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Original Research Article

Efficacy of oral roxadustat combined with L-carnitine for dialysis-induced anemia in patients with chronic renal failure

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Abstract

Purpose: *To investigate the efficacy of oral roxadustat plus L-carnitine for dialysis-induced anemia in patients with chronic renal failure (CRF).*

Methods: *This was a retrospective analysis of 46 patients conducted on 100 CRF cases with dialysis-induced anemia treated at Xinjiang Armed Police Crops Hospital from March 2020 to March 2023. The participants were randomly distributed into study (n = 54) and control groups (n = 46). The control group received oral roxadustat (100 mg for patients weighing 45 - 60 kg, and 120 mg for patients ≥ 60 kg, thrice per week), while the study group was administered roxadustat in combination with L-carnitine (2 g injected using the dialysis machine before the end of each session). Anemia indices, and iron metabolism indices in the two groups were assessed before treatment and 3 months after treatment. Adverse effects were compared between groups.*

Results: *The study group showed significantly higher red blood cell count, haemoglobin level as well as haematocrit after treatment compared to control group ($p > 0.05$). Also, total iron binding capacity, and serum iron and ferritin levels were significantly higher in the study group than in the control group ($p < 0.05$).*

Conclusion: *Roxadustat combined with L-carnitine significantly reduces anemia and improves iron metabolism without increasing adverse reactions. However, there is a need for additional studies to assess the therapeutic potential of this combined regimen.*

Keywords: *Roxadustat, L-carnitine, Chronic renal failure, Anemia, Efficacy*

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INTRODUCTION

Chronic renal failure (CRF) is commonly encountered in the nephrology, with haemodialysis being a frequent treatment [1]. Chronic renal failure (CRF) patients often develop anemia after haemodialysis due to reduced erythropoietin (EPO) production by the impaired kidneys, thus inhibiting haematopoiesis. [2]. Prevalence of anemia in CRF patients ranges

from 70 to 90 % [1]. Anemia in these patients may lower immunity, exacerbate their condition, and increase mortality, necessitating urgent treatment [3].

Roxadustat is a novel hypoxia-inducible factor-prolyl hydroxylase inhibitor, upregulates endogenous EPO production, improves iron metabolism, reduces hepcidin levels, and promotes erythropoiesis, thus alleviating anemia [4,5]. L-carnitine is a compound essential for mammalian energy metabolism particularly in myocardial cells [6,7]. It preserves red blood cell (RBC) functionality and extends RBC lifespan, thus effectively relieving anemia [8].

High doses of a single drug frequently lead to drug resistance and diminished therapeutic effectiveness [9]. Combined effect of roxadustat and L-carnitine in treating dialysis-induced anemia in CRF patients remains underexplored, highlighting the need for more investigation. Therefore, this study was aimed at investigating the efficacy of oral roxadustat combined with L-carnitine in managing anemia in CRF patients undergoing dialysis.

METHODS

Subjects

This study was a retrospective analysis of 120 CRF patients with dialysis-induced anemia treated at Xinjiang Armed Police Crops Hospital (Xinjiang Uygur Autonomous Region, Xinjiang, China) between March 2020 and March 2023. The patients were randomised into study (n = 54) and control groups (n = 46). This study received approval from the Medical Ethics Committee of Xinjiang Armed Police Crops Hospital (approval no. 2021ky008-ks001) and adhered to the Declaration of Helsinki guidelines [10].

Inclusion criteria

Patients who met the China Expert Consensus diagnostic criteria for dialysis-induced anemia [11], had undergone haemodialysis for over one year, maintained a stable condition, weighed at least 45 kg, and aged 18 - 70 y with comprehensive clinical records.

Exclusion criteria

Patients with pre-haemodialysis anemia or malnutrition, drug allergies, recent blood transfusion or donation (within the past month), presence of serious cardiovascular disease, hypertension, coagulopathy, tuberculosis, acute and chronic blood disorders or chronic bleeding conditions such as gastric ulcers and internal haemorrhoid bleeding. Out of the 120 patients screened, 100 met the study criteria.

Treatments

Both groups underwent haemodialysis using a Jinbao machine for 4.5 h three times per week, and received folic acid and antihypertensive medications. Control group received oral roxadustat (FibroGen (China) Medical Technology Development Co., Ltd., SFDA approval no.: H20180024; Specification: 20 mg/capsule). Patients weighing 45 - 60 kg took 100 mg, while those ≥ 60 kg took 120 mg, thrice a week. Dosage was adjusted every 4 weeks to maintain haemoglobin (Hb) between 100 - 120 g/L for 3 months.

Study group received L-carnitine injection (2 g, Huiyinbi Cohort Fuzhou Pharmaceutical Co., Ltd., SFDA approval no. H20113065; specification: 5 mL/2 g) administered via the venous jug before the end of each dialysis session for 3 months.

Evaluation of parameters/indices

Haematological parameters

Before treatment and 3 months after treatment, 2 mL of fasting venous was collected, centrifuged (10 min, 3,500 rpm) for serum separation, and stored at -40 ℃. Haemoglobin (Hb), RBC count, and haematocrit (Hct) were determined using a BC-5000 automatic blood cell analyzer (Nanjing Vedeng Medical Co., Ltd.).

Efficacy was assessed by Hb increase and symptom relief. Outcomes were classified as markedly effective (post-treatment Hb increase of ≥ 30 g/L with symptom improvement), effective (post-treatment Hb increase 15 – 29 g/L with symptom improvement), ineffective (failure to meet the above criteria). Overall response rate was calculated using Eq 1.

ORR = ((ME+E)/TC)100 …….. (1)

ORR = Overall response rate, ME = Markedly effective, E = Effective, TC = Total cases

Iron metabolism indices

Iron metabolism indices such as total iron binding capacity (TIBC), serum iron (FE), and ferritin in both groups were assessed using an automatic biochemical analyzer before treatment and 3 months after treatment.

Adverse reactions

Adverse reactions such as gastrointestinal function, hypertension, and fever in both groups within 6 months were recorded and compared.

Statistical analysis

Data was analysed using Statistical Packages for Social Sciences (SPSS) version 20.0 (IBM, Armonk, NY, USA) and GraphPad 8 (San Diego, USA) was used for graphic presentation. Measurement data are presented as mean ± standard deviation (SD) and compared using independent-samples T test and paired t test. Categorical data are displayed as frequency and percentages and compared using chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline clinical data

There was no significant difference in baseline clinical data (age, gender, body mass index, dialysis time, course of disease, and place of residence) in both groups ($p > 0.05$; Table 1).

Anemia indices

There was no significant difference in Hb, RBC count and Hct between the two groups before treatment ($p > 0.05$). However, study group showed significantly higher Hb (Figure 1 A), RBC (Figure 1 B), and Hct (Figure 1 C) after treatment compared to control group ($p < 0.05$; Figure 1).

Table 1: Baseline clinical data (N, %)

Factor		Study (n=54)	Control (n=46)	χ^2	*P*-value
Age (years)	≥55	20(37)	15(32.6)	0.214	0.644
	< 55	34(62.9)	31(67.4)		
Gender	Male	28(51.9)	25(54.3)	0.062	0.803
	Female	26(48.1)	21(45.6)		
Body mass index (kg/m²)	≥23	18(33.3)	20(43.5)	1.085	0.298
	< 23	36(66.7)	26(56.5)		
Dialysis time (months)	≥15	19(35.2)	18(39.1)	0.166	0.684
	< 15	35(64.8)	28(60.9)		
Course of disease (years)	≥2	21(38.9)	19(41.3)	0.060	0.806
	< 2	33(61.1)	27(58.7)		
Place of residence	Rural area	35(64.8)	25(54.3)	1.134	0.287
	Urban area	19(35.2)	21(45.7)		

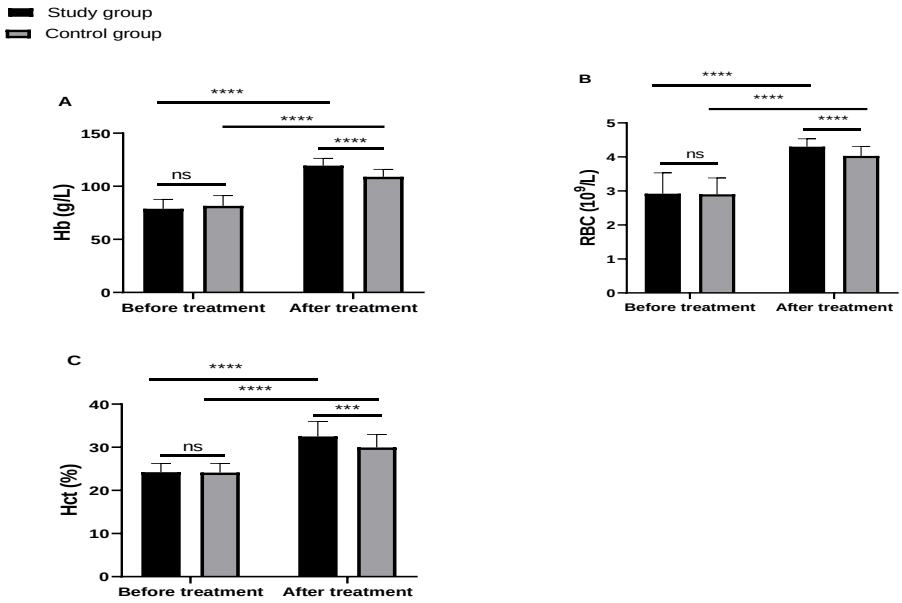

Figure 1: Anemia-related indices. A: Level of Hb. B: Level of RBC count. C: Level of Hct between the two groups before and after treatment. Ns means $p > 0.05$, $^{***}p < 0.001$, $^{****}p < 0.0001$; Hb: Hemoglobin; RBC: red blood cell; Hct: Hematocrit

Iron metabolism indices

There was no significant treatment in levels of TIBC, FE and ferritin between the two groups before treatment (p > 0.05). However, study group sowed significantly higher TIBC, FE, and ferritin compared to control group (p < 0.05; Figure 2).

Efficacy

Study group demonstrated significantly higher overall response rate compared to control group (p < 0.05; Table 2).

Incidence of adverse reactions

There was no significant difference in the incidence of adverse reactions between the groups (p > 0.05; Table 3).

DISCUSSION

Dialysis-induced anemia in CRF patients is a consequence of the progression of various chronic renal diseases, characterized by retained metabolic products, renal dysfunction and internal environment imbalance [12].

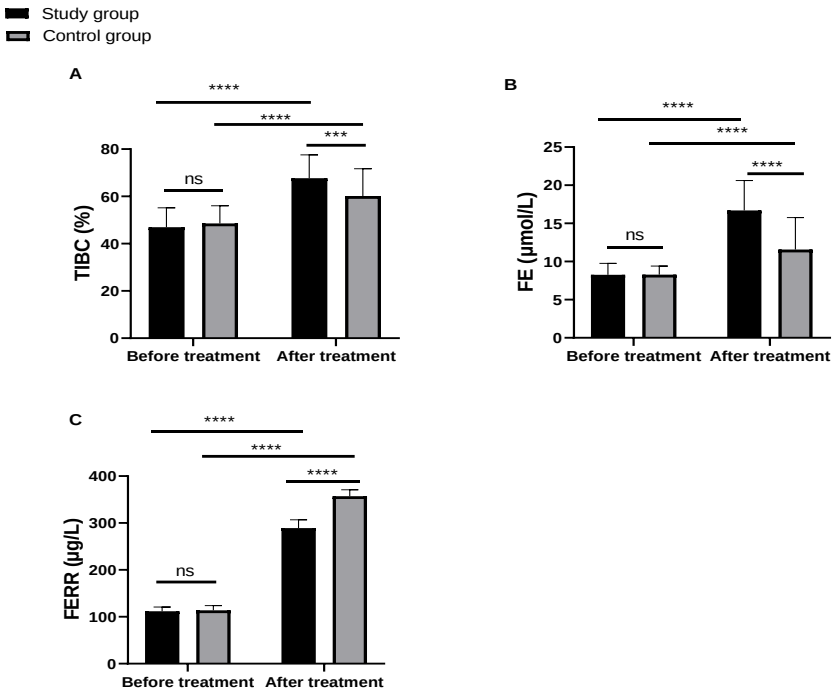

Figure 2: Iron metabolism indices between the two groups. A: Level of TIBC. B: Level of FE. C: Level of FERR between the two groups before and after treatment. ***Note:*** Ns means p > 0.05. ***P < 0.001, ****p < 0.0001. TIBC: Total iron binding capacity, FE: serum iron, FERR: Ferritin

Table 2: Comparison of efficacy between the two groups (N, %)

Group	Markedly effective	Effective	Ineffective	Overall response rate
Study (n=54)	27(50.00）	23(42.59）	4(7.41)	50(92.59)
Control (n=46)	19(41.30)	17(36.96)	10(21.74)	36(78.26)
χ^2	0.756	0.329	4.238	4.238
P-value	0.385	0.566	0.039	0.039

Table 3: Incidence of adverse reactions

Group	Weakened gastrointestinal function	Increased blood pressure	Fever	Total adverse reaction
Study (n=54)	2(3.70)	1(1.85)	1(1.85)	4(7.40)
Control (n=46)	2(4.35)	2(4.35)	1(2.17)	5(10.87)
χ^2	0.027	0.532	0.013	1.548,
P-value	0.870	0.466	0.909	0.214

Without timely effective treatment, it may trigger hypoxia, cardiovascular diseases, and reduced dialysis efficacy, posing significant risks to patient health and survival [13]. Treating dialysis-induced anemia in CRF often involves supplementing haematopoietic adjuvants to enhance RBC and Hb production [14]. Roxadustat, a novel agent, resolves anemia by inhibiting hypoxia-inducible factor prolyl hydroxylase, thus enhancing endogenous erythropoietin synthesis [15].

Prior research has revealed that L-carnitine supplementation significantly alleviates dialysis-induced anemia in CRF patients [16]. Accordingly, this study assessed combined effect of roxadustat and L-carnitine on dialysis-induced anemia. The results revealed that study group showed significant higher Hb, RBC, Hct, TIBC, FE, and ferritin after treatment compared to control group. This suggests that roxadustat combined with L-carnitine is more effective compared to roxadustat alone in restoring Hb, RBC, Hct, TIBC, FE, and ferritin levels in CRF patients undergoing dialysis. Also, study group exhibited significantly higher overall response rate, indicating the superior efficacy of the combination therapy. Roxadustat enhances iron absorption and transport by stabilizing hypoxia-inducible factor prolyl hydroxylase, while L-carnitine facilitates energy conversion from fat, potentially aiding in weight management [17-19]. The synergistic action likely contributes to the improved outcomes observed.

Study by Wanic-Kossowska *et al* [20] found that L-carnitine combined with erythropoietin effectively treats anemia in haemodialysis CRF patients, suggesting the advantage of combination therapy. Furthermore, there was no significant difference in incidence of adverse reactions between the two groups, thus indicating safety of the combined therapy.

Limitations of the study

This retrospective nature and small sample size of this study may limit generalizability of the findings. Also, lack of long-term follow-up may limit prevents a comprehensive understanding of the prolonged effects of this combination treatment on CRF patients with dialysis-induced anemia.

CONCLUSION

Roxadustat in combination with L-carnitine is more effective in treating dialysis-induced anemia in patients with CRF, improves both anemia-related and iron metabolism indices without increasing adverse effects. Future studies should focus on long-term outcomes to better assess the therapeutic potential of this combined regimen.

DECLARATIONS

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Ethical approval

The Medical Ethics Committee of Xinjiang Armed Police Crops Hospital, China approved this study (2021ky008-ks001).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Chun Zhang, Liutong Shang and Zhenjiang Liu conceived and designed the study, and drafted the manuscript. Lianqing An, Wei Liu and Yajun Zhang collected, analyzed and interpreted the experimental data. Yajun Zhang and Zhenjiang Liu revised the manuscript for important intellectual content. All authors read and approved the final draft of the manuscript for publication.

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