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Research Article
Roxadustat Improves Psychological Stress and Life Quality of Patients with Uremia During Hemodialysis

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Abstract

Background and Objective: Hemodialysis is the most commonly used renal replacement therapy. Roxadustat is a Hypoxia-Inducible Factor (HIF) stabilizer that can be used to treat anaemia in Hemodialysis (HD) patients. This study was designed to explore the role of roxadustat on patients with uremia during hemodialysis. **Materials and Methods:** Patients with uremia who received hemodialysis were divided into the control group and experimental group. Patients in the experimental group were given roxadustat and those in the control group were given recombinant human erythropoietin. The red blood cell indices and biochemical indices of patients were compared, the self-care ability and psychological stress reaction of patients were observed; nutriture and quality of life after treatment of patients and the total effective rate of the two groups were compared. **Results:** The levels of red blood cell indices in patients of both groups increased after the treatment and patients in the experimental group had higher levels of these indices than the control group. Versus the control group, the experimental group had reduced inflammation, higher self-care ability scores, lower self-rating anxiety scale and self-rating depression scale scores, better results of nutritional index examination and higher short form-36 health survey scores after treatment (all $p<0.05$). **Conclusion:** Roxadustat treatment significantly induces erythropoiesis and improves nutriture, negative emotion, self-care ability and quality of life of patients with uremia undergoing hemodialysis.

Key words: Roxadustat, uremia, hemodialysis, nutriture, negative emotion, quality of life, erythropoiesis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Chronic Kidney Disease (CKD) is a common disease that usually progresses to End-Stage Renal Disease (ESRD)[1]. Commonly manifested by ESRD, uremia is featured by electrolytes, metabolic abnormality and fluid and hormone imbalances resulting in the deterioration of renal function[2]. Risk factors, such as diabetes, increased creatinine or urea, chronic inflammation, hypertension, dyslipidemia and insulin resistance are associated with the occurrence and progression of uremia[3]. The incidence of uremia has been increasing with the increase in lifestyle changes and living standards. Uremia is usually accompanied by health-threatening complications and high mortality[4]. Hemodialysis is one of the main treatments of uremia. In hemodialysis, a dialysis membrane was used to eliminate or exchange small molecules from the dialysate and blood of the patients, to return the blood components to a normal level[5,6]. With the improvement of technology, hemodialysis has significantly decreased the mortality of uremia. Nevertheless, hemodialysis can also cause infection, which restrains the treatment of uremia[7,8]. Thus, it is urgent to explore effective counter measures for patients with uremia accepted hemodialysis.

Roxadustat (FG-4592) is an analogue of 2-oxoglutarate which is an orally managed and heterocyclic small molecule, functioning as an inhibitor of Hypoxia-Inducible Factor (HIF) Prolyl Hydroxylase (PH)[9]. As previously reported, the use of oral roxadustat is an accessible, safer and convenient alternative to parenteral Erythropoiesis-Stimulating Agents (ESAs) in anaemia following CKD[10]. It has also been demonstrated that in Dialysis-Dependent (DD) and dialysis independent (NDD) CKD patients, roxadustat increased haemoglobin level, serum transferrin and intestinal iron absorption and reduced hepcidin compared with epoetin-alfa[11]. More importantly, roxadustat caused positive results in Phase 3 superiority trials against current best medical therapies and was approved in Japan and China for CKD-related anaemia[12]. Roxadustat has been widely studied in anaemia secondary to CKD, however, further explorations are needed to reveal the clinical efficacy of roxadustat on patients with uremia during hemodialysis.

This study was designed to assess the role of roxadustat in nutriture, psychological stress reaction and quality of life of uremic patients accepting hemodialysis with recombinant human erythropoietin as the control.

MATERIALS AND METHODS

Study subjects: From December, 2019-2020, 112 patients with uremia that accepted hemodialysis in Hefei First People's Hospital were separated into the control group and experimental group. There were 50 patients in the control group (28 males and 22 females, the mean age of 51.26±9.26 years, mean duration of hemodialysis of 30.66±7.34 months) and 62 patients in the experimental group (34 males and 28 females, the mean age of 53.07±10.51 years, mean duration of hemodialysis of 29.82±8.13 months). Diagnostic criterion: patients conformed to the diagnostic criterion of uremia-induced renal anaemia described in the Clinical Practice Guideline of Chronic Kidney Disease and Hemodialysis. Inclusion criterion: all enrolled patients have accepted hemodialysis treatment for more than 6 months regularly and on time and in a stable condition. Exclusion criterion: patients with combined malignant tumour, severe liver damage; congestive heart failure (NYHA class IV), severe drug allergy history, history of intravenous iron therapy 4 weeks before recruitment. All the patients have signed the informed consent and this study was approved by the Ethics Committee of Hefei First People's Hospital. There was no statistical difference in age, gender and duration of hemodialysis between patients of the two groups (all $p>0.05$).

Method: Patients in the control group were given recombinant human erythropoietin treatment through subcutaneous injection after hemodialysis (3000 IU/time, 3 times/week). Patients in the experimental group were given roxadustat 1 hr before or 2 hrs after hemodialysis (oral administration, 1-2 mg kg^{-1} based on body weight of the patient, 3 times/week). Patients in both groups were treated for continuous 4 weeks.

Index observation: The red blood cell indices before and 4 weeks after treatment of patients from the two groups were compared. Fast venous blood (5 mL) from each patient was centrifuged at 3,000 r min^{-1} for 10 min and an automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA) was used to detect the levels of Red Blood Cell count (RBC), Haemoglobin (Hb) and Hematocrit (Hct).

The serum levels of C-Reactive Protein (CRP) and Interleukin-6 (IL-6) before and 4 weeks after treatment of patients from the two groups were compared. Blood sampling was the same as (1) and an Enzyme-Linked Immunosorbent Assay (ELISA) kit (Thermo Fisher Scientific, Whatman, MA, USA) was used for detection.

The self-care ability and psychological stress reaction of patients of the two groups were compared. Detection of self-care ability includes evaluation of knowledge of

hemodialysis and complication, compliance and rational diet, psychological stress reaction was assessed based on lower Self-rating Anxiety Scale (SAS), Self-rating Depression Scale (SDS) and Medical Coping Modes Questionnaire (MCMQ) scores. Higher SAS and SDS scores indicated severer anxiety and depression. MCMQ includes 20 items and mainly contains 3 coping modes: face, avoid and yield. The four-grade method was used for scoring. There were 8 items of the reverse score and the scores of all the items were accumulated. Higher scores indicated severer anxiety.

The levels of nutritional indices (vitamin B12, serum ferritin, transferrin, pre-albumin and albumin) of 4 weeks after treatment of patients of the two groups were compared.

Short Form-36 health survey (SF-36) was used to evaluate the quality of life of patients from the two groups, including pain, role-physical, physiological function, mental health, emotional character, social function, energy and general health. The score was positively correlated with the quality of life.

Statistical analysis: All data analyses were conducted using SPSS 22.0 software (IBM Corp. Armonk, NY, USA). The measurement data were expressed as Mean±standard deviation and analyzed using a t-test. The enumeration data were expressed as a rate (%) and analyzed using the χ^2 test. GraphPad Prism 6 software was used for analysis and graphing. The p-value<0.05 was indicative of a statistically significant difference.

RESULTS

Comparison of red blood cell indices of patients between the two groups: There was no significant difference in levels of RBC, Hb and Hct between the two groups before the treatment. Four weeks after the treatment, RBC, Hb and Hct levels increased in both groups and the experimental group had higher levels of these indices compared with a control group, indicating that roxadustat has a better effect on inducing erythropoiesis (Table 1).

Comparison of serum inflammatory cytokine levels of patients between the two groups: As shown in Fig. 1(a-b), no significant difference was found in serum levels of CRP and IL-6 of patients in the two groups before the treatment (both p>0.05). Both CRP and IL-6 levels in the two groups decreased significantly 4 weeks after the treatment (both p<0.05), suggesting that roxadustat could effectively reduce the serum levels of inflammatory cytokines of the patients.

Comparison of self-care ability of patients between the two groups: Experimental group had higher rates of knowledge of hemodialysis (93.5%), knowledge of complication (90.3%), compliance (98.4%) and rational diet (88.7%) than control group (80.0, 74.0, 84.0 and 70.0%, respectively) (Table 2).

Comparison of psychological stress reaction of patients between the two groups: Results of SAS and SDS scoring indicated that there was no significant difference in SAS and SDS scores between the two groups before treatment (both p>0.05), all the patients showed anxiety and depression. Four weeks after treatment, both SAS and SDS scores decreased in the two groups, whereas the experimental group had lower scores versus the control group (Table 3). MCMQ scoring results showed that the experimental group had better results of MCMQ scores compared with the control group (Table 4). These data implied that roxadustat could effectively relieve the negative emotion of the patients.

Table 1: Comparison of red blood cell indices of patients between the two groups

	RBC ($\times 10^{12}$ L^{-1})		Hb (g L^{-1})		Hct (%)	
Comparison	Before treatment	4 weeks after treatment	Before treatment	4 weeks after treatment	Before treatment	4 weeks after treatment
Control group (n = 50)	2.94±0.36	3.20±0.48	84.6±8.10	97.6±8.69	24.6±2.94	25.8±2.15
Experimental group (n = 62)	2.88±0.51	3.52±0.38	82.5±8.26	111.3±9.48	23.7±3.45	28.7±2.01
χ^2/t	0.7012	3.9386	1.3491	7.8888	1.4317	7.3580
p-value	0.4846	0.0001	0.1801	<0.0001	0.1550	<0.0001

RBC: Red blood cell count, Hb: Haemoglobin, Hct: Hematocrit

Table 2: Comparison of self-care ability of patients between the two groups

Comparison	Knowledge of hemodialysis	Knowledge of complication	Compliance	Rational diet
Control group (n = 50)	40 (80.0)	37 (74.0)	42 (84.0)	35 (70.0)
Experimental group (n = 62)	58 (93.5)	56 (90.3)	61 (98.4)	55 (88.7)
χ^2/t	4.6451	5.2351	7.7531	6.1381
p-value	0.0311	0.0221	0.0054	0.0132

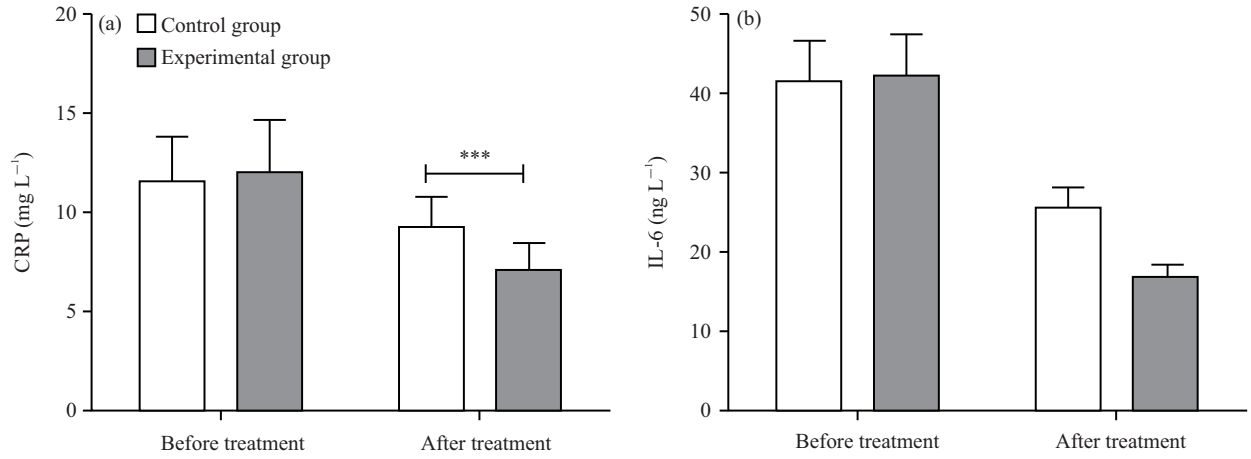

Fig. 1(a-b): Comparison of serum inflammatory cytokine levels of patients between the two groups, (a) Serum level of CRP of patients from the two groups and (b) Serum level of IL-6 of patients from the two groups

***p<0.001, the measurement data were expressed as Mean±standard deviation and analyzed using t-test

Table 3: Comparison of SAS and SDS scores of patients between the two groups

	SAS		SDS	
Comparison	Before treatment	4 weeks after treatment	Before treatment	4 weeks after treatment
Control group (n = 50)	52.6±3.26	34.6±2.15	54.6±4.11	39.4±3.05
Experimental group (n = 62)	53.4±3.51	26.5±2.33	54.9±4.28	28.4±2.64
χ^2/t	1.2376	18.9263	0.3753	20.4494
p-value	0.2185	<0.0001	0.7081	<0.0001

SAS: Self-rating anxiety scale, SDS: Self-rating depression scale

Table 4: Comparison of MCMQ scores of patients between the two groups

Comparison	Face	Escape	Yield
Control group (n = 50)	18.6±1.26	16.1±1.54	10.8±1.18
Experimental group (n = 62)	21.8±1.33	12.7±1.09	6.73±0.97
χ^2/t	12.9571	13.6578	20.0368
p-value	<0.0001	<0.0001	<0.0001

MCMQ: Medical coping modes questionnaire

Table 5: Comparison of quality of life of patients between the two groups

Comparison	Energy	Role-physical	Physiological function	Emotional character	Social function	Mental health	Pain	General health
Control group (n = 50)	45.6±16.8	54.9±11.4	78.3±16.4	62.5±14.4	65.9±17.3	49.2±11.2	73.7±20.2	53.5±11.5
Experimental group (n = 62)	54.2±15.2	66.9±13.3	84.6±15.3	74.3±12.5	82.7±18.6	59.0±10.5	84.7±16.5	62.8±10.9
χ^2/t	2.8398	5.0549	2.0978	4.6398	4.9015	4.7662	3.1726	4.3798
p-value	0.0053	<0.0001	0.0382	<0.0001	<0.0001	<0.0001	0.0019	<0.0001

Comparison of nutritional indices of patients between the two groups: It was discovered in Fig. 2(a-e) that there was no significant difference in the levels of vitamin B12, serum ferritin, transferrin, pre-albumin and albumin (all p>0.05). After 4 weeks of the treatment, patients in the experimental group had higher levels of vitamin B12, transferrin, pre-albumin and albumin and a lower level of serum ferritin than the control group (all p<0.05). The above results indicated that roxadustat could improve the nutriture of the patients.

Comparison of quality of life of patients between the two groups: After treatment, the quality of life of patients from two groups was assessed and compared. Based on the evaluation of pain, role-physical, physiological function, mental health, emotional character, social function, energy and general health, it was found that the experimental group had higher scores than the control group, indicating that roxadustat could improve the quality of life of the patients (Table 5).

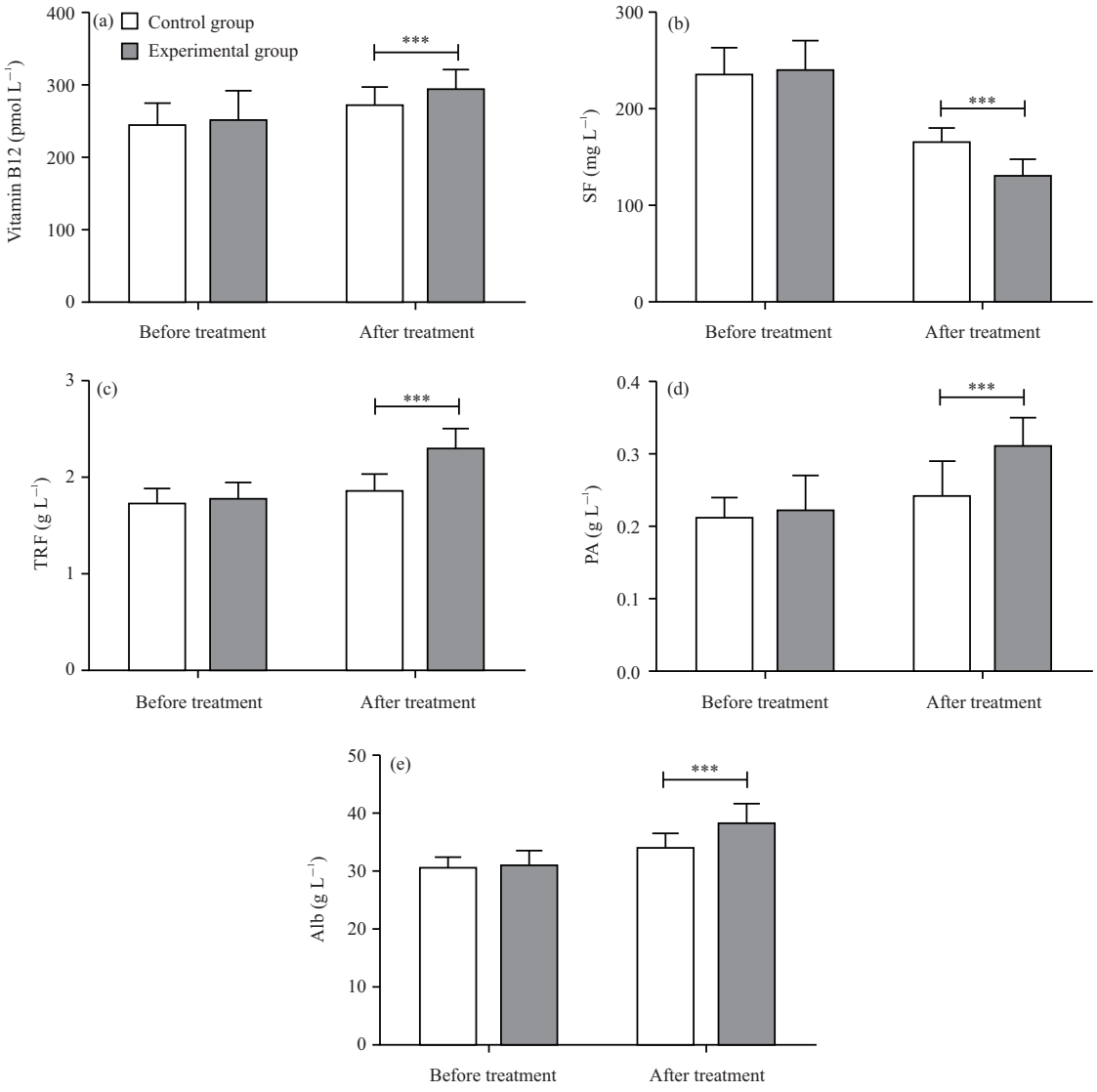

Fig. 2(a-e): Comparison of nutritional indices of patients between the level of (a) Vitamin B12, (b) Serum ferritin, (c) Transferrin, (d) Pre-albumin and (e) Albumin of patients from the two groups

***p<0.001, the measurement data were expressed as Mean±standard deviation and analyzed using t-test

DISCUSSION

This study aimed to explore the efficacy of roxadustat in nutriture, psychological stress reaction and quality of life of uremic patients during hemodialysis. Through the comparisons on red blood cell indices, serum inflammatory cytokine levels, self-care ability, psychological stress reaction, nutritional indices and quality of life of patients that had accepted treatment of roxadustat and recombinant human erythropoietin, it was found that roxadustat treatment significantly induced erythropoiesis and improved nutriture, negative emotion, self-care ability and quality of life of the patients in comparison to recombinant human erythropoietin.

Through simulating a response to a cellular reduction in oxygen levels and reducing HIF-PHs, roxadustat promotes erythropoiesis and enhances HIF activity. The intermittent dosing regimen of roxadustat, along with a short half-life, increases transient bursts of HIF activity, which is sufficient to induce the effective erythropoiesis[13]. Studies have revealed the role of roxadustat in anaemia following CKD. Provenzano *et al.*[10] have reported in their placebo-controlled study that the oral roxadustat is more convenient, more accessible and potentially safer than parenteral ESAs in treating anaemia in CKD patients. A publication has demonstrated that roxadustat transiently and moderately reduced hepcidin and increased endogenous erythropoietin

in anaemic NDD-CKD patients and the adverse events were similar in patients accepted treatment of roxadustat and placebo[14]. Moreover, Provenzano *et al.*[15] have compared the safety and efficacy of roxadustat and epoetin-alfa for CKD-related anaemia treatment. The results of their comparisons suggested that haemoglobin changed from baseline averaged>weeks 28-52 were 2.57 (1.27) and 2.36 (1.21) in epoetin-alfa and roxadustat groups and the percentages of patients with a haemoglobin response were 84.4 and 88.2% in epoetin alfa and roxadustat groups. These data indicated that roxadustat was non-inferior to epoetin-alfa. However, rates of adverse events between the two groups were comparable. Through the studies, we found that there still exists a controversy in the efficacy of roxadustat on patients during hemodialysis, especially, the role of roxadustat in uremic patients remains largely unknown.

To further evaluate the efficacy of roxadustat, we divided 112 patients with uremia into the control group (n = 50, administrated with recombinant human erythropoietin) and experimental group (n = 62, administrated with roxadustat) to compare the red blood cell indices, serum inflammatory cytokine levels, self-care ability, psychological stress reaction, nutritional indices and quality of life of patients. The results of comparisons in our research showed that to uremic patients treated with recombinant human erythropoietin, those treated with roxadustat had higher levels of RBC, Hb and Hct, lower CRP and IL-6 levels, higher self-care ability scores, lower SAS and SDS scores, better results of nutritional index examination and higher SF-36 scores. These findings suggested that roxadustat treatment-induced erythropoiesis and improved nutriture, negative emotion, self-care ability and quality of life of patients with uremia undergoing hemodialysis.

In the study by Akizawa *et al.*[16], the authors compared the effect of oral roxadustat in ESA-naïve (n = 75) and ESA-converted patients (n = 164) with anaemia of CKD on hemodialysis. Moreover, a study included patients randomized to epoetin-alfa (n = 521) or roxadustat (n = 522)15. By the comparisons, the limitation of this study exhibited as its relatively small sample size. A much larger sample size is needed to provide adequate power for the manifestation of the comparisons of nutriture, psychological stress reaction and quality of life between roxadustat and erythropoietin.

CONCLUSION

In conclusion, this study indicated that in comparison to the treatment of recombinant human erythropoietin, roxadustat had a better therapeutic effect on uremic patients on hemodialysis, with increased erythropoiesis and improved nutriture, negative emotion, self-care ability and quality of life of the patients. The research may guide the clinical use of oral roxadustat in uremia during hemodialysis. Nevertheless, a further study with a larger sample size and more evidence and data are required to confirm our findings.

SIGNIFICANCE STATEMENT

This study discovers the better therapeutic effect of roxadustat than recombinant human erythropoietin that can be beneficial for uremic patients on hemodialysis. This study will help the researcher to uncover the critical area of hemodialysis during uremia that many researchers were not able to explore. Thus, a new theory on roxadustat may be arrived at.

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