34.7±11.3	34.8±13.0	0.536
	G2	27.3±12.2	30.6±15.6	33.0±17.5	37.0±18.1	36.2±16.5	34.6±15.3	35.5±15.9	37.3±17.0	p<0.001
Sig. between groups		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	p=0.015
Ferritin (ng/ml)	G1	487±435	512±448	621±485	578±365	640±435	607±436	579±319	588±401	0.863
	G2	416±447	539±494	580±507	573±457	626±450	591±457	640±486	587±448	p<0.001
Sig. between groups		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EPO dose (IU/kg/w)	G1	83.7±51.9	87.9±58.5	76.9±61.2	74.1±58.6	66.4±56.2	59.2±51.6	38.2±37.2	36.2±35.6	0.916
	G2	75.0±57.7	71.2±53.6	70.3±60.1	49.8±51.9	50.0±51.1	54.8±54.6	50.4±57.1	44.5±50.5	p<0.001
Sig. between groups		n.s.	p=0.011	n.s.	p=0.001	p=0.022	n.s.	n.s.	n.s.	n.s.
Iron dose (mg/month)	G1	143.1±117	171.6±128	144.2±129	155.3±126	163.8±137	141.1±120	96.5±105	90.9±110.8	0.969
	G2	110.6±92.7	121.7±109	143.0±113	99.6±109	117±112	96.1±101	78.7±95.4	77.9±96.9	p<0.05
Sig. between groups		p=0.007	p=0.011	n.s.	p=0.001	p=0.011	p=0.017	n.s.	n.s.	n.s.
eKT/V	G1	1.17±0.33	1.22±0.24	1.28±0.28	1.27±0.24	1.35±0.22	1.36±0.17	1.32±0.20	1.30±0.21	0.855
	G2	1.28±0.30	1.27±0.25	1.35±0.27	1.40±0.23	1.42±0.24	1.42±0.22	1.38±0.22	1.39±0.23	p<0.001
Sig. between groups		p=0.001	n.s.	p=0.046	p<0.001	p=0.023	n.s.	n.s.	n.s.	p=0.041
Albumin (g/L)	G1	38.5±5.24	40.3±4.73	41.2±4.22	42.4±3.72	41.5±4.27	42.6±3.24	42.6±2.06	43.6±2.60	0.693
	G2	38.4±4.94	40.7±3.86	41.2±4.02	42.7±3.69	41.1±3.70	42.3±3.78	42.2±3.54	43.4±3.74	p<0.001
Sig. between groups		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
CRP (mg/L)	G1	17.5±32.7	13.7±28.4	11.0±18.4	12.3±25.7	14.4±31.3	10.1±20.4	9.04±17.5	10.0±15.7	0.934
	G2	12.0±15.7	8.48±17.9	8.09±17.7	8.82±14.5	9.01±17.9	7.67±13.9	7.57±12.4	8.46±26.3	p=0.002
Sig. between groups		p=0.034	p=0.027	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	p<0.001
PTH (pg/ml)	G1		148±142		149±203		155±153		143±100	0.934
	G2		433±558		304±355		281±337		298±345	p=0.002
Sig. between groups			p<0.001		p<0.001		p=0.021		p=0.029	n.s.

[a] Combined analysis of variance for repeated measures; G1-group-1; G2-group-2

Table 2. Predictors of hemoglobin variability in both groups of patients 9 months after admission by multivariate regression analysis

	Beta	Significance	Part
EPO	G1: - 0.377	p=0.031	- 0.283
	G2: - 0.376	p<0.0005	- 0.360
Iron dose	G1: 0.010	n.s.	0.008
	G2: - 0.119	p=0.037	- 0.114
Ferritin	G1: - 0.085	n.s.	- 0.075
	G2: - 0.215	p<0.0005	- 0.210
CRP	G1: - 0.345	p=0.030	- 0.286
	G2: - 0.106	n.s.	- 0.100
HD vintage	G1: 0.035	n.s.	0.033
	G2: 0.164	p=0.006	0.149

Model Summary: Dependent Variable Hb- 09th month, Group-1 (G1): ANOVA: F=3.057; R Square= 0.44; Sig. p = 0.008, Group-2 (G2): ANOVA: F=11.904; R Square= 0.316; Sig. p< 0.0005

Discussion

The most noteworthy aspect of intrapatient variability in Hb levels in HD patients is its common occurrence. Minor fluctuations above and below the target range may be normal in any setting. However, wide and prolonged fluctuations in Hb are usually associated with several internal and external factors that can influence ESA response and Hb stability. One study found that hemoglobin cycling more than 1.5 g/dL above or below the target range and lasting more than 8 weeks occurred in more than 90% of 281 HD patients, and that the mean number of hemoglobin excursions per patient was 3.1 per year, with a mean per-excursion amplitude of 2.5 g/dL and a mean duration of 10.3 weeks [12]. Among our study population, nearly 87% of patients in group-1 and 84% in group-2 showed some pattern of Hb level fluctuation over time, which is in accordance with findings of other studies [1,12]. The significant proportion of the patients in group-1 and much less in group-2 had Hb below target of 105 g/L at admission. The EPO doses were significantly reduced over the 21-month period after admission in both groups of patients as the average Hb level significantly increased in both groups. The hemoglobin increase was significantly faster and higher in group-1 of patients in comparison with group-2. Adjusting epoetin doses when patients' Hb levels exceed the upper level of the target range of 125 g/L may be a major source of the fluctuation of patients' levels once they reach that point. When evaluating the relation between ESA and hemoglobin levels cross-sectionally within the population, a higher ESA dose is associated with a lower hemoglobin level as a result of the "confounding by medical indication". This phenomenon, has been previously described for the administered doses of ESAs in CKD populations [18]. HD patients with ESA-hyporesponsive anemia paradoxically receive *higher* ESA doses to achieve the same hemoglobin target as those who are better responsive.

Besides EPO deficiency, the most common additional cause of anemia in CKD is iron deficiency [6]. Iron deficiency can be either absolute, whereby iron stores are depleted, or relative, whereby iron stores are replete but circulating iron is deficient. Relative iron deficiency is also known as *functional iron deficiency* because functionally available (transferrin-bound) iron is insufficient to meet physiological needs. The peripheral iron markers serum ferritin and TSAT are most commonly used as the basis for treatment decisions in CKD patients. In iron-deficient erythropoiesis, declining TSAT occurs in the presence of normal serum ferritin levels [14]. The KDOQI guidelines recommend iron supplementation as an adjuvant to ESA treatment of hemodialysis patients in order to maintain serum ferritin greater than 200 ng/mL and TSAT greater than 20% and to minimize the ESA dosage needed to achieve the target Hb range [15]. However, in view of the divergent TSAT and serum ferritin values TSAT is considered to have greater relevance as a predictor of positive response to iron therapy [14]. Intestinal absorption of oral iron is low and the clinical response is relatively slow. Intravenous iron readily corrects iron deficiency and avoids two limitations of oral iron formulations: impaired absorption and gastrointestinal side effects [16]. In our study population iron deficiency was significantly more frequent in group 1 of patients at admission and greater iron doses in the first 2 months after admission were administered in comparison with group 2 of patients. Therafter, the iron doses were significantly reduced over the 21-month period in both groups of patients as the mean TSAT and ferritin levels in both groups of our patients increased. There was a positive correlation between EPO dose and iron dose in both groups of patients. In group 1 of patients iron dose negatively correlated with ferritin level and in group 2 hemoglobin level negatively correlated with iron dose that confirms the above-mentioned phenomenon of "confounding by medical indication" [13].

Inflammation and oxidative stress are typically present in individuals with CKD [17]. Thus, responsiveness to endogenous EPO or ESA therapy may be impaired by anemia of chronic inflammation. The chronic inflammatory state of HD produces a state of functional iron deficiency due to reticulo-endothelial blockade requiring a much higher than normal serum ferritin to provide

adequate iron delivery to the marrow. Inflammation due to chronic comorbidities or intercurrent events, including hospitalization and hemodialysis itself, is now recognized as a major contributor to CKD-associated anemia and ESA hyporesponsiveness that may require administration of higher ESA doses [18,19]. In our study population the mean CRP level was significantly higher in group 1 of patients in comparison with group 2 of patients in the first 2 months after admission. The mean CRP levels in both groups of our patients significantly decreased over the period of 21 months. In both groups of patients there was a significant negative correlation between hemoglobin level and CRP, as well as hemoglobin and ferritin level, and positive between EPO dose and CRP, but in group 1 of patients there was a positive correlation between EPO dose and ferritin. These observations confirm the findings in other studies [18,19] that chronic inflammation worsens anemia in hemodialysis patients and higher EPO doses are required.

A large proportion of HD patients have also protein energy malnutrition and wasting, low serum albumin levels and a diminished nutritional status could be a feature of patients who are resistant to ESA treatment [20]. In our study population the mean albumin levels in both groups of our patients significantly increased over the period of 21 months. In group 1 of patients there was a significant positive correlation between hemoglobin and albumin level and negative between albumin and EPO dose, but in both groups there was a significant negative correlation between albumin and CRP that confirm the findings of other studies [19-21] that MIA syndrome worsens anemia in hemodialysis patients and higher EPO doses are required. In both groups of our patients there was a significant negative correlation between albumin and age that confirm the findings in another study that malnutrition is more common in elderly than in younger patients [21].

The benefit of adequate HD dose measured by KT/V in improving anemia and reducing the ESA dose required for anemia correction in patients with ESRD [7,8] may be due to the correction of oxidative stress, and the removal of molecules that inhibit erythropoiesis. In our study population the mean eKT/V value was significantly higher in group-2 of patients in comparison with group-1 in the first 12 months after admission. The mean eKT/V value in both groups of our patients significantly increased over the period of 21 months. In group-1 of patients there was a significant positive correlation between hemoglobin level and eKT/V and in group-2 there was a significant positive correlation beween eKT/V and HD vintage, and eKT/V and ferritin. These observations are in accordance with findings in other studies [7,8].

Hyperparathyroidism may directly cause ESA-hyporesponsiveness by diminishing endogenous erythropoietin synthesis, reducing bone marrow erythroid progenitors, and shortening erythrocyte survival [22]. Indirect effects include the association of renal osteodystrophy with bone marrow fibrosis [23], confirmed by the observation of the restored bone marrow space and concomitant rise of serum erythropoietin concentrations after parathyroidectomy [24]. In our study population the mean PTH level was significantly higher in group 2 of patients compared to group 1 of patients over the period of 21 months. The mean PTH levels in both groups of our patients significantly decreased over the period of 21 months. In both groups of patients there was a significant negative correlation between PTH and age that confirms the findings in another study that adynamic bone disease with low PTH level is prevalent in elderly HD population [25]. In group 2 of patients there was a significant positive correlation between PTH and HD vintage that confirms the findings of other studies [22, 26] that secondary hyperparathyroidism progresses in hemodialysis patients if inadequatly managed.

Limitations of the study

The main limitations of this study are its observational and retrospective nature and missing hospitalization and outcome data. Because of the retrospective nature of the study, our results should be interpreted as associative rather than causative. The hospitalization rate and the ESA dose during hospitalization were not accounted for and therefore we cannot determine its effect on our data and the resulting error term of the model may be increased. Another limitation of our study is that it is based on only 21-month follow-up period of the cohort, rather than a longitudinal one of several years.

Conclusions

Insufficient EPO therapy, iron deficiency and chronic inflammation with protein-energy wasting were the main factors of inadequate correction of anemia in patients on maintenance hemodialysis before admission, especially in the group of patients with hemodialysis vintage below 24 months.

Conflict of interest statement. None declared.

References

1. Ebben JP, Gilbertson DT, Foley RN, *et al*. Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. *Clin J Am Soc Nephrol* 2006; 1: 1205-1210.
2. Brimble KS, Clase CM. Hemoglobin variability in dialysis patients. *J Am Soc Nephrol* 2007; 18: 2218-2220.
3. Kalantar-Zadeh K, Aronoff GR. Hemoglobin Variability in Anemia of Chronic Kidney Disease. *J Am Soc Neph* 2009; 20(3): 479-487.
4. Singh N, Agarwal AK. Pumping iron: revisiting risks, benefits and strategies in treatment of iron deficiency in end-stage renal disease. *Clin Nephrol* 2012; 77: 188-195.
5. Besarab A. What are common misconceptions in dialysis patient care? *Seminars Dial* 2011; 24: 498-503.

6. Kalantar-Zadeh K, McAllister CJ, Lehn RS, *et al*. Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. *Am J Kidney Dis* 2003; 42: 761-773.
7. Movilli E, Cancarini GC, Zani R, *et al*. Adequacy of dialysis reduces the dose of recombinant erythropoietin independently from the use biocompatible membranes in haemodialysis patients. *Nephrol Dial Transplant* 2001; 16: 111-114.
8. Locatelli F, Del Vecchio L. Dialysis adequacy and response to erythropoietic agents: what is the evidence base? *Nephrol Dial Transplant* 2003; 18: 29-35.
9. Drueke TB, Eckardt KU. Role of secondary hyperparathyroidism in erythropoietin resistance of chronic renal failure patients. *Nephrol Dial Transplant* 2002; 17(5): 28-31.
10. Locatelly F, Barany P, Covic A, *et al*. Kidney Disease: Improving Global Outcomes guidelines on anemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant* 2013; 28(6): 1346-1359.
11. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012; 2(4): 279-335.
12. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int* 2005; 68: 1337-1343.
13. Cotter D, Zhang Y, Thamer M, *et al*. The effect of epoetin dose on hematocrit. *Kidney Int* 2008; 73: 347-353.
14. Fishbane S, Pollack S, Feldman HI, *et al*. Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988-2004. *Clin J Am Soc Nephrol* 2009; 4: 57-61.
15. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis* 2006; 47: S11-S145.
16. Macdougall IC. Iron supplementation in the non-dialysis chronic kidney disease patient: oral or intravenous? *Curr Med Res Opin* 2010; 26(2): 473-482.
17. Chonchol M, Lippi G, Montagnana M, *et al*. Association of inflammation with anaemia in patients with chronic kidney disease not requiring chronic dialysis. *Nephrol Dial Transplant* 2008; 23: 2879-2883.
18. Carrero JJ, Stenvinkel P. Inflammation in end-stage renal disease-what have we learned in 10 years? *Semin Dial* 2010; 23: 498-509.
19. Chawla LS, Krishnan M. Causes and consequences of inflammation on anemia management in hemodialysis patients. *Hemodial Int* 2009; 13: 222-234.
20. Gaweda AE, Goldsmith LJ, Brier ME, *et al*. Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response. *Clin J Am Soc Nephrol* 2010; 5(4): 576-581.
21. Qureshi AR, Alvestrand A, Danielsson A, *et al*. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney Int* 1998; 53(3): 773-782.
22. Brancaccio D, Cozzolino M, Gallieni M. Hyperparathyroidism and anemia in uremic subjects: a combined therapeutic approach. *J Am Soc Nephrol* 2004; 15(1): S21-S24.
23. Rao DS, Shih MS, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. *N Engl J Med* 1993; 328: 171-175.
24. Gallieni M, Corsi C, Brancaccio D. Hyperparathyroidism and anemia in renal failure. *Am J Nephrol* 2000; 20: 89-96.
25. Bover J, Urena P, Brandenburg V, *et al*. Adynamic bone disease: from bone to vessels in chronic kidney disease. *Semin Nephrol* 2014; 34(6): 626-640.
26. Drueke T, Ritz E. Treatment of secondary hyperparatrhyroidism in chronic kidney disease patients with Cinacalcet and/or Vitamin D derivatives. *J Am Soc Nephrol* 2009; 4: 234-241.