Original Article

Safety and effectiveness of recombinant human erythropoietin coupled with different doses of Roxadustat for treatment of renal anemia in patients on maintenance hemodialysis

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Received April 12, 2023; Accepted August 12, 2023; Epub August 15, 2023; Published August 30, 2023

Abstract: Objective: To investigate the safety and efficacy of recombinant human erythropoietin (rHuEPO) in combination with different doses of Roxadustat in treating renal anemia in patients on maintenance hemodialysis. Methods: Eighty patients with renal anemia on maintenance hemodialysis treated in Shuyang Hospital of Traditional Chinese Medicine from January 2020 to December 2021 were selected as study subjects, and they were divided into a study group (n=40, high-dose Roxadustat + rHuEPO therapy) and a control group (Con) (n=40, low-dose Roxadustat + rHuEPO therapy) in accordance with different therapies. The effects of anemia therapy, changes in anemia indicators (hemoglobin (Hb), hematocrit (Hct)), changes in iron metabolism indicators (transferrin saturation (TSAT), serum ferritin (SF)), changes in oxidative stress indicators Malondialdehyde (MDA), Superoxide Dismutase (SOD), and changes in microinflammatory indicators IL6, CRP were compared between the two groups. The occurrences of adverse effects during therapy were counted and compared between the two groups. Results: The therapy efficiency of the study group was 97.50% (39/40), which was higher than 85.00% (34/40) in the control group (\(P=0.048\)). The contents of Hb, Hct, TSAT, and SF were higher in the study group than the Con after therapy (all \(P<0.001\) or \(P=0.001\)). The contents of MDA, IL6, and CRP were significantly lower in the study group than the Con after therapy (all \(P<0.001\)). The occurrence of adverse effects was 10.00% in the study group, which was higher than 5.00% in the Con, but the difference was not significant (\(P=0.396\)). Conclusion: The combination of rHuEPO and high-dose Roxadustat (120 mg/time) has a better effect on improving anemia symptoms in maintenance hemodialysis patients than those who take low dose Roxadustat (100 mg/time). It can significantly improve anemia and iron metabolism indicators and alleviate patients’ inflammation and oxidative stress levels.

Keywords: Recombinant human erythropoietin, Roxadustat, maintenance hemodialysis, renal anemia, therapeutic effect, safety

Introduction

In recent years, with socioeconomic development and the prevalence of unhealthy lifestyles, chronic kidney disease has been increasing, affecting about 10% of the global population. It is a global social and economic burden. Data show that the prevalence of chronic kidney disease among adults in China is close to 11%, and the number is rising yearly [1, 2]. Hemodialysis is an essential measure to improve the clinical symptoms of chronic kidney disease. By the end of 2019, the number of dialysis patients in China had reached 735,000, including about 623,000 hemodialysis patients, with an annual growth rate of 11% [3]. Notably, even though hemodialysis can remove metabolic wastes and toxins from the body, its clearance rate is only about 20% of that of the kidneys. The impaired function can lead to complications such as anemia, abnormal bone metabolism, and metabolic acidosis, which affect the patient's therapy process [4, 5]. Renal anemia is one of the most common complications in hemodialysis patients with chronic kidney disease, and its occurrence increases yearly as the disease worsens [6]. It has been pointed out that when the individual glomerular filtration rate is lower than 60 ml/min·1.73 m², 21.5% will have varying degrees of anemia, which is an essential reason for the reduced quality of life in hemodialysis patients with chronic kidney diseases [7]. Recombinant
human erythropoietin (rHuEPO) is mainly used for the current therapy of renal anemia, but its use increases the risk of epilepsy, hypertension, and hypersensitivity [8]. Rosarostat is the first HIF-PHD inhibitor approved for marketing in China, and studies have confirmed that the drug has better safety, efficacy, and long-term benefits in patients with chronic kidney disease [9]. However, there is still limited research on different doses of Rosarostat in maintenance hemodialysis patients, thus appropriate guidance for the safe and rational use of medication for patients is not available. Based on previous studies, the feasibility of combination therapy has been demonstrated through quantitative comparison, which can provide good theoretical support for subsequent treatment.

Materials and methods

Research design

In this retrospective study, the application value of combined recombinant human erythropoietin with different doses of rosacea in maintenance hemodialysis patients was analyzed. The study subjects were screened based on inclusion and exclusion criteria by consulting hospital cases, and divided into a study group and a control group based on different treatment regimes. To ensure compatibility, the number of cases in the study and control groups was set at 1:1. The laboratory indicators during hospitalization and follow-up of the two groups of patients were compared and analyzed. The Shuyang Hospital of Traditional Chinese Medicine Ethics Committee approved this study. The specific research design is shown in Figure 1.

Study population

According to the following inclusion and exclusion criteria, maintenance hemodialysis patients who received treatment in our hospital from January 2020 to December 2021 were screened. Forty patients with recombinant human erythropoietin (rHuEPO) and high-dose Roxadustat (120 mg/dose) were assigned into
a study group. Then, according to the 1:1 matching method, 40 patients hospitalized in our hospital during the same period using rHuEPO coupled with a low dose of Roxadustat (100 mg/dose) were selected as the control group. For every high-dose patient randomly matched with low-dose patients, the age difference was within 2 years. All patients in the control group received rHuEPO (manufacturer: Shenyang Sansheng Pharmaceutical Co., Ltd., specification: 3000 IU/dose, approval number: Guoyao Zhunzi S19980074, application dose: 100 IU/kg per week, completed in three injections, used once per dialysis day) in combination with low-dose Roxadustat (manufacturer: Fabojin Pharmaceutical Technology Development Co., Ltd., specification: 50 mg/capsule, approval number: National Drug Approval No. H20180024, application dose: 100 mg/time, 3 times/week) for treatment. For the patients in the study group, the dosage of rHuEPO was the same as that of the control group, while Roxadustat was applied at high-dose (120 mg/dose, 3 times/week).

Inclusion criteria: (1) Patients with an age of 18-75; (2) Patients with complete clinical data; (3) Patients who had continuously received hemodialysis treatment for more than 3 months; (4) Patients who were treated with rHuEPO combined with Roxadustat; (5) Patients who were diagnosed with anemia.

Exclusion criteria: (1) Patients with mental disorders; (2) Patients with acute infections, hematologic disease, or malignant tumors; (3) Patients with severe visual, auditory, or articulatory impairments; (4) Patients with anemia caused by other disease.

Observation indicators and endpoint

(1) The effective rates of treatment for two groups of patients were as follows: significant improvement: Hb level increased by more than 30 g/L from baseline or a 10% increase in Hct at the end of the treatment period; effective improvement: Hb level increased by more than 15 g/L from baseline or a 5% increase in Hct at the end of the treatment period; and ineffective improvement: no improvement in Hb and Hct at the end of the treatment period. Effective rate = number of (significant improvement + effective improvement)/total number of cases × 100% [10]; (2) Blood sample were collected from two groups of patients before and after treatment, and the levels of anemia-related indicators Hb and Hct, the levels of iron metabolism indicators TSAT and SF, the levels of MDA and SOD, and the levels of IL-6 and CRP between the two groups of patients were compared. The above indicators were all detected using enzyme-linked immunosorbent assay (TSAT: XG-01H7846 (Shanghai Sig Bio); SF: JN(Bio)(07)-E6681 (Jining Shanghai); MDA: EKF60157 (Amyjet Scientific Inc.); SOD: XG-E989561 (Shanghai Sig Bio); IL-6: ab178013 (Abcam); CRP: ab260058 (Abcam)). The instrument used for examination was a Hitachi 7180 fully automatic biochemical analyzer; (3) The incidence of various adverse reactions such as dizziness, diarrhea, nausea, and vomiting during the treatment period were compared between the two groups of patients.

The observation endpoint is 12th week after the treatment.

Statistical methods

Categorical data were expressed as absolute values and relative frequencies (%), and continuous variables were expressed as mean and standard deviation (SD) or median (interquartile range). For continuous data with normal distribution and homogeneity of variance, the independent sample t-test was used for between-group comparison. Otherwise, the Mann-Whitney U test was used for comparison. The chi-square or Fisher’s exact test was used to compare categorical variables. \( P<0.05 \) indicated a significant difference.

Results

Comparison of basic data

Baseline data were compared between the two groups and the results revealed that there was no apparent distinction in terms of age, BMI, duration of disease, gender, or type of primary disease (all \( P>0.05 \)) (Table 1).

Comparison of therapy efficiency

The total effective rate was 97.50% in the study group, which was higher than that of 85.00% (34/40) in the Con (\( P=0.048 \)) (Figure 2).

Comparison of anemia-related indices

Before therapy, there was no apparent distinction in Hb and Hct levels between the two
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Table 1. Comparison of basic features (X ± s)/[n]

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Study group (n=40)</th>
<th>Control group (n=40)</th>
<th>t/χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>27</td>
<td>0.853</td>
<td>0.356</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>59.82±4.86</td>
<td>60.18±4.97</td>
<td>0.328</td>
<td>0.744</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.88±3.42</td>
<td>23.06±2.43</td>
<td>0.271</td>
<td>0.787</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>3.35±0.96</td>
<td>2.99±0.93</td>
<td>1.703</td>
<td>0.092</td>
</tr>
<tr>
<td>Type of primary disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>10</td>
<td>11</td>
<td>0.447</td>
<td>0.780</td>
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<tr>
<td>Hypertensive kidney damage</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>15</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>135.62±10.11</td>
<td>134.86±11.62</td>
<td>0.512</td>
<td>0.663</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>73.98±5.11</td>
<td>74.01±4.89</td>
<td>0.449</td>
<td>0.861</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.53±1.65</td>
<td>10.77±1.53</td>
<td>0.441</td>
<td>0.468</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>589.63±40.11</td>
<td>590.79±35.89</td>
<td>1.001</td>
<td>0.341</td>
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<td>History of cardiovascular disease</td>
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<td>1</td>
<td>0.536</td>
<td>0.557</td>
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<tr>
<td>History of stroke</td>
<td>3</td>
<td>0</td>
<td>0.441</td>
<td>0.812</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>0</td>
<td>1</td>
<td>0.6320</td>
<td>0.441</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>2</td>
<td>1</td>
<td>0.553</td>
<td>0.639</td>
</tr>
<tr>
<td>History of thromboembolic events</td>
<td>2</td>
<td>2</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1</td>
<td>0</td>
<td>0.6320</td>
<td>0.441</td>
</tr>
</tbody>
</table>

BMI: body mass index; BP: blood pressure.

Figure 2. Comparison of therapy efficiency. The treatment effective rate in the study group was 97.50% (39/40), which was higher than the 85.00% (34/40) in the control group (P<0.05). SG: Study group; CG: Control group.

changes in iron metabolism indices

Before therapy, there was no obvious distinction in TSAT and SF contents between the two groups (P>0.05). After the therapy, the TSAT and SF contents showed a significant increase in both groups (P<0.001, Figure 4), and the TSAT and SF contents in the study group were higher than those in the control group (P<0.001).

changes in oxidative stress indices

Before therapy, there was no obvious distinction in MDA and SOD contents between the two groups (P>0.05). After therapy, the MDA content in the study group was lower than that in the control group (P=0.002, Figure 5).

changes in microinflammatory indices

There was no obvious distinction in IL6 and CRP contents between the two groups before therapy (P>0.05). In contrast, the IL6 and CRP contents showed a decrease compared to those before therapy (P<0.001, Figure 6), and the IL6 and CRP contents in the study group
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Figure 3. Comparison of anemia-related indices. The levels of Hb (A) and Hct (B) in the study group were significantly higher (all \( P<0.05 \)). SG: Study group; CG: Control group; Hb: Hemoglobin; Hct: Hematocrit.

Figure 4. Changes in iron metabolism indices. After therapy, the TSAT (A) and SF (B) contents in the study group were significantly higher (all \( P<0.05 \)). SG: Study group; CG: Control group; TSAT: transferrin saturation; SF: serum ferritin.

Figure 5. Changes in oxidative stress indices. The MDA contents in the study group were lower (\( P<0.05 \)) (A). The difference in SOD contents was not significant (\( P>0.05 \)) (B). # represents a significant difference in groups for the same index. SG: Study group; CG: Control group; MDA: Malondialdehyde; SOD: Superoxide Dismutase.

Comparison of the occurrence of adverse therapy effects

The incidence of adverse effects in the study group was 10.00% (4/40), which was slightly but non-significantly higher than 5.00% (2/40) in the control group (Figure 7).

Discussion

In recent years, the number of patients with chronic kidney disease has continued to increase. Chronic kidney disease is a general term for heterogeneous diseases of chronic kidney structure and dysfunction caused by various reasons. According to epidemiological survey data, in 2014, the prevalences of diabetes and hypertension among people over 15 in China were...
35.1% and 14.25%, respectively. These patients need to take drugs long term, which will damage the kidney, increasing the prevalence of diabetic nephropathy and hypertensive nephropathy [11]. According to research data, 10.8% of people aged 18 and above in China suffer from chronic kidney disease, meaning that approximately 120 million people in China suffer from chronic kidney disease. According to statistics [12], approximately 2% of patients with chronic kidney disease experience end-stage kidney disease yearly. This group of patients has a high risk of death and a heavy disease burden. They can only choose kidney replacement therapy, hemodialysis, or peritoneal dialysis, which severely burdens their families and society. Therefore, chronic kidney disease is a severe social problem. Chronic kidney disease affects multiple organs and systems of the body, among which the first cause of death is chronic kidney disease [13]. Studies have also confirmed renal anemia increases the risk of vascular access thrombosis in dialysis patients [14].

HF-PHI is a novel small-molecule oral drug for the treatment of renal anemia. By inhibiting HF prolyl hydroxylase, HF-PHI stabilizes HF levels in vivo, and then regulates the transcription and expression of downstream target genes of the HIF signaling pathway. By promoting the production of erythropoietin (EPO) with endogenous physiologic concentration and receptor expression in the body, HF-PHI promotes the expression of proteins related to iron metabolism, while reducing the level of ferrimodulin, and comprehensively regulates the body to promote the production of red blood cells. Roxallistat is the first approved HIF-PHI drug in China, but there are few studies on the use of Roxallistat in the treatment of elderly patients with non-dialysis CKD anemia. Roxallistat promotes the expression of iron metabolism-related proteins in the regulation of iron metabolism, reduces ferrimodulin, and improves the absorption and utilization of iron. However, the adverse drug reactions of rosallistat are also of concern. For example, nausea, chest discomfort and dizziness, so the dose of rosallistat is worth exploring. In this paper, the therapeutic response of low and high doses of rosallistat was tested innovatively.

This study analyzed the validity of rHuEPO with different doses of Roxadustat in the therapy of renal anemia in maintenance hemodialysis. The results revealed that patients in the study group treated with rHuEPO in combination with high-dose Roxadustat had a better therapy efficiency in comparison to the control group treated with rHuEPO in combination with low-dose Roxadustat (97.50% vs. 85.00%). In a study of 84 patients with renal anemia on maintenance hemodialysis, the treatment efficacy in the control group treated with rHuEPO in combination with low-dose Roxadustat was 76.19%, notably less than that of the observation group treated with recombinant erythropoietin in combination with high-dose Roxadustat (92.85%) [15], which is similar to the results of this study. It has been found that patients with chronic kidney disease have a higher probability of developing anemia, which reduces their immune function and increases their risk of developing various diseases [11]. Therefore, actively correcting anemia is of great significance. However, iron supplementation alone can increase adverse reactions such as constipation, while on the other hand, the absorption effect of iron

Figure 6. Changes in microinflammatory indices. The contents of IL-6 (A) and CRP (B) in patients of the study group were lower (P<0.05). # represents an obvious distinction between groups for the same index. SG: Study group; CG: Control group; IL-6: Interleukin-6; CRP: C-reactive protein.
is poor. The combination of rHuEPO and Roxadustat can significantly improve the treatment efficacy and the quality of life of patients during long-term follow-up [16].

Iron supplementation is an essential measure to improve the symptoms of anemia. However, patients undergoing maintenance hemodialysis may suffer from reduced erythropoietin (EPO), which is an essential cause of their renal anemia, and iron supplementation alone has limited effect in such patients [17]. rHuEPO helps to improve the symptoms of EPO reduction in patients with nephrogenic anemia and helps to directly increase the content of EPO in the body and the red blood cell content, which, together with iron supplementation, can improve the therapeutic effect [18].

However, with the promotion of this therapy in clinical practice, its shortcomings have gradually become apparent; that is, combination therapy can increase the risk of hypersensitivity in patients with renal anemia. Therefore, the application value of Roxadustat in reducing adverse reactions has been emphasized [19, 20]. Rosasta is a HIF-PHI, which can inhibit HIF-PHI activity and help to increase the content of HIF in the body, thus improving the anemic state.

To further investigate the therapeutic mechanism of Roxadustat, a comparison of oxidative stress and microinflammatory values before and after therapy was also conducted, showing that MDA, IL6, and CRP contents were decreased in the study group compared to the control group. A prospective randomized controlled trial conducted in patients with renal anemia on maintenance hemodialysis found that the addition of Roxadustat to iron supplementation significantly improved the therapeutic effect and also improved the oxidative stress response of the body, which has a positive impact on accelerating the improvement of symptoms [21, 22].

We believe that although maintenance hemodialysis has a specific effect on prolonging the survival time and improving the quality of life of patients with chronic kidney disease, it cannot wholly replace the patient’s kidney function. Many metabolites are left in the human body, which can cause toxic damage to the patient’s hematopoietic system. This process is often accompanied by varying degrees of oxidative stress reactions. As the patient’s kidney function deteriorates, a large amount of oxygen free radicals will be released, leading to peroxidation damage in the body [23, 24]. In contrast, it has been pointed out that iron is an oxidant, and its supplementation further aggravates oxidative stress in the organism [25, 26]. The results of this study may be related to the ability of Roxadustat to exert antioxidant effects independently of the inflammatory state, which has been confirmed by more studies. Finally, the safety comparison shows that although the increased dose of Roxadustat raised the frequency of adverse effects, the difference was not significant, supporting its therapeutic safety.

Conclusion

rHuEPO, combined with high-dose Roxadustat, is effective in improving anemia symptoms in maintenance hemodialysis patients, notably improving the anemia index and iron metabolism index and alleviating the inflammation sta-
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tus and oxidative stress without increasing adverse reactions. It is recommended to be promoted in clinical practice.

Disclosure of conflict of interest

None.

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