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PREVALENCE AND DETERMINANTS OF HEMOGLOBIN VARIABILITY AND ITS IMPACT ON MORTALITY IN PATIENTS ON MAINTENANCE HEMODIALYSIS

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Treatment with erythropoiesis-stimulating agents (ESA) is the optimal therapy for renal anemia. However, maintaining hemoglobin (Hb) within narrow targets remains a significant clinical problem because during ESA treatment, the Hb levels usually fluctuate widely; this phenomenon is termed "hemoglobin variability" and is associated with higher mortality. Our study aimed to determine the prevalence and cause of hemoglobin variability in patients on chronic hemodialysis (HD) treatment and to estimate the association of Hb variability with all-cause mortality.

A prospective study was conducted on 193 chronic HD patients treated with ESA. Hemoglobin cycling was defined as Hb variability throughout at least eight weeks and amplitude of more than 1.5 g/dl from the Serbian target range of 10-11 g/dl.

During the one-year follow-up, there was 5.6 ESA dose modification per patient. 23.4% of patients had never experienced Hb cycling during the study period. The total number of 460 hemoglobin excursions were recorded in 76.6% of patients, with 2.42 ± 2.7 Hb excursions per year, mean amplitude of 2.13 ± 0.76 g/dL, and the average length of Hb excursion of 8.2 ± 2.7 weeks. The Hb cycling was not affected by the gender, age, weekly ESA dose, or the presence of diabetes or hypertension. However, Hb variability was associated with ESA dose change, CRP, and HD vascular access type. The odds ratio for 1-year all-cause mortality was 1.424 (95% CI: 1.231–1.682, P < 0.001).

Hemoglobin cycling frequently occurs in ESA treated HD patients as a result of current practice in ESA dosing, the presence of infection, and the type of vascular access for HD and these fluctuations predicted overall mortality.

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Key words: *hemoglobin variability, erythropoiesis-stimulating agents, hemodialysis*

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Introduction

Anemia is a common complication that is associated with adverse cardiovascular complications and poor outcomes in patients with chronic kidney disease (CKD) (1). The introduction of erythropoiesis-stimulating agents (ESA) has revolutionized the management of anemia in CKD, leading to substantial reductions in the blood transfusion requirements, improvement in energy, and physical function (2) and improvements in health-related quality of life (3). Even though the optimal target hemoglobin (Hb) concentration in hemodialysis (HD) patients continues to be a substantial dilemma, the European Best Practice Guidelines (EBPG) recommended that the target hemoglobin level should be determined on an individual basis, having in mind gender, age, ethnicity, activity, and comorbid conditions (4). Nevertheless, with the publication of CREATE and CHOIR studies, both the upper and lower limits for target Hb concentration was set to 10-12 g/dL (5, 6) as it was shown that targeting normal Hb levels did not result in better survival, but rather in increased cardiovascular events and mortality in HD patients. Keeping patients' Hb levels in such a narrow range is difficult considering the loss of physiological regulation of red cell generation and many other factors, such as iron deficiency, chronic inflammation, secondary hyperparathyroidism, malnutrition, and inadequate dialysis dose. The data confirm that only 30% of patients will belong to this hemoglobin range at any point in time because fluctuations in the Hb level result in frequent under-and overreaching the target level (7). This phenomenon is known as Hb

variability, and it is defined as repeated, cyclical, up and down movements of absolute Hb levels during ESA treatment. It is speculated that Hb variability may influence patients' survival. A few authors hypothesized that Hb variability increase mortality risk since fluctuations in Hb might affect oxygen delivery to tissues, thereby resulting in end-organ damage. Over the last decade, significant consideration has been given to the variability in Hb levels for dialysis patients. Several population-based studies investigating Hb fluctuation have been performed to date, but the results are controversial (7-10).

The aims of the study were to assess the prevalence and causes of Hb variability in hemodialysis patients and to estimate all-cause mortality depending on hemoglobin cycling in light of the Serbian regulatory restrictions in renal anemia management with lower target hemoglobin range of 10-11 g/d.

Patients and methods

This prospective study was carried out at the Nephrology Clinic of the Clinical Center Niš, Serbia from January 2015 to February 2016. The study was conducted in accordance with the Declaration of Helsinki for medical research. We included 193 stable patients over 18 years with end-stage renal disease who have been undergoing treatment with repeated hemodialysis for longer than three months. Patients with acute illness, malignancy, or active inflammatory diseases were excluded.

Baseline data including demographic characteristics, dialysis vintage, dialysis parameter (Kt/V), anthropometric parameters (body height, body weight), dose, type and regimen of ESA, hematological, and biochemical analyses as well as data on selected comorbidities. Hematological parameters were analyzed on Nihon Kohden Hematology Analyzer; biochemical data were measured on Siemens Dimension RXL Max Chemistry Analyser while serum measurement of PTH was done on Roche Cobas e411.

During the study period, anemia syndrome was corrected by subcutaneously applied ESA, which was used according to the current recommendations of the European Best Practice Guidelines and Health Insurance Fund of Serbia's policy for renal anemia treatment in HD patients. The nursing staff administered ESA into the left or right upper arm during the regular hemodialysis sessions. As intravenous ESA application requires higher doses, all our patients were on a subcutaneous dosing regimen.

Erythropoiesis-stimulating agents were started when the Hb level was below 10 g/dL. The starting and maintenance doses of erythropoietin alpha/beta were 50–150 and 25–75 μ/kg/week and of darbepoetin 0.25–0.75 and 0.13–0.35 μ/kg/ week. The erythropoiesis-stimulating agent was stopped after achieving an Hb level of 11 g/dL. Two hundred units of r-HuEPO is equivalent to 1 μg of darbepoetin, so we converted darbepoetin unit accordingly.

Initially, rHuEPO was administered three times a week to achieve target concentrations of Hb 10-11 g/dL while maintaining the obtained target Hb levels by an individual approach (hold, keep unchanged, increase or decrease the dose on a monthly basis). ESA therapy was stopped when hemoglobin level reached 12 g/dl. Intravenous iron sucrose was prescribed if ferritin was < 100 μg/L, or the transferrin saturation (TSAT) was < 20%, and Hb was below the target range. Patients received 100 mg intravenously over each of the next 10 HD treatments, and then every two weeks thereafter. Iron was withheld if ferritin was > 800 μg/L, or the TSAT was > 50%.

As per Fishbane and Berns (11), hemoglobin variability characterizes the fluctuation of hemoglobin above or below the target range over time. In our study group, Hb cycling was defined as an oscillation in Hb of ≥ 1.5 g/dl over > 8 weeks during which Hb levels increased or decreased and then reversed the initial trajectory in relation to target Hb of 10-11 g/dL. Patients were divided into two groups: without Hb fluctuation and with Hb fluctuation. The outcome measure was all-cause mortality during the twelve months follow-up.

The following laboratory parameters were monitored over the period of 12 months after inclusion: hemoglobin (Hb-g/L) monthly, hemodialysis dose (KT/V), 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. TSAT was calculated as the ratio of serum iron to total iron-binding capacity (TIBC). All laboratory values were measured by automated and standardized methods.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as number (N) or percentage (%). The Student's t-test was used to compare two groups of data (if there is a normal distribution of frequencies within the group), or the non-parametric Mann-Whitney Rank Sum test is used if the frequency distribution is uneven. Logistic regression analysis was performed to identify independent risk factors for Hb-variability. A Kaplan–Meier analysis was used to examine the effects of hemoglobin variability on all-cause mortality. P-value < 0.05 was considered as statistically significant. Statistics were generated using SPSS version 21.

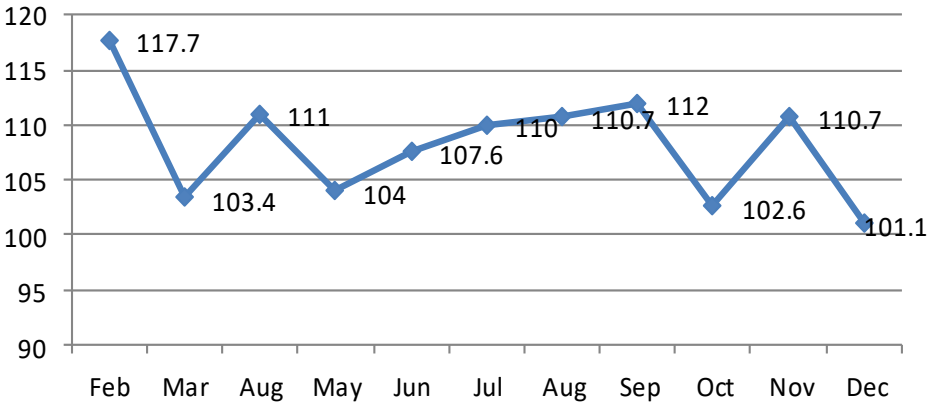
Results

The study included 193 stable ESRD treated with hemodialysis. The mean age of the patients was 63.88 ± 12.51 years, 61.1% of patients were male, dry weight was 64.3 ± 12.8 kg, and dialysis vintage was 66.67 ± 55.18 (range 14.9–284.1) months. Most of the patients (71.1%) suffered from hypertension, and 25.90% from diabetes. The characteristics of the participants are summarized in Table 1.

Table 1. Basic demographic, hemodynamic, anthropometric and biochemical characteristics of the HD subjects treated with ESA

Age (years)	63.88 ± 12.51
Men (%)	118 (61.1%)
Dialysis vintage (months)	66.67 ± 55.18
Arteriovenous fistula (%)	81.2
Kt/V	1.35 ± 0.64
Dry weight (kg)	64.3 ± 12.8
Interdialtic weight gain (kg)	2.9 ± 2.3
Body Mass Index (kg/m^2)	25.1 ± 3.2
Systolic blood pressure (mmHg)	135.2 ± 30.9
Diastolic blood pressure (mmHg)	91.7 ± 13.1
Hypertension (%)	135 (71.1%)
Diabetes mellitus (%)	50 (25.90%)
Hb (g/l)	103.17 ± 5.04
Iron (mmol/l)	13.7 ± 12.9
TIBC (µmol/L)	38.7 ± 20.4
Transferrin saturation (%)	32.6 ± 10.6
Ferritin (ng/mL)	246.1 ± 135.8
Cholesterol (mmol/l)	4.9 ± 1.5
Triglycerides (mmol/l)	2.6 ± 1.9
LDL-C (mmol/l)	3.1 ± 0.4
HDL-C (mmol/l)	1.6 ± 0.9
s. Albumins (g/l)	32.07 ± 4.37
Total protein (g/l)	66.78 ± 7.54
s. Creatinine (µmol/l)	809.64 ± 356.22
CRP (mg/l)	9.96 ± 7.55
PTH (pg/ml)	446.30 ± 294.81

Abbreviation: Hb, hemoglobin; TIBC-total iron binding capacity; LDL-C, low density cholesterol; HDL-C,high density cholesterol; CRP, C-reactive protein; PTH, parathormone.



Graph 1. Average monthly Hb level within HD study population

Graph 1 displays the mean hemoglobin values during one-year follow-up. Considering the whole study population, mean Hb was maintained within the target range most of the time.

However, apparently stable mean Hb levels in an overall study population can hide the occurrence of intra-individual variability in many patients which is shown in Figure 1.

Narrow hemoglobin target values resulted in frequent dose adjustments including the ESA withdrawal and consequent substantial hemoglobin fluctuations. During the one-year follow-up, there were an average 5.6 ESA dose changes, and 61% of patients had ≥ three dose changes (Graph 2). Regarding the number of hemoglobin cycling episodes, it was noticed that only 23.4% of patients had never experienced hemoglobin cycling during the study period.

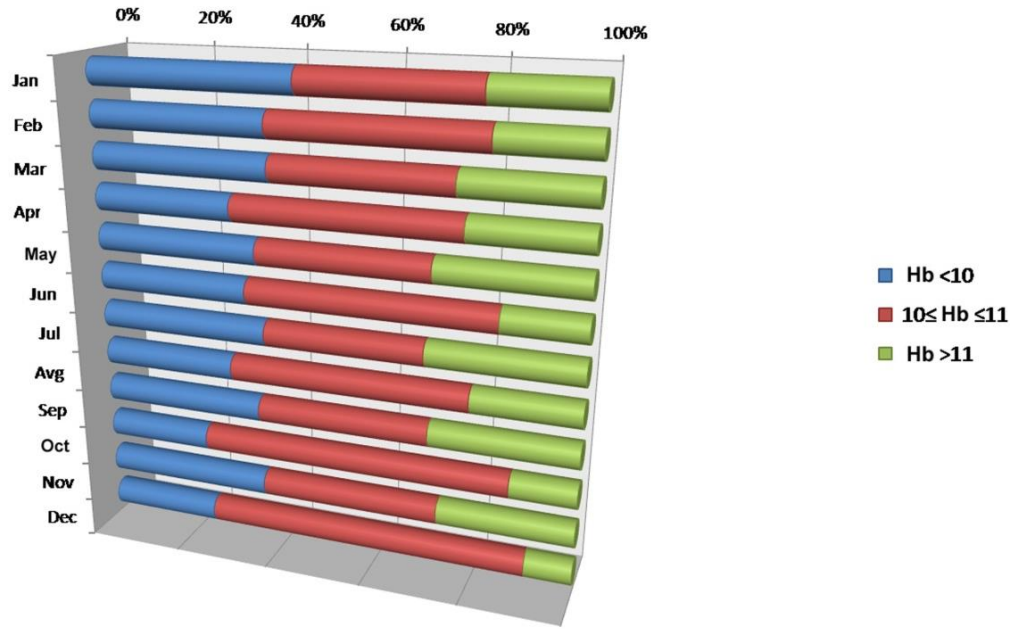
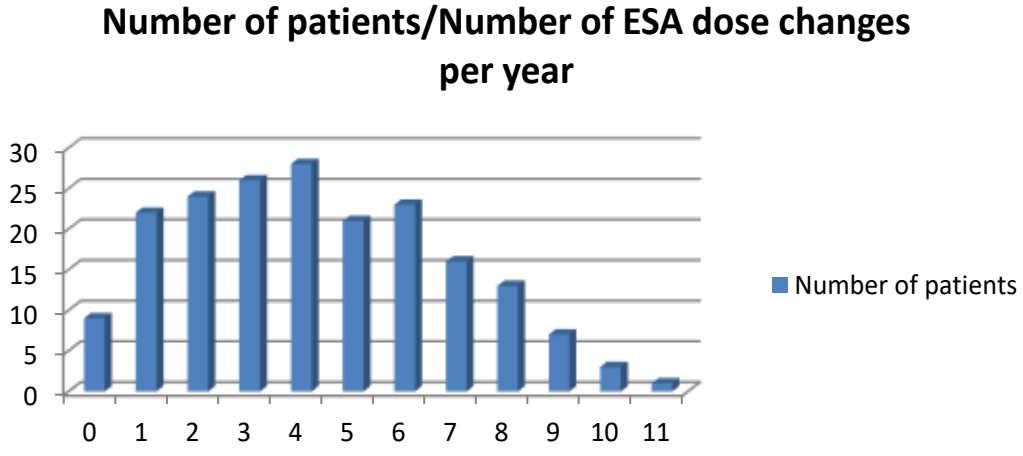


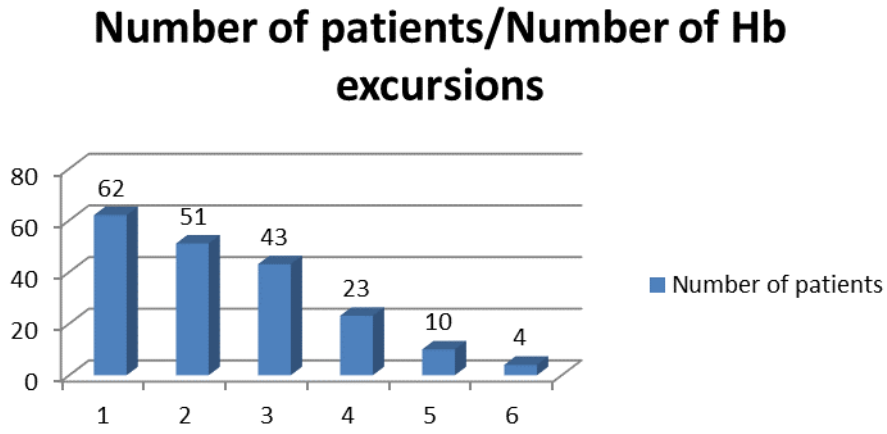
Figure 1. Distribution of monthly Hb levels in HD patients: below/within/above target percentage bar plot



Graph 2. Number of ESA dose changes per year

Simultaneously, out of 193 patients, hemoglobin excursions were recorded in 145 (76.6%). These patients experienced a mean of 2.42 ± 2.7 Hb excursions (defined as half of one full Hb cycle) per year, and the mean amplitude of excursions was 2.13 ± 0.76g/dL, while the average length of hemoglobin excursion was 8.2 ± 2.7 weeks. A total of 460 hemoglobin excursions were documented. Regarding the fluctuating pattern in hemoglobin levels over time, we recorded 188 excursions with Hb above the expected value (Hb values > 125g/dl) and 272 downward Hb excursions with Hb values < 85g/dl (Graph 3).

Finally, the study population was divided into two groups according to the presence or absence of Hb cycling during the follow-up time (Table 2).



Graph 3. Number of Hb excursions in HD patient treated with ESA

Table 2. Characteristics of patients with or without hemoglobin cycling

	Patients with Hb variability	Patients without Hb variability	p
Number of patiets	148	45	
Gender (males %)	60.7	61.7	0.578
Age (years)	61.32 ± 11.42	63.71 ± 12.02	0.612
AVF (%)	78.74	91.57	0.002
HD vintage (months)	59.76 ± 62.27	58.04 ± 55.13	0.05
DM (%)	19.2	21.8	0.246
HTA (%)	65.12	69.33	0.065
Frequency of ESA dose change	4.22 ± 2.44	2.95 ± 2.58	< 0.001
ESA dose (IU/kg/week)	70.08 ± 47.37	63.37 ± 55.52	0.822
Hb (g/dl)	101.53 ± 10.39	104.87 ± 4.57	0.004
Feritin (ng/mL)	639.37 ± 488.51	531.62 ± 319.78	0.003
TSAT (%)	30.82 ± 13.87	35.46 ± 32.87	0.758
CRP (mg/l)	14.32 ± 2.05	7.14 ± 2.4	< 0.001
Kt/V	1.31 ± 0.4	1.35 ± 0.2	0.17
PTH (pg/ml)	573.8 ± 496.2	241.6 ± 319	0.002

Abbreviation: Hb, hemoglobin; HD-hemodialysis; DM-Diabetes mellitus; HTA-hypertension; ESA erythropoiesis stimulating agents; TSAT-transferrin saturation; CRP, C-reactive protein; PTH, parathormone.

The change in Hb level was not affected by the gender, age, weekly ESA dose or the presence of diabetes or hypertension. However, the frequency of ESA dose change ($p < 0{,}001$), inflammation ($p < 0.001$), type of vascular access ($p = 0.002$) and secondary hyperparathyroidism ($p = 0.002$) significantly influenced hemoglobin variability.

Six variables with the highest correlation coefficient in the univariate analysis were included in the multiple linear regression analysis to determine the significant predictors of Hb variability. The results show that Hb variability was associated with ESA dose change (OR 1.56;95% CI 1.29–2.04, $p < 0.001$), CRP (OR 1.73; 95% CI 1.22–1.99, $p < 0.001$) and vascular access type (OR 2.13; 95% CI 1.56–3.18, $p = 0.033$) (Table 3).

Of 193 patients 31 of them (16.6%) died in 1A 2 month study period. The effects of hemoglobin fluctuation on mortality were evaluated by logistic regression analysis. Full adjustment was made with variables such as age, vascular access type, CRP, Hb, dialysis vintage, diabetes, hypertension and ESA dose.

The hazard ratios in HD patients were 1.458 (95% CI: 1.304–1.771, $p < 0.001$) for 6-month all-cause mortality, 1.424 (95% CI: 1.231–1.682, $Pp < 0.001$) for 1-year all-cause mortality after full adjustment (Table 4).

The cumulative 12-months survival rates of the two groups were statistically significant according to the Kaplan–Meier curve ($p < 0.001$ by log-rank test) (Graph 4).

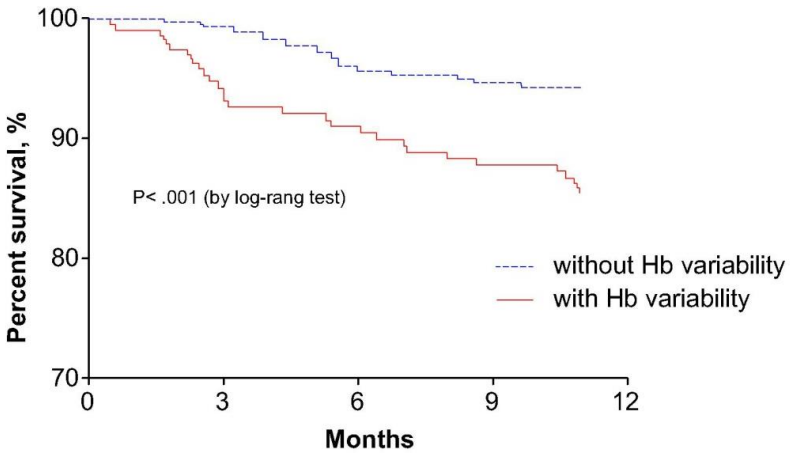
Table 3. Independent predictors of hemoglobin variability determined with logistic regression model

Variable	OR	95% Confidence Interval	p
ESA dose changes per patient (n)	1.56	(1.29 – 2.04)	< 0.001
CRP	1.73	(1.22 – 1.99)	< 0.001
Vascular access type	2.13	(1.56 – 3.18)	0.033

Table 4. Prediction of mortality according to Hb variability in HD patients***

	Age adjusted OR (95% CI)	Fully Adjusted OR (95% CI)***
6-months mortality	1.570 (1.341 – 1.897)‡	1.458 (1.304 – 1.771)‡
12-months mortality	1.420 (1.227 – 1.551)‡	1.424(1.231 – 1.682)‡

Adjusted by age, vascular access type, CRP, Hb, dialysis vintage, diabetes, hypertension and ESA dose, CI, indicates confidence interval; HR, hazard ratio; OR, odds ratio. ‡$p < 0.001$



Graph 4. The Kaplan Meier curve for the cumulative 12-month survival rates between patients with and without Hb variability. Log-rank test shows significant difference between two groups statistically.

Discussion

Keeping the constant Hb levels is obligatory to ensure continuous and sufficient oxygen delivery to tissues. In healthy subjects, individual variation in the Hb level occurs within the range of normal values, usually does not exceed 1 g/dL and have no clinical significance. However, for hemodialysis patients, substantial variability in the Hb level over time is not uncommon. Fluctuations in the Hb levels provoke repeated episodes of relative ischemia and tissue hypoxia, which may result in organ dysfunction or injury (10).

The key finding of this study is confirming that Hb cycling frequently occurs in hemodialysis patients. Over a one-year period, only 25% of patients using ESA had stable Hb levels within a target range of 10-11 g/dL. This reflects the difficulty of maintaining Hb levels within a narrow range as recommended by the most recent guidelines and hemoglobin management still remained a substantial challenge in the care of hemodialysis patients, with almost all patients moving between categories over fairly short time periods. The finding that patients receiving ESA had high variability agrees with previous studies and points to the current practice of prescribing ESA as one of the causes of Hb variability (12-14). The other possible factors that might affect patients' Hb variability were summarized in a review by Kalantar-Zadeh and Aronoff (15). These authors concluded that drug-related factors, patient demographics, iron deficiency, infections, inflammation, malignancies, and reimbursement-related factors all had an impact on Hb variability. Of these multiple factors, the ESA dose was the most actionable factor in the management of anemia for patients on dialysis therapy.

In the present study, we observed three major determinants of Hb fluctuation. The first was a frequent change in ESA dose. A positive correlation was seen between ESA dose change and amplitude of Hb excursion, implying that dose changes were causal, rather than reactive. That finding has also been published by others (16) and strongly implicates current dosing strategies and anemia management protocols in the pathogenesis of Hb cycling. Interestingly, compared with dose increases, dose reductions seemed to be a stronger predictor of cycling. We noted 272 downward Hb excursions. The Hb decline was mostly the consequence of ESA withdrawal (in 78.3% of cases) and dose reduction in 15%.

Evidence suggests that inflammation is an important factor associated with Hb variability. In a retrospective study of 225 hemodialysis patients, high CRP values were associated with less stable Hb levels (17). Likewise, Barany et al. reported a significant correlation between Hb variability and CRP levels (18). Similarly to these findings, we observed that higher CRP values significantly influence Hb variability. These results provide supporting evidence that inflammation can trigger hemoglobin variability. Thus, ESA dosage should be regularly reviewed, and patients should be monitor closely in the presence of inflammatory conditions.

Whereas the weekly dose of ESA was comparable regardless of the vascular access used, the weekly dose of ESA used in the patients with central vein catheter (CVC) was significantly higher than that used in those with AVF. This observation is consistent with other studies that indicate that CVC use as vascular accesses is associated with the need for higher doses of ESA secondly to blood loss during dialysis and possible catheter-related infections (19). Besides, the type of vascular access had an impact on Hb variability, possibly via intercurrent inflammation.

Studies about the clinical significance of Hb variability have been increased but results were conflicting. Regidor et al. (20) noticed that patients with Hb fall greater than 2 g/dL had the greatest mortality risk when compared with patients who showed Hb fall lower than 0.8 g/dL. In a cohort of 34,963 prevalent HD patients, Yang et al. (21) demonstrated that per every 1 g/dL increase of Hb variability, there is a 33% increase in mortality risk. On the contrary, Zeynep et al. found that hemoglobin variability has a modest association with morbidity and all-cause mortality in ESA treated dialysis patients (22). Persistently or transiently low Hb levels have also been associated with hospitalization and death (9, 23, 24, 25), as have downward Hb excursions (25). In our study, we likewise observed that Hb fluctuation was an independent determinant of mortality, which is in accordance with the recent study of Lin et al. (26). They also demonstrated that high Hb variability is an independent risk factor for cardiovascular mortality in HD patients and might influence the cardiac function.

Although the direct effects of Hb variation on patient outcome are still not fully understood, it is evident that large or frequent fluctuations are undesirable. Low Hb levels have a negative impact on symptoms and quality of life for patients; they also increase the requirement for blood transfusions. The myocardium may be particularly vulnerable to hemoglobin fluctuation because it has to compensate for periods of reduced oxygen delivery with increased output and myocardial cell growth. Hemoglobin levels higher than current target ranges may be associated with worse cardiovascular outcomes (7, 8), and higher Hb levels maintained with higher ESA doses have a significant cost implication. More frequent Hb fluctuations outside of target ranges require more clinician time to determine response in terms of ESA dose adjustment or of intravenous iron dosing.

Conclusion

Hemoglobin management remained a substantial challenge in the care of hemodialysis patients, with almost all patients moving between different hemoglobin categories over fairly short time periods. Our study demonstrates that both inflammation and the frequent changes of ESA dose were the major predictors of hemoglobin variability. The current ESA reimbursement practice demands constant adjustments of the ESA doses. The question is whether modification of treatment policies can contribute to reducing cycling and whether this influences the outcome. To answer this question, further studies are needed.

References

1. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279-335.
2. Baris A. The Relationship between Depressive Symptoms and Erythropoietin Resistance in Stable Hemodialysis Patients with Adequate Iron Stores. Int J Artif Organs 2013;36:314-19.[CrossRef] [PubMed]
3. Spinowitz B, Pecoits-Filho R, Winkelmayer WC, Pergola PE, Rochette S, Thompson-Leduc P et al. Economic and quality of life burden of anemia on patients with CKD on dialysis: a systematic review. J Med Econ 2019;[CrossRef] [PubMed]
4. Locatelli F, Bárány P, Covic A, De Francisco A, Del Vecchio L, Goldsmith D et al. Kidney disease: improving global outcomes guidelines on anaemia management in chronic kidney disease: a European renal best practice position statement. Nephrol Dial Transplant 2013;28:1346-59. [CrossRef] [PubMed]
5. Macdougall IC. Steering Committee of the CREATE trial; CREATE Study Group: CREATE: new strategies for early anaemia management in renal insufficiency. Nephrol Dial Transplant 2003;18:13-16.[PubMed]
6. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M et al; CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085-98.[CrossRef] [PubMed]
7. Brunelli SM, Lynch KE, Ankers ED, Joffe MM, Yang W, Thadhani RI et al. Association of hemoglobin variability and mortality among contemporary incident hemodialysis patients. Clin J Am Soc Nephrol 2008; 3:1733-40.[CrossRef] [PubMed]
8. Weinhandl ED, Peng Y, Gilbertson DT, Bradbury BD, Collins AJ. Hemoglobin variability and mortality: Confounding by disease severity. Am J Kidney Dis 2011; 57:255-65.[CrossRef] [PubMed]
9. Ebben JP, Gilbertson DT, Foley RN, Collins AJ. Hemoglobin level variability: Associations with comorbidity, intercurrent events, and hospitalizations. Clin J Am Soc Nephrol 2006;1:1205-10. [CrossRef] [PubMed]
10. Zhao L, Hu C, Cheng J, Zhang P, Jiang H, Chen J. Haemoglobin variability and all-cause mortality in haemodialysis patients: A systematic review and meta-analysis. Nephrology 2019;24(12):1265-1272. [CrossRef] [PubMed]
11. Fishbane S, Berns JS. Evidence and implications of haemoglobin cycling in anemia management. Nephrol Dial Transplant 2007;22:2129-32. [CrossRef] [PubMed]
12. Spiegel DM. Hemoglobin variability in chronic kidney disease: A cross-sectional study. Am J Med Sci 2009; 337:340-3.[CrossRef] [PubMed]
13. Minutolo R, Chiodini P, Cianciaruso B, Pota A, Bellizzi V, Avino D et al. Epoetin therapy and hemoglobin level variability in nondialysis patients with chronic kidney disease. Clin J Am Soc Nephrol 2009;4:552-9. [CrossRef] [PubMed]
14. Boudville NC, Djurdjev O, Macdougall IC, de Francisco AL, Deray G, Besarab A et al. Hemoglobin variability in nondialysis chronic kidney disease: examining the association with mortality. Clin J Am Soc Nephrol 2009;4:1176-82.[CrossRef] [PubMed]
15. Kalantar-Zadeh K, Aronoff GR. Hemoglobin variability in anemia of chronic kidney disease. J Am Soc Nephrol 2009;20:479-87.[CrossRef] [PubMed]
16. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int 2005;68:1337-43. [CrossRef] [PubMed]
17. de Francisco A, Stenvinkel P, Vaulont S. Inflammation and its impact on anaemia in chronic kidney disease: from haemoglobin variability to hyporesponsiveness. NDT Plus 2009;2:i18-i26.[CrossRef] [PubMed]
18. Barany P, Carrero JJ, Snaedal J'onsd'ottir S. Variability of hemoglobin (Hb) levels in relation to inflammatory status and iron metabolism in hemodialysis (HD) patients (Pts). Proceedings of the American Society of Nephrology Annual Congress; 2006; San Diego, USA.
19. Roberts TL, Obrador GT, St Peter WL, Pereira BJ, Collins AJ. Relationship among catheter insertions, vascular access infections, and anemia management in hemodialysis patients. Kidney Int 2004;66:2429-36. [CrossRef] [PubMed]
20. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol 2006;17:1181-91. [CrossRef] [PubMed]
21. Yang W, Israni RK, Brunelli SM, Joffe MM, Fishbane S, Feldman HI. Hemoglobin variability and mortality in ESRD. J Am Soc Nephrol 2007; 18:3164-70. [CrossRef] [PubMed]
22. Zeynep B, Bahar GD, Suleyman K, Emre T, Mehtap EU, Nurhan OAal. Factors Influencing Hemoglobin Variability and Its Association with Mortality in Hemodialysis Patients. Scientific World Journal 2018;18. [CrossRef] [PubMed]
23. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol 2006;17:1181-91. [CrossRef] [PubMed]
24. Gilbertson DT, Ebben JP, Foley RN, Weinhandl ED, Bradbury BD, Collins AJ. Hemoglobin level variability: associations with mortality. Clin J Am Soc Nephrol 2008;3:133-8.[CrossRef] [PubMed]
25. Ishani A, Solid CA, Weinhandl ED, Gilbertson DT, Foley RN, Collins AJ. Association between number of months below K/DOQI haemoglobin target and risk of hospitalization and death. Nephrol Dial Transplant 2008; 23:1682-9. [CrossRef] [PubMed]
26. Lin FJ, Zhang X, Huang LS, Ji G, Huang HD, Xie Yet al. Impact of hemoglobin variability on cardiovascular mortality in maintenance hemodialysis patients. Int Urol Nephrol 2018;50:1703-12.[CrossRef] [PubMed]

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PREVALENCIJA I DETERMINANTE VARIJABILNOSTI HEMOGLOBINA I NJEN UTICAJ NA MORTALITET KOD BOLESNIKA NA HRONIČNOM PROGRAMU HEMODIJALIZE

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Terapija agensima stimulacije eritropoeze (ASE) predstavlja optimalno lečenje renalne anemije. Međutim, održavanje hemoglobina (Hb) u okviru uskih ciljnih vrednosti ostaje značajan klinički problem, s obzirom na to da tokom primene ASE nivoi Hb obično značajno osciliraju; ovaj fenomen poznat je kao "varijabilnost hemoglobina", a udružen je sa povećanom smrtnošću bolesnika. Naše istraživanje imalo je za cilj da analizira učestalost i uzroke nastanka varijabilnosti hemoglobina kod bolesnika lečenih hemodijalizom (HD) i da proceni njen uticaj na mortalitet bolesnika.

Prospektivnom studijom obuhvaćeno je 193 bolesnika na hroničnoj HD, koji su lečeni ASE. Varijabilnost hemoglobina definisana je kao oscilacija koncentracije Hb u periodu od najmanje osam nedelja sa amplitudom većom od 1,5 g/dl od zadatih ciljnih vrednosti hemoglobina, koji u Srbiji za bolesnike na HD trenutno iznosi 10 g/dl — 11 g/dl.

Tokom jednogodišnjeg praćenja, bilo je 5,6 modifikacija doze ASE po bolesniku. 23,4% bolesnika nije imalo značajne oscilacije Hb tokom studijskog perioda. Ukupno 460 oscilacija (ekskurzija) hemoglobina zabeleženo je kod 76,6% bolesnika, sa 2,42 ekskurzije ± 2,7 ekskurzija godišnje, prosečne amplitude 2,13 g/dL ± 0,76 g/dL i prosečne dužine trajanja 8,2 nedelje ± 2,7 nedelja. Na osilaciju Hb nije uticala starost, pol, nedeljna doza ASE, kao ni prisustvo dijabetesa ili hipertenzije. Međutim, varijabilnost Hb zavisila je od promena doze ASE, CRP-a i tipa vaskularnog pristupa za HD.

Varijabilnost hemoglobina često se javlja kod bolesnika na HD lečenih ASE, kao posledica prakse učestalih promena doze ASE, prisustva infekcija i vrste vaskularnog pristupa za HD. Ove fluktuacije hemoglobina uticale su na povećanje mortaliteta kod naših bolesnika. Procena rizika za jednogodišnji mortalitet bila je 1,424 (95% CI: 1,231 – 1,682; P < 0,001).

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Ključne reči: *varijabilnost hemoglobina, agensi stimulacije eritropoeze, hemodijaliza*