BMC Nephrology

RESEARCH

Open Access

Explore the effect of HIF-PHI on blood pressure variation rate and anemia efficacy in maintenance hemodialysis patients

Yu-ting Yang[1,2†], Yu Wang[1,2†], Yuan Qi[3], Zhi-hui Fu[1,2], Yan-ping Hu[1,2], Jun-hui Wan[1,2], Xin-tian Shi[1,2], Jia-yan Huang[1,2], Hong He[1,2], Qin-kai Chen[1,2*] and Qing Zhao[1,2*]

Abstract

Objective This study aims to investigate the impact of hypoxia-inducing factor prolyl hydroxylase inhibitor (HIF-PHI), specifically Roxadustat, on blood pressure variability, blood pressure indices, hemoglobin, and other biochemical markers in maintenance hemodialysis (MHD) patients.

Methods In this retrospective, self-controlled study, regular hemodialysis and consistent use of Roxadustat for at least six months were conducted at the Hemodialysis Unit of the First Affiliated Hospital of Nanchang University between June 2019 and November 2022. The study involved MHD patients who had been using erythropoiesis-stimulating agents (ESAs) for at least six months prior to transitioning to Roxadustat. Blood pressure, routine blood data, biochemical parameters, and clinical data were collected before, during, and after dialysis over a 12-month period. Statistical comparisons were made of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and true variability in SBP (SBP-ARV), DBP (DBP-ARV), and MAP (MAP-ARV) in the patients before and after the transition to Roxadustat. Hemoglobin levels and daily antihypertensive drug dosage (DDD) were also analyzed.

Results A total of 54 MHD patients (32 males and 22 females) were included in the study. Primary diagnoses included chronic nephritis, hypertensive nephropathy, diabetic nephropathy, obstructive nephropathy, polycystic kidney disease, nephrotic syndrome, scleroderma-related kidney injury, and cases of unknown etiology. Repeated measures variance analysis indicated that blood pressure fluctuations during Roxadustat treatment were significantly smaller than during ESA treatment. Statistically significant differences were observed in SBP, DBP, and MAP before and after dialysis (P-values: 0.046, <0.001, 0.028, and 0.014, respectively). Paired t-tests revealed a significant reduction in SBP-ARV and MAP-ARV before and during dialysis in the Roxadustat group ($P=0.0018$, 0.008, and 0.006). Hemoglobin, erythrocyte count, and serum calcium were significantly higher in the Roxadustat group compared to ESA treatment

†Yu-ting Yang, Yu Wang contributed equally to this work and share first authorship.

*Correspondence:
Qin-kai Chen
timmyclz@163.com
Qing Zhao
goodluck992346126@163.com

Full list of author information is available at the end of the article

($P=0.013$, 0.012, and 0.003, respectively). In the high SBP variability group, a higher proportion of males, increased hospitalization rates, older age, and a higher prevalence of diabetes were observed.

Conclusion MHD patients treated with Roxadustat experienced fewer fluctuations in blood pressure compared to those treated with rHuEPO, and Roxadustat was more effective at increasing hemoglobin levels without compromising efficacy relative to ESAs.

Clinical trial number Not applicable

Keywords Maintenance hemodialysis, Blood pressure variability, Roxadustat, Erythropoiesis-stimulating agent

Introduction

Chronic kidney disease (CKD) remains a significant global public health concern. As the disease progresses, the number of individuals developing end-stage renal disease (ESRD) is rising, increasing the demand for renal replacement therapy (RRT). In 2019, the World Health Organization (WHO) reported that CKD accounted for 55.4 million deaths, constituting 2.35% of total global deaths. CKD has thus become one of the top ten causes of death worldwide, now regarded as an "epidemic" disease [1]. With more patients requiring RRT, three major options are available: hemodialysis, peritoneal dialysis, and renal transplantation. In China, more than half of ESRD patients undergo long-term hemodialysis (HD) to extend survival [2]. Despite advances in HD technology, complications such as anemia, renal bone disease, secondary hyperparathyroidism, and cardiovascular disease (CVD) remain common, and the quality of life and survival rates of patients have yet to meet expected standards [3, 4].

Renal anemia is one of the most frequent complications in maintenance hemodialysis (MHD) patients, with an incidence of 98.24% in those reaching ESRD, significantly higher than in the general population [5]. Patients with renal anemia are at increased risk of CVD, infections, hospitalization, and mortality [6]. Causes of anemia in MHD include erythropoietin (EPO) deficiency, iron deficiency (absolute and functional), EPO resistance, bone marrow suppression, shortened red blood cell lifespan, and malnutrition, with decreased endogenous EPO synthesis being the primary cause [7–9]. Symptoms of renal anemia, such as fatigue, pallor, and dyspnea, can worsen CKD progression and elevate the risk of death from CVD [10–13]. Therefore, proper management of renal anemia is crucial.

Traditional treatment for renal anemia includes erythropoiesis-stimulating agents (ESAs), iron supplements, folic acid, and blood transfusions [14, 15]. While these treatments have improved patient outcomes, studies show a significant proportion of patients exhibit a poor response to ESA, increasing risks of cardiovascular events and mortality [16–18]. Additionally, ESA use has been associated with blood pressure increases in about a third of treated patients, limiting its clinical effectiveness [19].

A new treatment option, Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), was approved in China in 2018 and has shown efficacy comparable to ESA in increasing hemoglobin levels. Roxadustat offers additional benefits, such as lowering LDL cholesterol, reducing intravenous iron use, and exhibiting fewer side effects [20, 21]. However, the impact of Roxadustat on blood pressure remains under investigation, with some studies suggesting that HIF-PHI may influence vasomotor genes, potentially affecting blood pressure [22–25].

Bloodtk 2 pressure variability (BPV) is increasingly recognized as an important predictor of cardiovascular outcomes in MHD patients [26–29]. Long-term and short-term BPV have been associated with increased mortality and cardiovascular events in MHD patients [30–32]. Mean true variability (ARV) is considered a more reliable indicator of BPV in predicting cardiovascular risks [33]. This study aims to evaluate the effects of Roxadustat on BPV, hemoglobin, and other biochemical parameters in MHD patients, providing insights into the management of complications in CKD patients [34–38].

Patients and methods

Subjects

Patients who had maintained hemodialysis for more than 3 months in the hemodialysis room of the First Affiliated Hospital of Nanchang University from June 2019 to November 2022 were selected. Those who met the inclusion criteria and had detailed data records were selected as the study subjects. Patients with Hb < 110 g/L after ESA treatment were switched to roxadustat treatment. The dialysis blood pressure, blood routine, biochemical data and clinical data were recorded before and after roxadustat treatment for 6 months.

Inclusion criteria

1) Ages 18 to 80 years.
2) Use roxadustat for ≥ 6 months;
3) ESA treatment duration ≥ 6 months before roxadustat treatment.
4) Maintenance hemodialysis for ≥ 3 months.

Exclusion criteria

1) Acute cardio-cerebrovascular complications such as acute myocardial infarction and acute heart failure.
2) Blood system diseases, tumors, acute inflammation and other kidney disease causes of anemia.
1) During the 3) into the group taking hormones, such as non-steroidal drugs affects blood pressure drugs.

Withdrawal criteria

1) To replace dialysis centers or death.
2) Conversion to peritoneal dialysis or renal transplantation.

Study design

Methods of treatment

Patients were administered ESA either as 3000 IU three times a week or as a single dose of 10,000 IU once a week. Anemia can be corrected after one week of oral Roxa treatment by adjusting the drug dosage based on the patient's weight. For MHD patients weighing less than 60 kg, the initial drug dose is 70 mg three times a week. For patients weighing 60 kg or more, the initial drug dose is 120 mg three times a week. The medication regimen can be adjusted during treatment as deemed appropriate by the healthcare provider.

Hemodialysis treatment

1) The dialysis frequency, mode and dialysis-related data of 54 MHD patients in the hemodialysis room of the First Affiliated Hospital of Nanchang University were as follows:
2) The frequency of hemodialysis was 2–3 times a week, and the dialysis time was 4 h each time.
3) Dialysis-related equipment: Blood dialysis machine (Fresenius Medical Supplies Shares and joint ventures): The model of the dialyzer is Fresenius 4008 S, and the dialyzer model is Hemoflow F6HPS, with a membrane area of 1.3m2; Dialysate components (Jiangxi Sanxin Medical Technology Co., LTD.): Calcium (Ca2+) 1.5mmol/L, sodium (Na^+) 137mmol/L/L, kalium (K^+) 2mmol/L/L, magnesium (Mg^{2+})0.5mmol/L, bicarbonate radical ($HCO3^-$) 31mmol/L, chlorine (Cl^-) 108mmol/ L, dialysate temperature 36℃.
4) Dialysis dehydration volume: the dehydration volume of each dialysis was the body weight before each dialysis minus the dry weight. The dry weight was evaluated by clinical professional doctors in our hospital. According to the ideal body weight when the patient felt dry and had no water retention and no water shortage, the dehydration volume of each dialysis was dynamically adjusted.
5) dialysis solution: In MHD patients included in the study, autologous static internal fistula or long-term central venous catheterization was used as vascular access; Dialysis modes included hemodialysis (HD), hemodiafiltration (HDF), hemodialysis + perfusion (HD + HP). Blood flow was set to 200 ml to 300 ml/min; During the dialysis process, ordinary heparin or low molecular weight heparin was used for anticoagulation, and patients with bleeding tendency were given heparin saline to circulate in the dialysis line.

Blood pressure measurement

(1) MHD patients had regular dialysis 2–3 times a week. Before each dialysis, they took antihypertensive drugs normally on the day, were in a stable mood, did not drink coffee, strong tea or strenuous exercise, and sat down before the machine after 30 min of rest. The professional nurses in the Hemodialysis Center of the First Affiliated Hospital of Nanchang University used the appropriate cuff size to place the two fingers above the horizontal line of the elbow of the non-arteriovenous fistula side according to the standard procedures, and the stethoscope was placed at the pulse to measure. The position of the blood pressure monitor and the cuff was kept at the level of the heart position. (If the blood pressure is not consistent with the patient's usual blood pressure, it should be measured again after 5 min of rest, or replaced with an electronic sphygmomanometer). Blood pressure was measured at 1 h, 2 h, 3 h, and 4 h during dialysis, after the completion of dialysis, and after washing the extracorporeal circuit after dialysis. Each blood pressure measurement included systolic blood pressure (SBP) and diastolic blood pressure (DBP). Before and after dialysis, mean arterial pressure (mean artery pressure, MAP) = DBP + (SBP-DBP) / 3.

(2) The index of blood pressure variability(BPV) was calculated using ARV formula:

$$ARV = \frac{1}{\sum w} \sum {}^{n-1}_{k-1} w \times |BP_{K+1} - BP_K|$$

k is a measure of the order, the range of 1 to N-1, and w is the time interval between the BP_k and BP_{k-1}. N is the number of blood pressure readings.

Methods for calculating the dose of antihypertensive drugs

The World Health Organization recommends medication daily dose (DDD) (https://www.whocc.no/atc_ddd_index/) to calculate the daily antihypertensive drug dos age, drugs DDD is a major indication for adults assume

that the average maintenance dose every day is a fixed unit of measurement, It is not affected by price, currency, package size and strength. By searching the corresponding dose of antihypertensive drugs at DDD 1, the DDD of each antihypertensive drug = the actual daily dosage of the drug/the corresponding dose when the DDD of the drug was 1, and the daily DDD value of antihypertensive drugs was equal to the sum of the DDDS of the antihypertensive drugs taken.

Clinical and demographic information: age, sex, number of hospitalizations, antihypertensive medication, systolic and diastolic blood pressure data before, during and after dialysis.

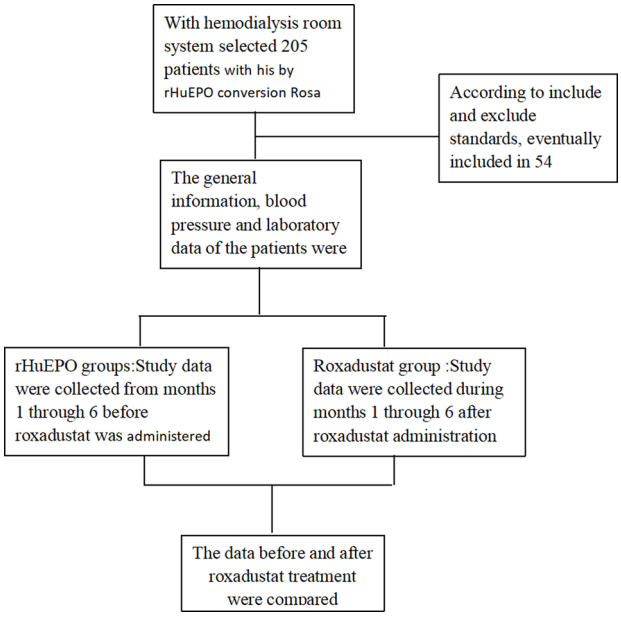
Laboratory data during drug use included white blood cells, red blood cells, hemoglobin, platelet, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, serum albumin, serum creatinine, blood urea, serum uric acid, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, serum potassium, serum sodium, serum calcium, serum phosphorus, etc.

Indicators of observation

The primary observation indexes are the rate of blood pressure variability, changes and trends in blood pressure during roxadustat treatment and ESA treatment.

Secondary observation indexes are the Hb level changes and other biochemical indexes before and after the change in medication.

The technology roadmap



Rosallistat side effects statistics

To calculate the adverse reactions caused by roxallistat, we counted the occurrence and severity of adverse reactions during the administration, and the patients with each adverse reaction (hypotension, hyperkalemia, Gastrointestinal reaction, Dizziness and headache, anaphylaxis, thrombosis, Total incidence). The total incidence of adverse reactions was compared between the two groups.

Statistical methods

The data were analyzed by spss26.0 statistical software. The measurement data with normal distribution were expressed by mean ± standard deviation, and the measurement data with non-normal distribution were described by median (M) and quartile (P25, P75), and the non-parametric test was used for comparison. A paired t-test (normal distribution) or Wilcoxon signed rank test (non-normal distribution) was used to compare the biochemical indicators and drug scores before and after roxadustat treatment. Frequency (n) and percentage (%) were used to describe the count data. Blood pressure was analyzed using repeated measures analysis to compare the blood pressure before and after the use of Rosa. A paired sample t-test was used to assess the changes in blood pressure. Patients were categorized into two groups based on the median average systolic blood pressure ARV during hemodialysis under roxadustat treatment. Independent sample T-test was used to compare the age and laboratory test data of patients in different groups, and $P<0.05$ was considered statistically significant.

Results

Included subjects

This study collected data of 205 patients after screening the eventually included 54 patients with MHD, during the study period, a total of 6480 times hemodialysis treatment (Fig. 1). Among 54 patients, there were 32 males and 22 females, with an average age of 56.7 ± 13.1 years. The frequency of dialysis was 2 times/week accounting for 22.22%, 3 times/week accounted for 77.78%, and the prevalence of hypertension was 57.4% (31 cases). Primary diseases: 1, 15 cases of chronic nephritis syndrome (27.78%), 2, 8 cases of hypertensive nephropathy (14.81%), 3, 19 cases of diabetic nephropathy (35.18%), 4, 2 cases of obstructive nephropathy (3.70%), 5, 6 cases of polycystic kidney disease (11.11%), 6, 2 cases of nephrotic syndrome (3.70%). 7, scleroderma renal injury in 1 case (1.86%), 8, unknown etiology in 1 case (1.86%). See Fig. 1 below for details.

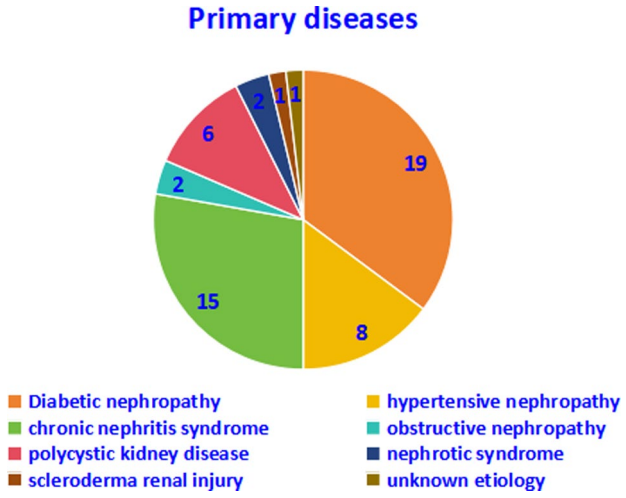


Fig. 1 Distribution of major disease types

Table 1 Results of paired t-test analysis of drug scores during ESA use and roxadustat use

Name	Paired (mean ± SD)		t	*p*
	ESA (*n* = 54)	Roxadustat (*n* = 54)		
Antihypertensive medication integral	1.85 ± 1.42	1.92 ± 1.60	-0.546	0.587

* $p < 0.05$ ** $p < 0.01$. All experiments were repeated at least three times, and the average was selected as the observed data

Comparison of medication scores before and after switching to roxadustat

To compare the average daily antihypertensive drug use before and 6 months after roxadustat treatment in MHD patients (Table 1). Blood pressure medication doses, according to the World Health Organization recommended limit drug dose calculation of antihypertensive drugs, according to the instruction to recommend routine dose and daily use. The antihypertensive drug's daily DDD value is equal to the addition of antihypertensive drugs by DDD combined. 54 patients with dialysis antihypertensive drugs including calcium channel blockers, (CCB), angiotensin-converting enzyme inhibitors (angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), β receptor blocker, α receptor blocker, a diuretic, neprilysin inhibitor, etc., before and after medication scores comparison, The difference was not statistically significant ($P > 0.05$). All experiments were repeated at least three times, and the average was selected as the observed data.

Comparison of blood pressure during roxadustat treatment and ESA treatment before roxadustat treatment

Repeated measures analysis of variance was used to determine the effect of roxadustat on blood pressure changes before, during and after dialysis in MHD patients (Fig. 2). When using ESA drugs, with time, before the dialysis patients with SBP, DBP, and MAP, dialysis in SBP

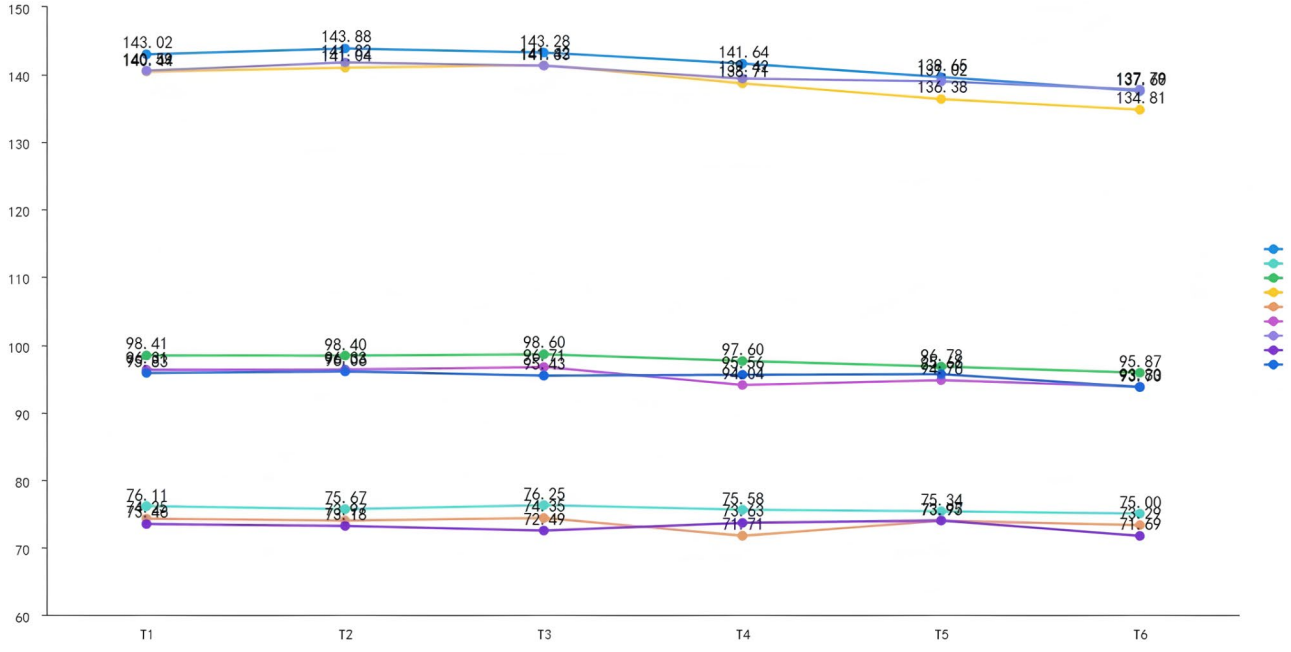


Fig. 2 The mean blood pressure after comparing patients before each month Note: T1: The sixth months before switching to roxadustat, T2: The third months before switching to roxadustat, T3: The first months before switching to roxadustat, T4: Switch to roxadustat for the first month, T5: Switch to roxadustat for the third month, T6: Switch to roxadustat for the sixth month All experiments were repeated at least three times, and the average was selected as the observed data

Table 2 Comparison of differences in systolic blood pressure, diastolic blood pressure, and mean arterial pressure among patients before, during, and after dialysis at each time point

Index	Number of cases	T1($n=54$)	T2($n=54$)	T3($n=54$)	T4($n=54$)	T5($n=54$)	T6($n=54$)	F	*p*
SBP before dialysis	54	143.02 ± 17.47	143.88 ± 15.17 **f**	143.28 ± 21.57	141.64 ± 17.09	139.65 ± 15.14	137.60 ± 14.69 **b**	2.293	0.046*
DBP before dialysis	54	76.11 ± 9.38	75.67 ± 9.36	76.25 ± 9.20	75.58 ± 8.68	75.34 ± 8.87	75.00 ± 8.08	0.371	0.869
MAP before dialysis	54	98.41 ± 10.48	98.40 ± 9.02	98.60 ± 10.67	97.60 ± 9.35	96.78 ± 9.01	95.87 ± 8.18	1.444	0.209
Mean SBP during dialysis	54	140.44 ± 15.98	141.04 ± 13.86 **f**	141.42 ± 17.33 **f**	138.71 ± 15.16	136.38 ± 14.41	134.81 ± 13.07 **bc**	4.645	0.000**
Mean DBP during dialysis	54	74.25 ± 8.13	73.97 ± 8.23	74.35 ± 7.89	71.71 ± 7.11	73.95 ± 7.21	73.29 ± 6.64	2.553	0.028*
Mean MAP during dialysis	54	96.31 ± 9.61	96.33 ± 8.21	96.71 ± 9.23	94.04 ± 7.94	94.76 ± 8.25	93.80 ± 7.46	2.907	0.014
After dialysis SBP	54	140.59 ± 16.08	141.82 ± 15.68	141.33 ± 16.64	139.42 ± 16.26	139.02 ± 14.66	137.79 ± 13.32	1.501	0.190
After dialysis DBP	54	73.46 ± 8.33	73.18 ± 8.49	72.49 ± 8.11	73.63 ± 7.93	73.97 ± 7.36	71.69 ± 7.02	1.269	0.277
After dialysis MAP	54	95.83 ± 9.83	96.06 ± 8.70	95.43 ± 8.99	95.56 ± 9.28	95.66 ± 8.16	93.73 ± 7.76	1.152	0.333

* $p<0.05$ ** $p<0.01$, T1: The sixth months before switching to roxadustat, T2: The third months before switching to roxadustat, T3: The first months before switching to roxadustat, T4: Switch to roxadustat for the first month, T5: Switch to roxadustat for the third month, T6: Switch to roxadustat for the sixth month. Compared to T1, a: *P*<0.05,A: *P*<0.001;Compared to T2, b:*P*<0.05,B: *P*<0.001; Compared to T3, c:*P*<0.05,C: *P*<0.001; Compared to T4, d:*P*<0.05,D: *P*<0.001; Compared to T5, e:*P*<0.05,E: *P*<0.001; Compared to T6, f:*P*<0.05,F: *P*<0.001 All experiments were repeated at least three times, and the average was selected as the observed data

Table 3 Comparison of blood pressure variability in patients before and during roxadustat treatment

Variable	Group(mean ± standard deviation)		t	*p*
	1 to 6 months before roxadustat treatment ($n=54$)	Roxadustat was used for 1–6 months($n=54$)		
SBP-ARV before dialysis	5.46 ± 5.54	3.41 ± 4.64	2.450	0.018*
DBP-ARV before dialysis	4.71 ± 3.30	3.90 ± 4.09	0.107	0.915
MAP-ARV before dialysis	5.68 ± 4.89	3.76 ± 3.78	2.784	0.008**
SBP-ARV during dialysis	4.67 ± 4.16	3.22 ± 2.52	2.902	0.006**
DBP-ARV during dialysis	3.96 ± 3.78	3.81 ± 3.64	0.648	0.520
MAP-ARV during dialysis	4.49 ± 4.93	3.91 ± 4.11	1.935	0.059
SBP-ARV after dialysis	4.65 ± 6.39	4.45 ± 5.43	1.223	0.227
DBP-ARV after dialysis	3.26 ± 4.55	3.27 ± 3.30	0.748	0.458
MAP-ARV after dialysis	4.15 ± 5.63	3.69 ± 3.26	0.742	0.462

Note: * $p<0.05$ ** $p<0.01$ All experiments were replicated at least three times, and the average was chosen as the observed data

and SBP after dialysis MAP and high blood pressure are rising trend, ESA can lead to a rise in blood pressure. After the use of roxadustat in MHD patients, the SBP before dialysis, DBP, MAP, SBP during dialysis, and SBP after dialysis, under the premise of no significant difference in antihypertensive drugs, blood pressure has a downward trend. Before dialysis SBP and SBP, DBP, and MAP during dialysis in the treatment group before and after comparison with significant differences statistically ($P<0.05$) were 0.046, < 0.001, 0.028, 0.014. After comparing the two analysis results (Table 2): SBP before dialysis before using Rosa department of his 3 months than in the use of Rosa company 6 months after he was 7.01 (95% CI: 0.1690, 12.7175), statistically significant difference ($P<0.05$); The mean SBP during dialysis was 6.22 (95%CI: 0.5345, 11.9178) and 6.60 (95%CI: 0.9130, 12.2963) higher in the 2nd and 3rd month before roxadustat treatment than in the 6th month after roxadustat treatment, and the difference was statistically significant ($P<0.05$). In other patients with blood pressure there was no statistically significant difference at various time points ($P>0.05$).

Comparison of blood pressure variability before and after changing to roxadustat

MHD patients hemodialysis blood pressure data each month for the first time a week in replacement of Rosa company he continuous measurement before and after 6 months calculation MHD patients during taking real blood pressure variability. Paired T-test was used to compare the true variability of blood pressure in MHD patients at 6 months before and after roxadustat treatment. SBP-ARV, DBP-ARV, MAP-ARV before dialysis, SBP-ARV, DBP-ARV, MAP-ARV during dialysis, and SBP-ARV, DBP-ARV, MAP-ARV after dialysis were compared (Table 3).

The biochemical indexes of patients before and after roxadustat treatment were compared

A paired t-test was used to compare the laboratory parameters of MHD patients before and after roxadustat treatment. The red blood cells, hemoglobin and serum calcium were higher, and the difference was statistically significant ($P<0.05$), while other biochemical data such as platelet, reactive protein, alanine aminotransferase, triglyceride, high-density lipoprotein, low-density lipoprotein and so on were not statistically significant (Table 4).

Systolic blood pressure high and low blood pressure variation group general data and laboratory indexes

The median of SBP-ARV during 6 months of roxadustat use in maintenance hemodialysis patients was 3.018 as the standard, and they were divided into two groups: the high systolic blood pressure variability group and the low systolic blood pressure variability group. The number of hospitalizations, gender, age, diabetes complications, and biochemical data of the two groups were compared. The P values of gender, age, diabetes complications, red blood cells, haemoglobin and serum calcium were 0.027 ($P<0.05$), 0.004 ($P<0.01$), 0.046 ($P<0.05$), 0.003 ($P<0.01$), 0.046 ($P<0.05$) and 0.003 ($P<0.01$), respectively. Our data showed that serum iron (SI), serum ferritin (SF), total iron binding capacity (TIBC), and transferrin saturation (TSAT) were higher in both groups after rosallistat treatment than before treatment (Table 5).

Discussion

Our study was conducted to explore the changes in anemia, blood pressure and its volatility in MHD patients who were replaced with Roxadustat by ESA. The results showed that blood pressure showed a decreasing trend and continued to decrease in MHD patients after switching to Roxadustat department. In addition, there was a reduction in the duration of medication before dialysis and in the volatility of blood pressure during dialysis. The efficacy of ESA in correcting anemia resulted in higher hemoglobin levels. However, no statistically significant difference was found in the DDD of antihypertensive drugs [39–41].

Relationship between roxadustat and blood pressure

Hypertension serves as the primary adverse effect of ESA, with its underlying mechanism being highly intricate. Currently, it is postulated to be associated with cardiovascular factors and substances that elevate blood pressure. Pulse Wave Velocity (PWV) constitutes a means to assess the extent of arterial stiffness, while erythropoietin exhibits a linear relationship with PWV in individuals suffering from renal anemia. Medications containing ESA have the potential to directly induce constriction in small resistance vessels, ultimately resulting in vascular compression [42]. Furthermore, ESA facilitates endothelial cell proliferation and angiogenesis by activating erythropoietin receptors present on vascular endothelial cells [43]. In MHD patients experiencing a

Table 4 Comparison of blood laboratory indicators before and after switching to roxadustat

Variable	Group(mean ± standard deviation)		t/z	*p*
	Before roxadustat treatment *N* = 54	After the administration of roxadustat *N* = 54		
leukocyte(10^9/L)	5.75 ± 1.85	5.92 ± 2.26	-0.550	0.585
Red blood cells(10^12/L)	3.09 ± 0.76	3.34 ± 0.67	-2.589	0.013*
hemoglobin(g/L)	87.04 ± 17.44	96.65 ± 24.75	-2.593	0.012*
Blood platelets(10^9/L)	175.33 ± 79.21	160.24 ± 61.65	1.662	0.103
Serum C-reactive protein(mg/L)	7.93 ± 15.77	2.96 ± 2.91	1.493	0.150
Alanine aminotransferase(U/L)	17.30 ± 31.72	15.32 ± 14.81	0.394	0.695
Aspartate aminotransferase(U/L)	19.22 ± 28.82	17.36 ± 9.19	0.442	0.661
Serum albumin(g/L)	37.02 ± 4.80	39.03 ± 4.50	-2.560	0.142
Creatinine(μmmol/L)	888.21 ± 377.84	894.86 ± 380.08	-0.122	0.903
Urea nitrogen(mmol/L)	22.59 ± 9.14	21.99 ± 9.16	0.345	0.731
Uric acid(μmmol/L)	430.31 ± 146.72	433.10 ± 129.28	-0.110	0.913
Blood glucose(mmol/L)	10.22 ± 9.73	7.16 ± 3.18	1.777	0.085
Total cholesterol(mmol/L)	2.86 ± 1.41	2.06 ± 0.55	-0.998	0.125
triglyceride(mmol/L)	2.90 ± 2.02	2.47 ± 1.54	0.916	0.367
High density lipoprotein(mmol/L)	1.10 ± 0.46	1.14 ± 0.46	-0.315	0.755
Low density lipoprotein(mmol/L)	1.84 ± 0.63	1.74 ± 0.71	0.686	0.497
potassium(mmol/l)	4.97 ± 0.82	4.88 ± 0.90	0.573	0.570
sodium(mmol/l)	135.39 ± 19.62	137.87 ± 3.09	-0.869	0.389
calcium(mmol/l)	2.27 ± 0.25	2.27 ± 0.17	-0.233	0.896
phosphorus(mmol/l)	1.84 ± 0.62	2.11 ± 2.00	-0.889	0.378

Note: * $p<0.05$ ** $p<0.01$ All experiments were replicated at least three times, and the average was chosen as the observed data

Table 5 Comparison of general data and laboratory indicators between high and low blood pressure true variability groups

Variable	Low systolic blood pressure variation group (*n* = 27)	High systolic blood pressure variation group (*n* = 27)	t/x^2	*p*
Number of hospitalizations during roxadustat treatment(Number of times)	0.58 ± 0.95	0.93 ± 0.78	2.154	0.148
Male, n(%)	12(44.44%)	20(74.07%)	4.909	0.027*
Age(years)	52.19 ± 9.81	62.19 ± 13.65	9.559	0.004**
diabetes complications, n(%)	6(22.22%)	13(48.15%)	3.979	0.046*
leukocyte(10^9/L)	6.01 ± 2.00	5.84 ± 2.52	0.258	0.797
Red blood cells 10^12/L	3.59 ± 0.62	3.06 ± 0.61	3.093	0.003**
hemoglobin(g/L)	103.15 ± 24.12	89.35 ± 23.85	2.050	0.046*
Blood platelets(10^9/L)	167.68 ± 63.34	153.08 ± 60.35	0.843	0.403
Serum C-reactive protein(mg/L)	7.96 ± 17.37	6.30 ± 6.74	0.396	0.695
Alanine aminotransferase(U/L)	17.98 ± 18.25	12.44 ± 8.95	1.383	0.173
Aspartate aminotransferase(U/L)	17.50 ± 10.65	16.83 ± 7.61	0.257	0.798
Serum albumin(g/L)	39.06 ± 4.76	33.07 ± 5.01	1.454	0.042*
Creatinine(μmmol/L)	904.68 ± 366.41	881.08 ± 390.42	0.222	0.825
Urea nitrogen(mmol/L)	23.48 ± 7.35	20.17 ± 10.31	1.313	0.195
Uric acid(μmmol/L)	433.57 ± 141.05	434.23 ± 114.49	-0.018	0.985
Blood glucose(mmol/L)	6.65 ± 3.05	7.12 ± 2.88	-0.538	0.593
Total cholesterol(mmol/L)	18.89 ± 77.21	2.57 ± 1.19	1.013	0.286
triglyceride(mmol/L)	2.39 ± 1.65	2.20 ± 1.63	0.392	0.697
High density lipoprotein(mmol/L)	0.76 ± 0.32	0.94 ± 0.31	-1.925	0.061
Low density lipoprotein(mmol/L)	1.55 ± 0.71	1.74 ± 0.68	-0.967	0.339
potassium(mmol/l)	4.88 ± 0.97	4.85 ± 0.83	0.122	0.903
sodium(mmol/l)	137.42 ± 3.54	138.03 ± 3.27	-0.641	0.525
calcium(mmol/l)	2.16 ± 0.26	2.28 ± 0.21	-0.12	0.003**
phosphorus(mmol/l)	1.81 ± 0.69	2.38 ± 2.65	-1.045	0.301

Note: * $p < 0.05$ ** $p < 0.01$ All experiments were replicated at least three times, and the average was chosen as the observed data

sub-inflammatory state, it fosters the development of a pathological condition characterized by an abundance of smooth muscle cells within blood vessels. This, in turn, leads to the contraction of smooth muscle in large arteries, diminishes vascular compliance, and exacerbates atherosclerotic lesions [44]. A clinical investigation [45] revealed a notable increase in the vasoactive substances endothelin and norepinephrine following the administration of ESA, a finding that was corroborated by animal studies [46]. Rats treated with ESA exhibited a significantly heightened sensitivity to the vasoactive substances endothelin and norepinephrine, ultimately contributing to the manifestation of hypertension.

Some research have indicated that peripheral blood pressure adjusts following the administration of a drug by Rosa, leading to an increase in bodily involvement, and a dose-dependent reduction in hypertension among mice [47]. This reduction is achieved by lowering the expression of AGTR1 receptors in aortic tissue and AGTR2 receptors. The AGTR1 receptor primarily facilitates hypertension development due to water and sodium retention, whereas the AGTR2 receptor's activation promotes cell differentiation, growth suppression, and vasodilation. These two receptors function in opposition to one another [29]. The HIF family consists of three members: HIF1, HIF2, and HIF3. HIF1α enhances systolic, diastolic, and mean arterial pressure (MAP) in mouse vascular smooth muscle cells (VSMCs). Overexpression of HIF2α exacerbates pulmonary hypertension [25]. Hifphi can suppress the expression of HIF-regulated genes by mediating HIF prolyl hydroxylase domain proteins (HIF-PHDs), thereby lowering blood pressure [48, 49]. Clinical trials have also verified that mean arterial pressure decreases after the administration of roxadustat [50], although the precise mechanism by which roxadustat reduces blood pressure requires further investigation. In MHD patients, hypertension is a prevalent complication, with a prevalence rate ranging from 60 to 90% [51], and the leading cause of death is the occurrence of various cardiovascular diseases [52]. Blood pressure is an independent risk factor for cardiovascular events [53, 54]. It is possible that roxadustat has a lesser impact on blood pressure than ESA in MHD patients, thereby reducing the incidence of cardiovascular disease and consequently the mortality rate [55].

Relationship between roxadustat and blood pressure variability

Roxadustat lowers serum cholesterol and triglycerides in patients while treating anemia, with superior effects on lipid metabolism compared to ESA [56]. It reduces blood pressure variability in a lipid-lowering manner. Blood pressure fluctuations in MHD patients are often linked to target organ damage, including vascular endothelial cell damage and increased inflammatory response [57]. These fluctuations can lead to myocardial cell apoptosis and cardiogenic edema [58], particularly in patients with compromised cardiac function where low blood pressure management becomes crucial [59]. Inadequate volume control and salt restriction during dialysis intervals contribute to weight gain and fluid retention, which are key factors in blood pressure variability. Reducing blood pressure fluctuation can help remove vasoconstrictive substances, maintain blood volume and acid-base balance, and improve dialysis adequacy [60]. Roxadustat use during dialysis can decrease the risk of cardiovascular events and mortality, reduce vascular endothelial cell damage, improve vascular stiffness, protect residual renal function, and enhance water and sodium removal during dialysis.

Relationship of laboratory data to roxadustat

Sphoglyceric acid kinase 1 (PGK1), lactate dehydrogenase (LDH), and additional factors that modulate HIF are engaged in cellular processes such as metabolism, mitochondrial function, inflammation, vascular function, and oxidative stress. These processes can trigger the endogenous production of EPO in hemodialysis patients [61, 62, 63]. In a multicenter, randomized, open-label phase 3 trial, it was observed that the therapeutic effect of the Rosa company's treatment for anemia was comparable to or even superior to ESA, with a shorter time to effect and a lower incidence of adverse events. Clinical trials have also demonstrated that roxadustat can significantly lower hepcidin levels and enhance the utilization of serum iron compared to ESA. Particularly in iron-deficient conditions, roxadustat's efficacy in treating anemia surpasses that of ESA [64, 65]. Maintenance hemodialysis (MHD) anemia is a chronic inflammatory condition that hampers erythropoiesis by suppressing EPO production and disrupting bone marrow erythrocyte development and iron metabolism. Roxadustat operates independently of the inflammatory status, suggesting it could be a suitable clinical approach for treating renal anemia in patients with a poor response to ESA due to high inflammation levels [66]. Although ESA typically maintains hemoglobin levels within the target range and reduces the need for red blood cell transfusions, its use in advanced chronic kidney disease elevates the risk of cardiovascular events [67]. Roxadustat is anticipated to decrease the cardiovascular risks associated with traditional ESA treatment while addressing anemia [68].

In our study, roxadustat was effective in maintaining serum calcium levels within safe limits, although there was no significant difference in calcium levels between the treatment groups **T**he blood calcium level in the high systolic blood pressure variability group was higher than that in the low systolic blood pressure variability group, while the hemoglobin level was lower and the difference was statistically significant, which was similar to the results of Fang Zhenyu [69]. Therefore, combined with the results of previous studies and this study, it can be seen that hypertensive variability may aggravate the damage of target organs in MHD patients. The variability of hypertension may lead to the decline of renal function, and then cause a variety of complications such as renal anemia, abnormal calcium and phosphorus metabolism, and secondary hyperparathyroidism. It is speculated that bone metabolism indexes such as calcium, phosphorus, parathyroid hormone and CKD-MBD may lead to blood pressure fluctuation by affecting vascular structure and function. Thus, hypertension variability and kidney injury may act on each other to promote a vicious cycle [55].

The cardiovascular safety of Roxat should not be ignored. Related studies have demonstrated that Roxallistat not only raises Hb to the level achieved by ESAs, but does not significantly increase the risk of cardiovascular events [69, 70]. In this study, the main adverse reactions of patients were hyperkalemia, gastrointestinal reaction, dizziness, headache, allergic reaction and thrombosis. There was no significant difference in the overall incidence of adverse reactions of Roxallistat compared with ESAs, and no serious adverse events occurred. In a recent meta-analysis, Roxallistat was associated with an increased risk of vomiting, hypotension, diarrhea, and arteriovenous fistula thrombosis, and a decreased risk of heart failure, which was roughly consistent with our observations. But compared to placebo, Roxallistat was associated with higher serious adverse reactions, high blood pressure, and deep vein thrombosis in an evaluation study. Not long ago, the U.S. Food and Drug Administration (FDA) voted against approving Roxalstat for dialysis dependent patients, citing its potential thromboembolism and cardiovascular risks. To date, the adverse effects of Roxat on the cardiovascular system have not reached consistent results, its clinical impact has not been fully studied, and more results from real-world practice are needed in the future to verify the safety of Roxat.

In conclusion, roxadustat, as compared with ESA, was effective in reducing BP and BP variability before and during dialysis and reducing CVD risk and mortality in MHD patients. In addition, the fluctuation process of blood pressure in MHD patients is related to multiple

factors, including gender, hemoglobin level, serum calcium, diabetes, nutritional status [71], and disease changes. Since this study is a retrospective analysis of its own, the sample size of data is not large, and the conclusions still need to be supported by prospective studies with larger samples.

Conclusion

Compared with rHuEPO, roxadustat has less fluctuation of blood pressure and less impact on blood pressure in MHD patients during the use of roxadustat, and roxadustat can improve hemoglobin level, and the therapeutic effect is not inferior to that of ESA.

Deficiencies and prospects

This study has many shortcomings: (1) Since it is a retrospective study, the severity of the patients in the two stages before and after switching to drug therapy may not be consistent, which may affect the comparability of the two stages. (2) The biochemical data during dialysis are not perfect and seriously missing, and there are some discrepancies with the previous published literature; Further data collection and the extension of research time are needed. (3) This study did not determine the exact pathophysiological mechanism of roxadustat affecting the fluctuation of blood pressure during hemodialysis and the influence of different dialysis methods such as ultrafiltration method, dialysate and temperature on the fluctuation of blood pressure. In the study, we observed Rosa division of dialysis has of certain influence on blood pressure variability at different times, choosing correct anemia drugs in patients with maintenance hemodialysis for reference, for the results of the study need to be the more perfect design and further increase the prospective design study sample size.

Acknowledgements
Thanks to all those who helped with the study but were not listed as co-authors due to insufficient contributions.

Author contributions
Yu-ting Yang, Yu Wang designed the study. Yuan Qi, Zhi-hui Fu, Yan-ping Hu, Jun-hui Wan wrote the original draft. Xin-tian Shi, Jia-yan Huang, Hong He collected raw data. Qin-kai Chen, and Qing Zhao performed statistical and bioinformatics analyses. Qin-kai Chen, and Qing Zhao supervised the study. All authors have given consent to publish.

Funding
This study did not receive any funding in any form.

Data availability
The data used to support this study are available from the corresponding author upon request.

Declarations

Ethical approval
This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Jiangxi Medical College, Nanchang University(NO. JXMCST).

Informed consent
All patients obtained written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Nephrology, the First Affiliated Hospital of Nanchang University, Nanchang University, Nanchang, China
[2]Key Laboratory of Urinary System Diseases of Jiangxi Province, Nanchang, China
[3]Department of Nephrology, Guangxi Hospital Division of The First Affiliated Hospital, Sun Yat-son University, Nanning, China

Received: 21 September 2024 / Accepted: 24 December 2024
Published online: 29 May 2025

References

1. Coresh J, Stevens LA, Levey AS. Chronic kidney disease is common: what do we do next?[J]. Nephrol Dial Transpl. 2008;23(4):1122–5.
2. Zhang L, Zhao MH, Zuo L et al. China Kidney Disease Network (CK-NET) 2016 Annual Data Report[J]. Kidney Int Suppl (2011), 2020,10(2):e97-e185.
3. Morfin JA, Fluck RJ, Weinhandl ED, et al. Intensive hemodialysis and treatment complications and Tolerability[J]. Am J Kidney Dis. 2016;68(5S1):S43–50.
4. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey[J]. Lancet. 2012;379(9818):815–22.
5. Lin Pan D, Xiaoqiang Y, Min, et al. Anemia in patients with chronic kidney disease illness survey [J]. Fudan Univ J Med Sci. 2009;4(5):562–5.
6. Kuragano T, Matsumura O, Matsuda A, et al. Association between hemoglobin variability, serum ferritin levels, and adverse events/mortality in maintenance hemodialysis patients[J]. Kidney Int. 2014;86(4):845–54.
7. Haase VH. HIF-prolyl hydroxylases as therapeutic targets in erythropoiesis and iron metabolism[J]. Hemodial Int. 2017;21(Suppl 1):S110–24.
8. Batchelor EK, Kapitsinou P, Pergola PE, et al. Iron Deficiency in chronic kidney disease: updates on pathophysiology, diagnosis, and Treatment[J]. J Am Soc Nephrol. 2020;31(3):456–68.
9. Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease[J]. Kidney Int. 2017;92(2):306–12.
10. Wang Yang W, Ribao. Chronic kidney disease (CKD) is the basis and clinical studies of renal anemia status and progress [J]. Chin J Integr Traditional Western Nephrol. 2019;20(5):452–5.
11. Portoles J, Gorriz JL, Rubio E, et al. The development of anemia is associated to poor prognosis in NKF/KDOQI stage 3 chronic kidney disease[J]. BMC Nephrol. 2013;14:2.
12. Sato Y, Fujimoto S, Konta T, et al. Anemia as a risk factor for all-cause mortality: obscure synergic effect of chronic kidney disease[J]. Clin Exp Nephrol. 2018;22(2):388–94.
13. Anees M, Mumtaz A, Ibrahim M, et al. Effect of anemia and hyperhomocysteinemia on mortality of patients on hemodialysis[J]. Iran J Kidney Dis. 2010;4(1):60–5.
14. Kawahara K, Minakuchi J, Yokota N et al. Treatment of renal anaemia with erythropoiesis-stimulating agents in predialysis chronic kidney disease patients: Haemoglobin profile during the 6 months before initiation of dialysis[J]. Nephrol (Carlton), 2015,20 Suppl 4:29–32.
15. Comin-Colet J, Ruiz S, Cladellas M, et al. A pilot evaluation of the long-term effect of combined therapy with intravenous iron sucrose and erythropoietin in elderly patients with advanced chronic heart failure and cardio-renal anemia syndrome: influence on neurohormonal activation and clinical outcomes[J]. J Card Fail. 2009;15(9):727–35.

16. Li Y, Shi H, Wang WM, et al. Prevalence, awareness, and treatment of anemia in Chinese patients with nondialysis chronic kidney disease: first multicenter, cross-sectional study[J]. Med (Baltim). 2016;95(24):e3872.
17. McCullough PA, Barnhart HX, Inrig JK, et al. Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease[J]. Am J Nephrol. 2013;37(6):549–58.
18. Bailie GR, Larkina M, Goodkin DA, et al. Data from the Dialysis outcomes and practice patterns study validate an association between high intravenous iron doses and mortality[J]. Kidney Int. 2015;87(1):162–8.
19. Maschio G. Erythropoietin and systemic hypertension[J]. Nephrol Dial Transpl. 1995;10(Suppl 2):74–9.
20. Csiky B, Schomig M, Esposito C, 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)[J]. Adv Ther. 2021;38(10):5361–80.
21. Fishbane S, Pollock CA, El-Shahawy M, et al. Roxadustat Versus Epoetin Alfa for Treating Anemia in patients with chronic kidney disease on Dialysis: results from the Randomized Phase 3 ROCKIES Study[J]. J Am Soc Nephrol. 2022;33(4):850–66.
22. Strandberg TE, Pitkala K. What is the most important component of blood pressure: systolic, diastolic or pulse pressure?[J]. Curr Opin Nephrol Hypertens. 2003;12(3):293–7.
23. Del VL, Lusenti T, Del RG, et al. Prevalence of hypertension in a large cohort of Italian hemodialysis patients: results of a cross-sectional study[J]. J Nephrol. 2013;26(4):745–54.
24. Abdelazeem B, Shehata J, Abbas KS, et al. The efficacy and safety of roxadustat for the treatment of anemia in non-dialysis dependent chronic kidney disease patients: an updated systematic review and meta-analysis of randomized clinical trials[J]. PLoS ONE. 2022;17(4):e266243.
25. Huang Y, Di Lorenzo A, Jiang W, et al. Hypoxia-inducible factor-1alpha in vascular smooth muscle regulates blood pressure homeostasis through a peroxisome proliferator-activated receptor-gamma-angiotensin II receptor type 1 axis[J]. Hypertension. 2013;62(3):634–40.
26. Mokas S, Lariviere R, Lamalice L, et al. Hypoxia-inducible factor-1 plays a role in phosphate-induced vascular smooth muscle cell calcification[J]. Kidney Int. 2016;90(3):598–609.
27. Dao HH, Essalihi R, Bouvet C, et al. Evolution and modulation of age-related medial elastocalcinosis: impact on large artery stiffness and isolated systolic hypertension[J]. Cardiovasc Res. 2005;66(2):307–17.
28. Yu J, Wang S, Shi W et al. Roxadustat prevents Ang II hypertension by targeting angiotensin receptors and eNOS[J]. JCI Insight, 2021,6(18).
29. Satoh M, Ohkubo T, Asayama K, et al. Combined effect of blood pressure and total cholesterol levels on long-term risks of subtypes of cardiovascular death: evidence for Cardiovascular Prevention from Observational cohorts in Japan[J]. Hypertension. 2015;65(3):517–24.
30. Arima H, Murakami Y, Lam TH, et al. Effects of prehypertension and hypertension subtype on cardiovascular disease in the Asia-Pacific Region[J]. Hypertension. 2012;59(6):1118–23.
31. Barengo NC, Antikainen R, Kastarinen M, et al. The effects of control of systolic and diastolic hypertension on cardiovascular and all-cause mortality in a community-based population cohort[J]. J Hum Hypertens. 2013;27(11):693–7.
32. Omboni S, Parati G, Castiglioni P, et al. Estimation of blood pressure variability from 24-hour ambulatory finger blood pressure[J]. Hypertension. 1998;32(1):52–8.
33. Johansson JK, Niiranen TJ, Puukka PJ, et al. Prognostic value of the variability in home-measured blood pressure and heart rate: the Finn-Home Study[J]. Hypertension. 2012;59(2):212–8.
34. Webb A, Mazzucco S, Li L, et al. Prognostic significance of blood pressure variability on beat-to-beat monitoring after transient ischemic attack and Stroke[J]. Stroke. 2018;49(1):62–7.
35. Carrero JJ, de Jager DJ, Verduijn M, et al. Cardiovascular and noncardiovascular mortality among men and women starting dialysis[J]. Clin J Am Soc Nephrol. 2011;6(7):1722–30.
36. Jiang D, Tokashiki M, Hayashi H, et al. Augmented blood pressure variability in Hypertension Induced by Angiotensin II in Rats[J]. Am J Hypertens. 2016;29(2):163–9.
37. Flythe JE, Kunaparaju S, Dinesh K, et al. Factors associated with intradialytic systolic blood pressure variability[J]. Am J Kidney Dis. 2012;59(3):409–18.
38. Stergiou GS, Parati G, Vlachopoulos C, et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: current status and future directions - position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability[J]. J Hypertens. 2016;34(9):1665–77.
39. Pierdomenico SD. Indices of blood pressure variability and cardiovascular risk[J]. Hypertension. 2010;56(2):e21. author reply e22.
40. Mena L, Pintos S, Queipo NV, et al. A reliable index for the prognostic significance of blood pressure variability[J]. J Hypertens. 2005;23(3):505–11.
41. Zhao Yu-chao, Hui-ping ZHAO, Bei WU, et al. Effect of roxadustat on blood pressure in maintenance peritoneal dialysis patients [J]. Chin J Blood Purif. 2012;21(9):633–7.
42. McEniery CM, Wallace S, Mackenzie IS, et al. Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans[J]. Hypertension. 2006;48(4):602–8.
43. Sakaguchi Y, Hamano T, Wada A, et al. Types of erythropoietin-stimulating agents and mortality among patients undergoing Hemodialysis[J]. J Am Soc Nephrol. 2019;30(6):1037–48.
44. Janmaat ML, Heerkens JL, de Bruin AM, et al. Erythropoietin accelerates smooth muscle cell-rich vascular lesion formation in mice through endothelial cell activation involving enhanced PDGF-BB release[J]. Blood. 2010;115(7):1453–60.
45. Xianglan B, Ying B. Clinical observation of hypertension induced by recombinant human erythropoietin [J]. Chin J Gerontol. 2006;26(6):825–6.
46. Johannsson G, Bengtsson BA, Ahlmen J. Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: anabolic effect and functional improvement[J]. Am J Kidney Dis. 1999;33(4):709–17.
47. Flamme I, Oehme F, Ellinghaus P, et al. Mimicking hypoxia to treat anemia: HIF-stabilizer BAY 85-3934 (Molidustat) stimulates erythropoietin production without hypertensive effects[J]. PLoS ONE. 2014;9(11):e111838.
48. Yu ZK, Han YJ, Chen DD, et al. [Association between genetic polymorphisms of HIF-2alpha gene and high altitude pulmonary hypertension in Han population][J]. Zhonghua Yi Xue Za Zhi. 2016;96(40):3213–7.
49. Hwang S, Nguyen AD, Jo Y, et al. Hypoxia-inducible factor 1alpha activates insulin-induced gene 2 (Insig-2) transcription for degradation of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase in the liver[J]. J Biol Chem. 2017;292(22):9382–93.
50. Chen N, Hao C, Liu BC, et al. Roxadustat Treatment for Anemia in patients undergoing long-term Dialysis[J]. N Engl J Med. 2019;381(11):1011–22.
51. Agarwal R, Nissenson AR, Batlle D, et al. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States[J]. Am J Med. 2003;115(4):291–7.
52. Zhou D, Wang S, Tian T. Uncontrolled hypertension and risk of Cardiovascular Mortality in China[J]. JAMA Intern Med. 2016;176(8):1233–4.
53. Lewington S, Lacey B, Clarke R, et al. The Burden of Hypertension and Associated Risk for Cardiovascular Mortality in China[J]. JAMA Intern Med. 2016;176(4):524–32.
54. Deter HC, Buchholz K, Schorr U, et al. Salt-sensitivity and other predictors of stress-related cardiovascular reactivity in healthy young males[J]. Clin Exp Hypertens. 2001;23(3):213–25.
55. Yoneki K, Kitagawa J, Hoshi K, et al. Association between frailty and bone loss in patients undergoing maintenance hemodialysis[J]. J Bone Min Metab. 2019;37(1):81–9.
56. Hirai K, Kaneko S, Minato S, et al. Effects of roxadustat on anemia, iron metabolism, and lipid metabolism in patients with non-dialysis chronic kidney disease[J]. Front Med (Lausanne). 2023;10:1071342.
57. Abramson JL, Lewis C, Murrah NV. Body mass index, leptin, and ambulatory blood pressure variability in healthy adults[J]. Atherosclerosis. 2011;214(2):456–61.
58. Chou JA, Streja E, Nguyen DV, et al. Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients[J]. Nephrol Dial Transpl. 2018;33(1):149–59.
59. Cautela J, Tartiere JM, Cohen-Solal A, Bellemain-Appaix A, Theron A, Tibi T, Januzzi JL Jr, Roubille F, Girerd N. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. Eur J Heart Fail. 2020;22(8):1357–65.
60. Park J, Rhee CM, Sim JJ, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival[J]. Kidney Int. 2013;84(4):795–802.
61. Sasaki N, Tsunoda M, Ikee R, et al. Efficacy and safety of eldecalcitol, a new active vitamin D3 analog, in the bone metabolism of postmenopausal women receiving maintenance hemodialysis[J]. J Bone Min Metab. 2015;33(2):213–20.

62. Nazarian A, Hasankhani M, Aghajany-Nasab M, et al. Association between Klotho Gene polymorphism and markers of bone metabolism in patients receiving maintenance hemodialysis in Iran[J]. Iran J Kidney Dis. 2017;11(6):456–60.
63. Bernhardt WM, Wiesener MS, Scigalla P, et al. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD[J]. J Am Soc Nephrol. 2010;21(12):2151–6.
64. Barratt J, Andric B, Tataradze A, et al. Erratum to: Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a phase 3, randomised, open-label, active-controlled study (DOLOMITES)[J]. Nephrol Dial Transpl. 2022;37(4):805.
65. Ogawa C, Tsuchiya K, Tomosugi N, et al. Hypoxia-inducible factor prolyl hydroxylase domain inhibitor may maintain hemoglobin synthesis at lower serum ferritin and transferrin saturation levels than darbepoetin alfa[J]. PLoS ONE. 2021;16(6):e252439.
66. Li ZL, Tu Y, Liu BC. Treatment of renal Anemia with Roxadustat: advantages and Achievement[J]. Kidney Dis (Basel). 2020;6(2):65–73.
67. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin[J]. N Engl J Med. 1998;339(9):584–90.
68. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease[J]. N Engl J Med. 2006;355(20):2085–98.
69. Zhen yu, yong-mei liu. Correlation between intradialytic blood pressure variability and chronic kidney disease-mineral and bone abnormalities in maintenance hemodialysis patients [J]. J Bengbu Med Univ, 2017 (12): 1652–3.
70. Song J, Chen X, Zhou L, Yu W, Liu H, Yuan F. Roxadustat treatment for erythropoiesis-stimulating agent-hyporesponsive anemia in maintenance hemodialysis patients. J Int Med Res. 2023;51(10):3000605231204475.
71. Denny GB, Deger SM, Chen G et al. Leucine disposal rate for assessment of amino acid metabolism in maintenance hemodialysis patients[J]. BMC Nutr, 2016,2.

Publisher's note