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Hemoglobin variability in patients receiving EPO and roxadustat during maintenance hemodialysis: a self-control study

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Abstract. – OBJECTIVE: The aim of this study was to investigate the hemoglobin variability in patients undergoing maintenance hemodialysis during the application of erythropoietin (EPO) and roxadustat.

PATIENTS AND METHODS: For this retrospective study, we analyzed the clinical records of 80 patients with renal anemia on maintenance hemodialysis (MHD) admitted to our hospital between January 2017 and December 2022. We adopted a self-control design comparing the hemoglobin variability of the values before and after roxadustat administration in each patient. The patients received EPO from January 2017 to December 2019 and roxadustat from January 2020 to December 2022. We compared the levels of serum ferritin, transferrin saturation, and hemoglobin and calculated the hemoglobin variabilities by comparing values before and after roxadustat treatments.

RESULTS: We found higher transferrin saturation levels at different time points after the roxadustat treatments ($p<0.01$); meanwhile, the serum ferritin and hemoglobin levels were significantly higher after the roxadustat treatment ($p<0.001$). During the treatments with EPO and roxadustat, the transferrin saturation, serum ferritin, and hemoglobin levels differed significantly at different time points for each patient ($p<0.05$). After roxadustat administration, the hemoglobin levels were significantly higher than after EPO administration ($p<0.001$) and changed more rapidly after roxadustat administration than after EPO administration ($p<0.05$). The hemoglobin variability after roxadustat administration was significantly lower than that after EPO administration ($p<0.05$).

CONCLUSIONS: Treatment with roxadustat led to higher hemoglobin levels and less hemoglobin variability than the treatment with EPO, with high transferrin saturation and higher ferritin levels in patients with renal anemia on MHD.

Key Words:
MHD, Renal anemia, Roxadustat, Hemoglobin variability.

Introduction

Chronic kidney disease (CKD), a leading cause of mortality worldwide, affects more than 10% of the global population[1,2]. Anemia is a common CKD complication, and its prevalence, ranging from 8.4% to 53.4%, increases with the disease progression[3]. Renal anemia is due to decreased erythropoietin (EPO) production and is associated with physiological dysfunction, mental health problems, and cardiovascular complications, all factors that decrease the quality of life (QoL) and may lead to death[4-6]. Patients on long-term maintenance hemodialysis (MHD) can develop renal anemia, and timely correction of hemoglobin levels can significantly improve their physiological functions, shorten hospitalizations, reduce complications, and improve their QoL.

Erythropoiesis stimulating agents (ESAs) and iron therapy are the most common and standard treatments for renal anemia[7]. ESAs act on erythroid hematopoietic progenitor cells in the bone marrow to promote their proliferation and differentiation, thereby relieving anemia symptoms[8]. However, some patients fail to respond to ESAs or develop EPO resistance, and they necessitate drug dosage increases to elevate their hemoglobin levels. High EPO doses may lead to excessive fluctuations in red blood cell counts, increased blood pressure, induced thrombosis, and other adverse reactions that increase the incidence of cardiovascular diseases and the risk of mortality. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline[9], the target hemoglobin level should be maintained between 110 g/L and 130 g/L. However, patients on MHD usually display hemoglobin fluctuations due to the effects of dialysis, iron supplementation, and the doses and frequency of ESA administration; therefore, maintaining appropriate hemoglobin

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levels in them is difficult[10]. Hemoglobin variability has been associated with high mortalities in both patients with CKD and the general population[11,12]. Therefore, novel, safe, and effective treatments resulting in less hemoglobin variability are needed to improve hemoglobin levels in patients with anemia and low EPO responses.

Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), which stimulates erythropoiesis, regulates iron metabolism and promotes hemoglobin synthesis[13]. Studies[14,15] have demonstrated that roxadustat can effectively improve hemoglobin levels and is safe for patients undergoing dialysis. The literature on the impact of ESAs on hemoglobin variability is extensive, but few studies[10,16] have focused on the impact of roxadustat on hemoglobin variability or compared the effects of roxadustat with those of ESAs. Therefore, we compared the hemoglobin variabilities of patients on MHD during their treatments with EPO and roxadustat to provide a basis for the clinical application of roxadustat.

Patients and Methods

We included data from the clinical records of 80 patients with renal anemia on MHD admitted to our hospital between January 2017 and December 2022. We applied a patient self-control design to compare the hemoglobin variabilities before and after roxadustat administration. The patients received EPO from January 2017 to December 2019 and roxadustat from January 2020 to December 2022. The Ethics Committee of The First Affiliated Hospital of Zhengzhou University approved the study (Approval number, 2021300062). The study was conducted in accordance with the Declaration of Helsinki tenets. The authors obtained signed patient informed consent forms from the participants.

Inclusion Criteria

1. Patients older than 18 years.
2. CKD Patients on MHD for more than 3 months, who had undergone regular hemodialysis procedures 3 times a week.
3. Patients diagnosed with renal anemia: hemoglobin levels <110 g/L[9].
4. Patients with complete clinical data.

Exclusion Criteria

1. Patients with other causes of anemia, such as thalassemia, aplastic anemia, tumor-related anemia, or myelodysplastic syndrome.
2. Patients with acute cardiovascular or cerebrovascular diseases, severe infections, or malignant tumors.
3. Patients with hemorrhagic diseases.
4. Patients with hematological disorders.
5. Pregnant and/or lactating women.

Treatment Methods

All patients underwent MHD with high flux hemodialysis. The median blood flow was 280 mL/min, and the membrane areas ranged from 1.4 m^2 to 1.8 m^2. Dialyses were performed three times a week, and hemofiltration once every two weeks, with the single-pool Kt/V maintained above 1.2.

(1) EPO treatment: recombinant human EPO rHuEPO doses were injected subcutaneously after hemodialysis. The initial dosages were between 100 IU/kg and 150 IU/kg based on the patients' body weight each week, divided into 2 or 3 injections. We gradually reduced the dosages according to the patients' hemoglobin levels (maintained between 110 g/L and 130 g/L) and hematocrit (maintained between 30% and 36%). The EPO therapy was discontinued for at least 3 days before initiating roxadustat treatments.

(2) Roxadustat treatment: patients were given roxadustat (FibroGen China, Medical Technology Development; Specification, 20 mg 3 capsules/box and 50 mg 3 capsules/box; National drug approval number: H20180023 and H20180024) at initial dosages determined according to the body weight of the patients. Patients weighing <60 kg received a 100 mg/dose and those weighing ≥60 kg received a 120 mg/dose, 3 times/week. During the roxadustat treatment, we measured hemoglobin levels every 2 weeks and adjusted the dosages according to the hemoglobin levels using a gradient of doses (20 mg, 40 mg, 50 mg, 70 mg, 100 mg, 120 mg, 150 mg, and 200 mg) to maintain the hemoglobin level in a range between 110 g/L and 130 g/L. We used an adjustment protocol published by Chen et al[17]. If the hemoglobin level reached ≥130 g/L, we suspended the dosing. After that, if the hemoglobin level was reduced to <110 g/L, we resumed the doses, initiating with a dose lower than the last one.

During treatment, we also administered 0.1 g of intravenous iron supplementation twice a week to patients with transferrin saturation ≤20% or serum ferritin <200 μg/L.

Observation Indicators

(1) Baseline characteristics: we recorded general patient information, including gender, age, weight, and MHD duration history.

(2) Physiological indicators: we measured patients' hemoglobin levels and iron metabolism indicators, including serum ferritin levels and transferrin saturation. Hemoglobin measurements were detected with a fully automatic hematology analyzer Mindray BC6800 plus (Mindray Medical International Limited, Shenzhen, Guangdong, China) from 4 mL early morning fasting blood serum samples separated after centrifugation and anticoagulation. Serum ferritin and transferrin saturation values were obtained using a Roche Cobas C701 automatic chemistry analyzer (Roche Diagnostics, Basel, Switzerland).

(3) Determination of hemoglobin variability: we conducted a linear regression analysis on hemoglobin values at each time point, defining the basic hemoglobin level as the intercept of the linear equation, and the speed of value changes over time as the slope of the line. The hemoglobin variability was represented by the residual standard deviation[18].

Statistical Analysis

We analyzed all data using SPSS 20.0 (IBM Crop., Armonk, NY, USA). We expressed normally distributed continuous data as means ± standard deviations (M±SD) using paired *t*-tests for self-control comparisons and non-normally distributed continuous data as medians (quartile ranges) using Wilcoxon tests for self-control comparisons. We applied repeated measures ANOVA for comparisons of multiple time points within one group and described qualitative data as frequencies and percentages (n, %). We used the Wald test for comparisons between linear regression variables. We considered all $p<0.05$ as indicative of statistical significance.

Table I. Baseline characteristics of patients.

Variables	Number of patients (n = 80)
Gender (n %)	
Male	45 (56.25)
Female	35 (43.75)
Age (years)	50.67±10.28
Weight (kg)	69.36±12.47
MHD duration (years)	8.45±1.29
Causes of CKD	
Glomerulonephritis	38 (47.50)
Diabetic nephropathy	13 (16.25)
IgA nephropathy	9 (11.50)
Hypertensive nephropathy	7 (8.75)
Other causes	13 (16.25)

Maintenance hemodialysis (MHD), Chronic kidney disease (CKD), Immunoglobulin A (IgA).

Results

Baseline Characteristics

We analyzed data from 80 patients for this study, including 45 men and 35 women, with a mean age of 50.67±10.28 years, mean weight of 69.36±12.47 kg, and mean hemodialysis history of 8.45±1.29 years (Table I).

Comparison of Transferrin Saturation, Serum Ferritin, and Hemoglobin Levels After Each Treatment

The transferrin saturations were significantly higher in the roxadustat treatment group at various time points than that in the EPO treatment group. In addition, during the treatments with either EPO or roxadustat, the transferrin saturations changed significantly at different time points within each group ($p<0.001$; Table II).

Table II. Self-control comparison of transferrin saturation levels (%) after different treatments.

Time points	EPO treatment	Roxadustat treatment	*p*
1 month after treatment	14.90 (8.68-23.48)	26.21 (18.53-36.61)	<0.001
3 months after treatment	13.70 (10.98-23.83)	26.70 (18.00-40.15)	<0.001
6 months after treatment	13.75 (9.74-19.30)	29.75 (23.25-45.95)	<0.001
12 months after treatment	18.32 (11.74-27.06)	31.32 (20.40-42.37)	<0.001
16 months after treatment	21.99 (11.90-27.12)	35.10 (24.38-40.64)	<0.001
24 months after treatment	21.10 (14.80-33.13)	40.10 (26.66-52.11)	<0.001
36 months after treatment	21.40 (12.23-34.03)	42.40 (31.34-55.03)	<0.001
p	<0.001	<0.001	

Data presented as medians (quartile ranges). Erythropoietin (EPO).

Table III. Self-control comparison of serum ferritin levels after different treatments.

Time points	EPO treatment	Roxadustat treatment	*p*
1 month after treatment	118.20 (31.25-156.45)	191.20 (92.40-293.50)	<0.001
3 months after treatment	129.40 (60.00-300.98)	192.40 (123.00-363.98)	0.006
6 months after treatment	172.00 (83.33-279.10)	232.00 (137.45-340.85)	0.015
12 months after treatment	176.60 (65.75-274.68)	234.05 (121.15-320.25)	0.015
16 months after treatment	164.00 (44.90-287.10)	227.00 (107.90-350.10)	0.015
24 months after treatment	176.90 (125.18-346.60)	239.90 (188.18-409.60)	0.009
36 months after treatment	229.50 (81.00-446.48)	249.45 (221.25-445.45)	0.027
p	0.027	0.042	

Data presented as medians (quartile ranges). Erythropoietin (EPO).

Table IV. Self-control comparison of hemoglobin levels after different treatments.

Time points	EPO treatment	Roxadustat treatment	*p*
1 month after treatment	90.35 ± 15.48	104.65 ± 14.13	< 0.001
3 months after treatment	100.75 ± 13.98	111.04 ± 13.64	< 0.001
6 months after treatment	101.67± 15.84	111.05 ± 15.83	< 0.001
12 months after treatment	101.85 ± 17.77	113.89 ± 18.98	< 0.001
16 months after treatment	102.00 ± 15.96	115.31 ± 15.99	< 0.001
24 months after treatment	103.67 ± 19.27	120.97 ± 18.86	< 0.001
36 months after treatment	104.99 ± 21.73	122.29 ± 21.15	< 0.001
p	< 0.001	< 0.001	

Erythropoietin (EPO).

The serum ferritin levels at different time points after application of roxadustat differed significantly from the levels after EPO treatment ($p<0.05$). In addition, the serum ferritin levels at different time points within each treatment group also differed significantly ($p<0.05$; Table III).

The hemoglobin levels at different time points after the application of roxadustat were significantly different from those after the EPO treatment ($p<0.001$). In addition, the hemoglobin levels differed significantly at different time points within each treatment group ($p<0.001$; Table IV).

Comparison of Hemoglobin Variability

After the roxadustat treatment, the hemoglobin levels increased more significantly than after the EPO treatment ($p<0.01$), and the roxadustat treatment resulted in faster hemoglobin level changes ($p<0.05$). The hemoglobin variability after roxadustat treatment was significantly lower than that after EPO treatment ($p<0.05$; Table V).

Discussion

Hemodialysis is the main treatment for end-stage renal disease (ESRD), and it can prolong the survival of patients, but it makes them prone to renal anemia. In the clinic, EPO and iron supplementation are commonly used to treat renal anemia, but the application of EPO tends to cause excessive erythropoiesis and predisposes

Table V. Self-control comparison of hemoglobin variability after different treatments.

Methods	Hemoglobin intercept	Hemoglobin slope	Residual standard deviation
EPO treatment	95.28 (93.34 - 97.21)	0.34 (0.23 - 0.45)	18.47 (16.7 - 20.24)
Roxadustat treatment	106.97 (105.06 - 108.88)	0.49 (0.38 - 0.60)	16.89 (14.87 - 18.91)
p	0.006	0.044	0.017

Data presented as mean (95% confidence interval). Erythropoietin (EPO).

to thromboses and cardiovascular adverse effects. Thus, we analyzed the hemoglobin variability of patients after the administration of the promising oral drug roxadustat to obtain evidence needed for improving renal anemia management. We found that roxadustat is effective in treating renal anemia and that it improved their transferrin saturation and serum ferritin levels with low hemoglobin variability after receiving roxadustat.

Hemoglobin level changes are common in patients on MHD, but the underlying mechanisms remain unclear. The variability is associated with the number of hospitalizations, the platelet counts, and the patient's age, and it is inversely correlated with the erythropoietin dose per body surface area[19]. A systematic review and meta-analysis by Zhao et al[20] showed a 9% increase in the adjusted rate of death for each 1 g/dL increase in hemoglobin variability. Therefore, maintaining stable hemoglobin levels is crucial. Two studies[10,16] have been published on hemoglobin variability and on the hemoglobin level changes of patients receiving roxadustat[15,21], but we are not aware of publications on the hemoglobin variability in patients receiving roxadustat. To the best of our knowledge, this is the first retrospective self-control study to analyze the hemoglobin variability of patients on MHD receiving roxadustat.

Some meta-analyses[22-24] have demonstrated the efficacy of roxadustat for treating renal anemia, but the results on the transferrin saturation and serum ferritin levels are conflicting. A systematic review and meta-analysis[22] of twenty-one randomized controlled trials involving 1,408 patients reported higher transferrin saturations and serum ferritin levels in the roxadustat group than in the ESA group, while others[23,24] reported higher transferrin saturation, but reduced serum ferritin levels for the same group. We found that both the serum ferritin level and the transferrin saturation improved significantly after the application of roxadustat, which was constistent with Liang et al[22]. The discrepancy between those studies[23,24] and ours may be attributed to the different populations and sample sizes of the studies. In addition, the study design may have also contributed as this was a retrospective self-control study, and the others were meta-analyses of randomized controlled trials.

We found higher hemoglobin levels after roxadustat treatment than after EPO treatment, a finding consistent with the studies by Zhang et al[25] and Zhu et al[26]. Moreover, we found that the roxadustat treatment resulted in faster hemoglobin level changes than the EPO treatment. This result needs to be confirmed in future studies. We also found fewer hemoglobin variabilities in the roxadustat treatment group, which supports the findings by Besarab et al[27,28]. The clinical trials by Besarab et al[27,28] showed that roxadustat could effectively promote erythropoiesis and maintain EPO levels at or around the normal physiological ranges. As a HIF-PHI, roxadustat inhibits the activity of the HIF-PH enzyme, which hydrolyzes HIF; thus, roxadustat increases HIF levels to promote endogenous EPO production and increase hemoglobin levels, improving the absorption and utilization of iron, and exerting anti-anemia effects[29,30]. The pharmacokinetics and pharmacodynamics of roxadustat allow it to mimic the body's natural response to hypoxia, maintaining the EPO levels at or around the normal physiological ranges.

Limitations

This study has some limitations. First, this was a single-center retrospective study with a small sample size, which limits the extrapolation of our results. Second, we used only linear regression analysis to evaluate the hemoglobin variability; other methods should be used to confirm our findings. Finally, we failed to assess the inflammation status of our patients, which can affect the hemoglobin variability in patients.

Conclusions

In our study, the treatment with roxadustat resulted in higher hemoglobin levels, less hemoglobin fluctuations and less variability than the treatment with EPO, with high transferrin saturation rates, and high ferritin levels in patients on MHD with renal anemia.

Conflict of Interest
The authors declare that they have no conflict of interests.

Funding
No funding was received.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

XW conceived and designed the study. NZ, WZ and PW collected the data and performed the analysis. XW was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics Approval

The Ethics Committee of The First Affiliated Hospital of Zhengzhou University approved the study (Approval number: 2021300062). The study was conducted in accordance with the Declaration of Helsinki tenets.

Informed Consent

We obtained signed patient informed consent forms from the participants.

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