Research Paper

Evaluation of Efficacy and Safety of Roxadustat in Hemodialysis with Renal Anemia

QIXIAN WU, WEN CHEN, XIAOJU FU AND RONGYU LIN*

Department of Nephrology, Hainan Chengmei Hospital, Haikou, Hainan Province 570100, China

Objective of this study was to explore the effectiveness and safety of roxadustat in the treatment of hemodialysis and renal anemia. Clinical data of 84 individuals having maintenance hemodialysis and renal anemia treated in the dialysis department of our hospital from October 2022 to October 2023 were selected for the analysis and were randomly divided into two groups, control and observation groups each with 42 individuals (n=42). Control group was given intravenous injection of recombinant human erythropoietin while the observation group was given oral roxadustat treatment. The treatment course for both groups was 12 w. After treatment, the clinical effects and various indicators of the two groups of patients were compared, including anemia indicators (red blood cells, hemoglobin and hemocrit value), iron metabolism indicators (serum ferritin, transferrin saturation and transferrin) and the incidence of adverse reactions was analyzed comparatively. After treatment, the drug efficacy of the observation group was higher than that of the control group ($p<0.05$). Similarly, after treatment anemia indicators and iron metabolism indicators in both groups were higher than before treatment ($p<0.05$). The adverse reactions of the observation group were less than those of the control group ($p<0.05$). Roxadustat has a significant effect in treating renal anemia which can effectively improve anemia indicators and iron metabolism indicators. Further, it can also promote blood circulation, ensure the balance of blood and iron metabolism and reduce the incidence of adverse reactions.

Key words: Roxadustat, hemodialysis, renal anemia, erythropoietin, hypoxia inducible factor, prolyl hydroxylase

Maintenance Hemodialysis (MHD) is a replacement therapy for patients with end-stage renal disease. It mainly removes blood endotoxins through a semipermeable membrane to maintain the body's electrolyte balance[1]. According to the statistics, the incidence of renal anemia in MHD patients is approximately around 98.2 %[2], which seriously threatens the health and safety of patients. In case of renal anemia, patients show symptoms such as fatigue, pale complexion, drowsiness, palpitations and shortness of breath[3]. Clinical treatment of hemodialysis combined with Renal Anemia (RA) which often uses drugs such as recombinant human (rh) Erythropoietin (EPO) and iron supplements, but some patients will develop functional iron deficiency, renal insufficiency and even myocardial infarction after using them.

Roxadustat belongs to the Hypoxia Inducible Factor-Proline Hydroxylase Inhibitor (HIF-PHI) class of drugs. It inhibits prolyl hydroxylase, promotes the production of endogenous EPO in the body and improves the anemic state[4]; thus it effectively relieves and alleviates the symptoms of renal bleeding and it has good effect in the treatment of renal anemia.

MATERIALS AND METHODS

Data source:

This group of data was collected from 84 patients by conducting a retrospective analysis who were diagnosed with MHD and RA in our hospital from October 2022 to October 2023. Among all the 84 individuals, 48 were males while 36 were females of an average age of (42.6-58.3) y old and weight (44.8-65.1) kg. All the individuals were randomly divided into two groups, observation and control groups. The observation groups included 23 males and 19 females with average age (44.2-56.8) y and weight (45.6-65.1) kg while the control group included 25 males and 17 females with age (42.8-58.3) y and weight (44.8-64.9) kg. This study was approved by the Ethics Committee of the Hainan Chengmei Hospital (Approval No: 202100193).

***Address for correspondence**
E-mail: 13876367149@163.com

Inclusion criteria: Primarily, 14 individuals had hypertensive nephropathy, 15 individuals had chronic nephritis, 28 individuals had diabetic nephropathy and 27 individuals with other diseases were included. Further, patients who met the diagnostic criteria for renal anemia; patients who were examined for continuous MHD for >3 mo and patients whose age was (40-60) y having strong compliance were included in the study.

Exclusion criteria: Similarly, the patients who were involved in blood transfusion or other drug treatment before treatment; patients with coronary heart disease, liver and kidney dysfunctioning; patients having infectious diseases or malignant tumors and patients with abnormal coagulation function or malnutrition were excluded from the study.

Treatment method:

Patients of the two groups were first given basic treatment. Then the control group was intravenously injected with 80-150 U/kg of rhEPO (Harbin Pharmaceutical Group; Batch No: 210824 and specification: 3000 U/vial), each time, 3 times/week. Similarly, the observation group was orally administered with 100-120 mg of roxadustat (Fabojin China Pharmaceutical Company, National Medicine Standard No: H20180023; Batch No: 2101031 and specification: 20 mg×3 tablets/box), each time. 120 mg/time was given for patients with body weight >60 kg. 100 mg of drug was given to patients with body weight <60 kg once every time for 3 w. Hemoglobin (Hb) level was tested for every 2 w until it was stable and the dosage was adjusted according to the change of Hb level. Hb was maintained at 100-120 g/l. Both the groups were treated for 12 w and the changes in various indicators were closely observed and strictly recorded.

Outcome measurements:

Indicators such as anaemia indices, iron metabolism indicators, clinical drug efficacy and the adverse effects occurred during the treatment period were studied.

Anaemia indicators: The changes in anemia indicators and iron metabolism indicators were mainly observed. The lower these two indicators were, the more serious the condition was. Morning fasting venous blood was collected before and after medication. Subsequently, indicator levels such as Hb level, Red Blood Cells (RBC) and Hematocrit (HCT) levels were detected by Enzyme-Linked Immunosorbent Assay (ELISA).

Iron metabolism indicators: Similarly, iron metabolism indicators such as Serum Ferritin (SF), Transferrin Saturation (TSAT) and Transferrin (Tf) levels were detected and studied using radioimmunoassay double antibody method.

Clinical efficacy: The clinical medication effects of the two groups of patients were observed and compared. The treatment standards for RA were used as the basis for the judgment of clinical efficacy of the drug. If the patient's anaemia symptoms were significantly improved or disappeared by restoring all the indicators to normal range or level after administration of the medication, then it was considered to be significantly effective. If the patient's clinical symptoms and other indicators show minor improvement, then it was comprehended as effective. Similarly, if the clinical symptoms and signs seemed to be unchanged or aggravated after treatment period, then it was referred to as ineffective.

Total effective rate=number of effective cases (n)/total number of cases×100 %

Drug safety: We further observed the adverse events that occur during the medication period between the patients of the two groups and strictly recorded them.

Statistical analysis:

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 23.0 software, using t or Chi-square (χ^2) test. The data was represented in terms of mean±standard deviation ($\bar{x}\pm s$) where $p<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Primarily drug efficacy was compared between the two groups. After medication, the total effective rate of the observation group and the control group was found to be 92.6 % and 71.43 %, respectively. Additionally, we found that there was no significant difference in the general data between the two groups ($p>0.05$) (Table 1).

Then, the anemia indicators between the two groups were compared. Before treatment, there was no significant difference in the anemia index levels between the two groups of patients ($p>0.05$). However, after treatment anemia indices of the two groups of patients were higher than before treatment and the observation group was higher ($p<0.05$) (Table 2).

Further, iron metabolism indicators between the two groups were compared. Before treatment, there was

no significant difference in the iron metabolism index levels between the two groups of patients (p>0.05). After treatment, the iron metabolism indices of the two groups of patients were higher than before treatment and the observation group was higher (p<0.05) (Table 3).

Subsequently, the adverse reactions between the two groups were also compared. After taking the medication, 6 patients were identified with adverse reactions in the observation group, including 2 patients with headache, 1 patient with increased blood pressure and 3 patients having nausea and vomiting; there were no patients with abdominal pain and heart failure or stroke. The incidence of adverse reactions was found to be 14.29 %.

We found 12 patients who denoted adverse reactions in the control group, including 3 patients with headache, 4 patients with elevated blood pressure, 3 patients with nausea and vomiting, and 2 patients having abdominal pain. There were no cases of heart failure or stroke. The incidence of adverse reactions was found to be 28.57 %. There was a significant difference between the two groups (p<0.05) (Table 4).

TABLE 1: COMPARISON OF THE EFFICACY OF THE TWO GROUPS OF DRUGS, n (%)

Group (n=42)	Effective	Efficient	Invalid	Total effective rate
Observation	30 (71.43)	9 (21.43)	3 (7.14)	39 (92.86)
Control	25 (59.53)	5 (11.90)	12 (28.57)	30 (71.43)
χ^2	31.274	31.65	33.76	31.637
p	0	0	0	0.001

TABLE 2: COMPARISON OF ANEMIA INDICATORS BETWEEN THE TWO GROUPS OF PATIENTS (x̄±s)

Group (n=42)	RBC ($\times 10^{12}$/l)		HB (g/l)		HCT (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	3.10±0.16	4.01±0.19	90.12±7.50	119.13±9.30	25.10±4.62	39.24±5.16
Control	3.21±0.17	3.57±0.23	91.14±7.50	110.21±9.22	24.21±4.57	33.10±5.02
t	0.352	0.589	0.075	3.386	0.287	4.803
p	0.697	<0.001	0.935	<0.001	0.854	<0.001

TABLE 3: COMPARISON OF IRON METABOLISM INDICATORS BETWEEN THE TWO GROUPS OF PATIENTS (x̄±s)

Group (n=42)	SF (μg/l)		TSAT (%)		TRF (μg/l)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	114.18±12.02	278.19±15.46	16.23±2.15	33.23±4.82	1.65±0.36	2.58±0.59
Control	115.32±12.11	235.06±15.15	16.14±2.20	27.42±4.61	1.64±0.37	2.11±0.43
t	0.892	10.649	0.462	5.832	1.387	4.803
p	0.398	0.000	0.637	0.000	0.170	0.000

TABLE 4: COMPARISON OF ADVERSE REACTIONS BETWEEN THE TWO GROUPS, n (%)

Group (n=42)	Headache	High blood pressure	Nausea	Vomiting	Overall incidence
Observation	2 (4.76)	1 (2.38)	3 (7.14)	0	6 (14.29)
Control	3 (7.14)	4 (9.2)	3 (7.14)	2 (4.76)	12 (28.57)
χ^2	32.557	35.32	33.882	34.909	39.42
p	0	0	0	0	0

Hemodialysis is a replacement therapy for patients with kidney disease. RA is a common complication of MHD. As renal function gradually declines, the degree of RA will gradually worsen. RA is one of the risk factors for cardiovascular and cerebrovascular accidents in MHD. In RA, due to the increase of metabolism in the body, the intake of nutrients is affected and increase in urea toxins inhibits RBC production[5]. Iron balance is disturbed, blood is lost and the survival rate of RBC decreases, resulting in a decrease in the body's resistance and subsequent inflammation[6]. Anemia can lead to various adverse conditions and even cause the occurrence and development of cardiovascular diseases, which has an extremely adverse effect on the patient's prognosis[7]. Therefore, preventing and alleviating RA is the prevention and control goal of patients on maintenance hemodialysis[8]. The degree of RA is mainly determined by the anemia indicators and iron metabolism indicators. Low RBC value reflects that the body is in anemic state. Hb is a protein in RBCs that transport oxygen. Decrease in Hb value indicates that the body's RBC production is reduced, destroyed or lost in large quantities. Low HCT value reflects the body's anemic status and degree. Studies have shown that a decrease in Hb will increase the burden on the heart and may even lead to heart failure, Chronic Kidney Disease (CKD), anemia and other cardiorenal anemia syndromes[9].

For every 10 g/l increase in Hb, the all-cause mortality rate can be reduced by about 11 %[10]. Therefore, if renal anemia is not treated promptly and effectively, it will aggravate kidney damage and increase the risk of death[11]. Iron deficiency and metabolic disorders are also important factors affecting renal anemia. Iron metabolism indicators mainly include SF, TSAT and Tf. SF refers to the bound iron in the blood. Decrease in SF value will cause iron deficiency, anemia, blood loss, diarrhea or other diseases. An increase in TSAT value is seen in a variety of anemic diseases and polycythemia vera, while decrease in TSAT value indicates iron deficiency in the body. Tf is a (β) Beta-globulin that binds and transports iron in serum and can reflect a variety of diseases such as iron deficiency anemia. Decreased Tf expression inhibits the release of cellular iron, reduces the amount of iron used in erythropoiesis, leads to iron deficiency, and worsens anemia symptoms[12]. When the body's iron metabolism is disrupted and iron metabolism disorder occurs, the values of the above iron metabolism indicators will decrease to varying degrees, indicating the body's anemia state and severity.

MHD associated RA not only shows a decrease in Hb, RBC, HCT and other indicators, but also an imbalance in iron metabolism indicators such as SI, TRF and TS. Therefore, only by improving iron metabolism indicators anemia can be effectively controlled, and controlling anemia is an important guarantee for stabilizing renal function and improving cardiac function[13]. Clinically, RA is often treated with rhEPO as a stimulating agent, iron supplementation and blood transfusion. EPO is a hormone secreted by the kidneys and liver that promotes erythropoiesis; it is also an acidic glycoprotein. Its main components include peptide and carbon chains. The peptide chain includes 4 sugar chains which is connected to 165 amino acids through disulfide bonds to form a stable Alpha (α) helical structure[14]. Its main function is to promote the formation and proliferation of RBCs in the bone marrow, thereby increasing the amount of RBCs and Hb in the blood, increasing the oxygen carrying capacity of the blood and maintaining the body's redox balance.

The main function of rhEPO is to promote RBC differentiation, release mature RBCs into the blood and thus improve the symptoms of RA[15]. Some studies have shown that rhEPO has the effect of promoting the release of RBCs, but has no significant effect on iron metabolism[16]. Moreover, rhEPO can also lead to a variety of adverse conditions such as hypertension and functional iron deficiency[17].

HIF-PHI can promote the production of EPO in liver and kidney cells, rapidly increase the EPO value in the body and enhance the activity of EPO receptors. It can also reduce hepcidin and ferritin in the body by improving iron absorption, utilization and transport, thereby improving iron metabolism levels, maintaining a stable state of iron in the body and improving RA[18]. Therefore, it is effective in treating RA.

Roxadustat is a new type of HIF-PHI drug whose mechanism of action is to regulate EPO transcription factor under hypoxic conditions, effectively increase EPO levels by inhibiting prolyl hydroxylase and rate-limiting enzymes; it works by enhancing SF, TRF and TSAT levels and related receptor activity, thereby improving anemia. Roxadustat can effectively increase EPO, regulate iron metabolism levels[19], inhibit prolyl hydroxylase, maintain HIF in liver and kidneys, smoothly synthesize endogenous

EPO and increase the number and sensitivity of EPO receptors[20]. At the same time, it can also avoid the effects of inflammation and abnormal iron metabolism; it does not have the various limitations caused by the combination of erythropoiesis stimulating agents and iron agents. However, it has a significant effect on improving anemia[21]. Roxadustat also has a significant effect on improving anemia, promoting iron absorption and transport, helping the body store iron to participate in hematopoiesis, reduce the supplementation of exogenous iron[22], maintaining iron metabolism balance and stability[23] and by increasing the intestinal absorption and utilization of iron, reducing the effect of hepcidin on RBC production, further enhancing anti-RA effect[24]. Further, it has a good effect on the treatment of RA. In addition, roxadustat can also change the bone marrow microenvironment, indirectly promote erythropoiesis[25], regulate EPO to make it close to physiological levels, increase the levels of Hb, RBC and other indicators, promote blood circulation, and thus improve the patient's anemia condition. Studies have shown that roxadustat can improve Hb levels in patients with RA more than rhEPO group (control group) and its effect on improving iron markers is more obvious among patients of the rhEPO group[26]. Sun *et al*.[27] showed that roxadustat can effectively improve RA in hemodialysis patients and increase Hb levels.

The efficacy of the observation group after treatment was found to be 92.6 % which was higher than that of the control group which was found to be 71.43 % ($p<0.05$), indicating that roxadustat is significantly better than rhEPO in the treatment of MHD and RA. In this study, RBC, Hb and HCT values of the two groups of patients after medication were higher than those before medication while the observation group denoted higher levels than the control group ($p<0.05$), indicating that compared with EPO, roxadustat can quickly improve the level of anemia indicators in the initial treatment stage of anemia and has better effects on the prevention and treatment of anemia.

The values of TSAT, SF and TF in both the groups increased compared with those before treatment, and the observation group had a higher value ($p<0.05$), indicating that roxadustat can significantly improve the body's poor iron metabolism, correct and relieve anemia symptoms, and significantly improve the body's iron metabolism while correcting the body's anemia. The adverse reaction rate in the observation group of this study was lower than that in the control group ($p<0.05$), which may be related to the fact that rhEPO affects the body's immune function and damages vascular endothelial cells. It can be seen that roxadustat has a high clinical safety in the treatment of MHD and RA, can effectively avoid and reduce the occurrence of adverse reactions, and has a safe and stable efficacy. This study is consistent with the results of Shi *et al*.[28].

In this study, the number of sample was small and the conclusions drawn would have certain limitations. Additionally, the choice of drugs also had certain limitations; rhEPO in the control group and roxadustat in the observation group did not belong to the same type of drugs. In future studies, comparative studies of drugs of the same type (class) should be considered to understand the advantages and disadvantages of different drugs in better way.

In summary, RA can lead to a variety of adverse prognosis; even increase the risk of cardiovascular events and all-cause mortality in MHD patients, which adversely affects the quality of life of patients. Roxadustat has a good effect in alleviating anemia and maintaining iron metabolism balance, especially in the treatment of renal anemia associated with hemodialysis, and is suitable for clinical promotion and application.

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Wei S, Sun J, Xu K, Li Y, Zhang Y. Efficacy of roxadustat as a substitute for high-dose recombinant human erythropoietin in the treatment of anemia in maintenance hemodialysis patients. Am J Transl Res 2021;30(3):217-21.
2. Hu D, Li E, Liu N. Efficacy of roxadustat on renal anemia in patients with maintenance hemodialysis and its effects on iron and lipid metabolism. Chin Med Innov 2023;20(14):50-5.
3. Csiky B, Schömig M, Esposito C, Barratt J, Reusch M, Valluri U, *et al*. Roxadustat for the maintenance treatment of anemia in patients with end-stage kidney disease on stable dialysis: A European phase 3, randomized, open-label, active-controlled study (PYRENEES). Adv Ther 2021;38(10):5361-80.
4. Chen N. The application of roxadustat in the treatment of renal anemia in patients with chronic kidney disease. Chin J Int Med 2019;58(12):919-20.
5. Zhao T, Zhu D, Shi Y. Effect of invigorating spleen and invigorating kidney on the therapeutic effect and blood biochemical indices of patients with chronic renal failure complicated by maintenance dialysis. J Liaoning Univ Chin Med 2020;22(5):67-70.
6. Fishbane S, El-Shahawy MA, Pecoits-Filho R, van BP, Houser MT, Frison L, *et al*. Roxadustat for treating anemia in patients with CKD not on dialysis: Results from a randomized phase 3 study. J Am Soc Nephrol 2021;32(3):737-55.
7. Cong Y, Li M, Wei D. Effect of oral iron supplementation

combined with roxadustat in the treatment of renal anemia in hemodialysis patients with uremia and its influence on adverse reactions. Contemp Med 2022;28(3):28-30.
8. Wang S, Bi S, Bai Q. The effectiveness and safety of combined use of erythropoietin and low dose roxadustat in the treatment of renal anemia in hemodialysis patients. Chin Blood Purif 2022;21(3):158-61.
9. McCullough PA. Anemia of cardiorenal syndrome. Kidney Int Suppl 2021;11(1):35-45.
10. Zheng C, Liu X, Li L. Efficacy of roxadustat in patients with renal anemia and its effect on hemoglobin in initial dialysis patients. J Rare Dis 2021;28(6):60-2.
11. Xiaoqing L. Effects of different hemodialysis filtration frequencies on anemia efficacy and quality of life in maintenance hemodialysis patients. Chin Med Sci 2022;12(9):196-200.
12. Chen Z, Tian L, Gao Y. Preparation and preliminary quality evaluation of roxadustat capsules. Chin Prescription Drugs 2022;20(4):28-30.
13. Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A. The association between congestive heart failure and chronic renal disease. Curr Opin Nephrol Hypertens 2004;13(2):163-70.
14. Qingru L, Wang D, Lv Y. Efficacy of recombinant human erythropoietin and roxadustat in the treatment of peritoneal dialysis patients with renal anemia observation of clinical efficacy. Inner Mongolia Med J 2024;56(3):354-56.
15. Hong D, Tian En, Li M. Effect of roxadustat on iron metabolism in patients with chronic kidney disease and renal anemia. Chin J Pract Int Med 2020;40(12):1024-7.
16. Li H, Liang J, Ma Q. Effect and prognosis of roxadustat capsule and recombinant human erythropoietin in the treatment of renal anemia. China Med Guide 2020;17(8)178-81.
17. Li ZL, Tu Y, Liu BC. Treatment of renal anemia with roxadustat: Advantages and achievement. Kidney Dis 2020;6(2):65-73.
18. Chen Y, Liu J, Jia G. Effect of roxadustat in treatment of renal anemia in patients with maintenance peritoneal dialysis. Guangdong Med 2022;42(2):216-20.
19. Fishbane S, Pollock CA, El-Shahawy M, Escudero ET, Rastogi A, van BP, *et al*. Roxadustat *vs*. epoetin alfa for treating anemia in patients with chronic kidney disease on dialysis: Results from the randomized phase 3 ROCKIES study. J Am Soc Nephrol 2022;33(4):850-66.
20. Koury MJ, Haase VH. Anaemia in kidney disease: Harnessing hypoxia responses for therapy. Nature Rev Nephrol 2015;11(7):394-410.
21. Chen N. The application of roxadustat in the treatment of renal anemia in patients with chronic kidney disease. Chin J Int Med 2019;58(12):919-20.
22. Gong W, Zhu L, Chen X. Evaluation of roxadustat for maintenance dialysis renal poverty based on real-world data efficacy and safety in blood patients. J Pharmacoepidemiol 2023;32(8):849-55.
23. Zhuo JQ. Effect of recombinant human erythropoietin combined with roxadustat in the treatment of patients with renal anemia and its effect on inflammatory factors. Int Med 2022;17(2):195-7.
24. Liu Q, Zhou Z. Effect of roxadustat on iron metabolism in patients with microinflammatory hemodialysis anemia. Chin Blood Purif 2021;20(7):465-8.
25. Kurata Y, Tanaka T, Nangaku M. An evaluation of roxadustat for the treatment of anemia associated with chronic kidney disease. Expert Opin Pharmacother 2022;23(1):19-28.
26. Chen N, Hao C, Liu BC, Lin H, Wang C, Xing C, *et al*. Roxadustat treatment for anemia in patients undergoing long-term dialysis. New Engl J Med 2019;381(11):1011-22.
27. Sun Y, Xie H, Kang Z. Efficacy of roxadustat in the treatment of renal anemia in 20 patients undergoing initial hemodialysis. Chin J Pract Int Med 2020;40(11):942-6.
28. Shi Z, Wang X. Clinical effect of roxastat combined with recombinant human erythropoietin in the treatment of renal anemia and its effect on blood lipids influence of Ping. Chin Med Sci 2024;14(6):72-5.

This article was originally published in a special issue, "Clinical Advancements in Life Sciences and Pharmaceutical Research" Indian J Pharm Sci 2024:86(5) Spl Issue "284-289"