

Clinical study of Shengxuening tablet combined with rHuEPO for the treatment of renal anemia of maintenance hemodialysis patients

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Abstract. The aim of the present study was to investigate the clinical effects of Shengxuening tablet (silkworm excrement) combined with recombinant human erythropoietin (rHuEPO) for the treatment of renal anemia of maintenance hemodialysis (MHD) patients. Seventy-two MHD patients with renal anemia were included in the study and randomly divided into the control (n=34) and observation (n=38) groups. Patients in the control group were treated by hypodermic injection of 100-150 U/(kg·w) rHuEPO and patients in the observation group were treated by rHuEPO + 1.0 g t.i.d. p.o. Shengxuening tablet. The two groups were assisted by conventional treatments including iron, folic acid, vitamin B12 and L-carnitine. After 3 and 6 months, improvement of anemia was compared. After 3 months, the hemoglobin, hematocrit, serum ferritin and transferrin saturation levels of the observation group were significantly higher than those of the control group (p<0.05). In addition, C-reactive protein and superoxide dismutase levels of the observation group were significantly lower than those of the control group (p<0.05). After 6 months, indices of the observation group were ameliorated while the improvement of control group was not obvious, and indices of the observation group were significantly higher than those of the control group (p<0.05). Consumption of rHuEPO in the observation group was significantly less than that of the control group, and the total effective rate was significantly higher than that of the control

group (p<0.05). In conclusion, Shengxuening tablet combined with rHuEPO was safe and effective for the treatment of renal anemia of MHD patients.

Introduction

Chronic renal failure is the final outcome of various renal diseases, such as chronic glomerulonephritis and diabetic nephropathy, and systemic diseases, such as heart and liver failure (1). Continuous improvement of various blood purification technology and equipment have significantly improved the living quality and lifetime of patients with end-stage renal disease (ESRD) (2).

Approximately 80-85% ESRD patients have renal anemia and 55-70% exhibit moderate and severe anemia (3). Maintenance hemodialysis (MHD) can further aggravate the anemia, filter out some recombinant human erythropoietin (rHuEPO) and reduce the curative efficacy (4). A number of clinical studies have indicated that Shengxuening tablet were very effective for iron deficiency anemia, blood loss anemia and perinatal anemia (5). However, the clinical application of Shengxuening tablet is poor.

The aim of the present study was to investigate the clinical effects of Shengxuening tablet combined with rHuEPO for the treatment of renal anemia of MHD patients. After administration of the treatment, it was identified that Shengxuening tablet combined with rHuEPO was safe and effective for the treatment of these patients.

Patients and methods

Patients. Seventy-two MHD patients, diagnosed with renal anemia at the Zhengzhou TCM Hospital (Henan, China) from March, 2014 to March, 2015 were included in the study. The patients conformed to the diagnostic criteria of chronic nephropathy proposed by the Kidney Disease Improving Global Outcomes (<http://kdigo.org>). Anemia criteria referred to male hemoglobin (Hb) <120 g/l and female Hb <110 g/l and excluded the anemia caused by other diseases, such as iron

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deficiency anemia, hemorrhagic anemia, aplastic anemia and multiple myeloma.

Inclusion criteria for the present study were: i) age ≥ 8 and < 75 years; ii) conformed to the abovementioned anemia criteria; and iii) first-time treatment, without adverse reactions. Exclusion criteria for the study were: i) patients with secondary hematological diseases, severe heart, liver and other organ dysfunction, severe hypotension; ii) patients with irrefractable anemia and requiring blood transfusion; iii) patients with renal transplantation history, severe secondary parathyroid function (iPTH $> 1,000$ pg/l), active ulcerative disease, malignant tumor, active infection, severe malnutrition; and iv) patients with poor compliance.

Approval for the study was obtained from the ethics committee of the Zhengzhou TCM Hospital. Informed consent of patients and families was also obtained. Subsequently, the patients were randomly divided into the control (n=34) and observation (n=38) groups. The control group included 18 men and 16 women, with an age range of 52-73 years, and an average of 63.5 ± 6.7 years; serum creatinine ranged from 436.7 to 698.3 $\mu\text{mol/l}$, average 546.2 ± 54.5 $\mu\text{mol/l}$; weight ranged from 58.6 to 72.5 g, average of 63.3 ± 5.8 kg; urea nitrogen ranged from 16.5 to 37.4 mmol/l, average of 24.1 ± 8.2 mmol/l. The observation group included 20 men and 18 women, with an age range of 48-72 years and an average of 64.2 ± 6.9 years; serum creatinine ranged from 443.6 to 721.4 $\mu\text{mol/l}$, average of 569.8 ± 62.3 $\mu\text{mol/l}$; weight ranged from 57.3 to 71.6 g, average of 62.9 ± 5.7 kg; urea nitrogen ranged from 17.2 to 35.5 mmol/l, average of 25.3 ± 8.8 mmol/l. Differences of the two groups regarding gender, age, weight, urea nitrogen and serum creatinine levels were not statistically significant ($p > 0.05$).

Method. The patients in the control group were administered with hypodermic injection of 100-150 U/(kg·w) rHuEPO (3SBio, Inc., Shenyang, China). The Hb was regularly monitored, and the dose was reduced by 25-30% if Hb ≥ 110 g/l. The patients were observed for one month, by continually reducing the dose by 25-30% if Hb ≥ 110 g/l, and maintained treatment with the minimum dose. The patients in the observation group were administered with rHuEPO+1.0 g t.i.d. p.o. Shengxuening tablets (GYZZ Z20030088, 0.25 g/piece, sodium iron chlorophyllin > 0.15 mg/piece; Wuhan United Pharmacy, Wuhan, China). The two groups were assisted by conventional treatments including iron, folic acid, vitamin B12 and L-carnitine.

Hemodialysis therapy. The dialysis machine used was Dialog+ Dialysis system machine (B. Braun Melsungen AG, Melsungen Germany). Hemodialysis filtration and hemodialysis perfusion was applied on the basis of general dialysis, 2-3 times/week and 4 h per time. The bicarbonate dialysis liquid system, blood flow rate was of 200-250 ml/min, dialysis fluid flow rate was of 500 ml/min, and dialysis fluid temperature was of 36.5°C. Drugs were combined to control blood pressure, blood glucose and electrolyte balance.

Observation indices. After 3 and 6 months, the improvement of anemia of the two groups were compared including Hb, hematocrit (Hct), serum ferritin (SF) and transferrin saturation (TSAT) levels; inflammatory indices, including C-reactive protein (CRP), and superoxide dismutase (SOD)

Table I. Comparisons of the improvement of anemia index.

Group	Control group	Observation group	t	P-value
Pre-treatment				
Hb (g/l)	72.5 \pm 3.2	69.8 \pm 3.4	0.632	0.514
Hct (%)	23.4 \pm 5.6	22.5 \pm 5.2	0.427	0.326
SF (ng/ml)	154.3 \pm 23.4	146.7 \pm 25.5	0.531	0.428
TSAT (%)	17.8 \pm 6.3	16.6 \pm 6.1	0.963	0.694
After 3 months				
Hb	77.3 \pm 4.1	80.5 \pm 4.2	4.621	0.042
Hct	26.7 \pm 4.7	29.6 \pm 4.6	4.824	0.039
SF	223.5 \pm 26.9	258.5 \pm 25.7	4.932	0.037
TSAT	24.6 \pm 5.7	27.8 \pm 5.9	4.562	0.043
After 6 months				
Hb	79.4 \pm 4.3	83.3 \pm 4.5	5.321	0.026
Hct	27.5 \pm 4.8	33.4 \pm 4.5	5.426	0.024
SF	236.7 \pm 21.3	279.6 \pm 23.4	5.927	0.018
TSAT	26.3 \pm 5.3	30.2 \pm 5.5	5.648	0.022

Hb, hemoglobin; Hct, hematocrit; SF, serum ferritin; TSAT, transferrin saturation.

levels; as well as consumption of rHuEPO and improvement of total efficiency.

Statistical analysis. SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data were presented as mean \pm standard deviation. Comparison between groups was made using the Student's t-test. Enumeration data were expressed as a percentage. The comparison between groups was made using the χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Comparison of the improvement of anemia index. Prior to treatment, differences of Hb, Hct, SF and TSAT levels of the two groups were not statistically significant ($p > 0.05$). After 3 months of treatment, Hb, Hct, SF and TSAT levels of the observation group were significantly higher than those of the control group ($p < 0.05$). After 6 months of treatment, the above indices of the observation group were ameliorated while improvement of the control group was not obvious, and the observation group was significantly higher than the control group ($p < 0.05$) (Table I).

Comparison of the improvement of inflammation indices. Prior to treatment, differences of the CRP and SOD levels of the two groups were not statistically significant ($p > 0.05$). After 3 months of treatment, CRP and SOD levels of the observation group were significantly lower than those of the control group ($p < 0.05$). After 6 months of treatment, the above indices of the observation group further decreased while improvement of the control group was not obvious, and the observation group was significantly lower than the control group ($p < 0.05$) (Table II).

Table II. Comparison of the improvement of inflammation indices.

Group	Control group	Observation group	t	P-value
Pre-treatment				
CRP (mg/l)	8.2±1.3	8.4±1.2	0.127	0.302
SOD (U/l)	46.5±5.2	48.2±5.5	0.234	0.612
After 3 months				
CRP	6.3±1.1	5.7±1.3	4.521	0.041
SOD	43.2±4.3	40.6±4.4	4.326	0.043
After 6 months				
CRP	6.1±1.2	5.3±1.2	5.523	0.022
SOD	42.7±4.6	37.5±4.2	5.421	0.024

CRP, C-reactive protein; SOD, superoxide dismutase.

Comparison of rHuEPO dose and total efficiency. After 6 months, the consumption of rHuEPO in the observation group was significantly less than that of the control group, and the total effective rate was significantly higher than the control group ($p < 0.05$) (Table III).

Discussion

Renal anemia can lead to cardiac enlargement, ventricular hypertrophy, angina, congestive heart failure, menstrual cycle disorder, nocturnal penile erectile dysfunction, immune response abnormality, and increased MHD mortality (6). Causes of renal anemia of MHD patients includes (7): i) decreased EPO secretion or EPO reactivity; ii) uremic toxins' affecting of bone marrow hematopoietic microenvironment; iii) malnutrition, which resulted in a lack of iron, folic acid and vitamin B12; iv) potential bleeding; and v) shortened life of red cell and hemolysis. The lack of EPO is the most important factor. The appearance of rHuEPO has greatly promoted the treatment of anemia of ESRD patients, effectively improved anemia, enhanced the body's resistance, reduced the risk of infection, improved the quality of life and prolonged patient survival (8). Since iron is essential for hemoglobin synthesis, deficiency of iron is a leading cause that can affect the clinical effects of EOP (9). Common iron supplements include oral administration type and intravenous injection type. Oral administration is low in bioavailability and intravenous

injection can aggravate oxidative stress and result in a variety of complications (10).

Shengxuening tablet is a quasi-heme iron. It is a second-grade new medicine that is made from silkworm excrement and by modern manufacturing process. Its main component, sodium iron chlorophyllin, has a similar structure to heme. It is absorbed by the exclusive channel of heme receptor of small intestinal villi mucosa cells and is not affected by the competitive inhibition of other divalent metal ions or diet, and does not produce free ion or irritate the gastrointestinal tract (11,12). Additionally, sodium iron chlorophyllin can improve iron metabolism, increase the saturation of serum iron and transferrin, and promote hematopoiesis and improve anemia (13,14). Hb and Hct are the most important indices for the diagnosis of renal anemia, SF and TSAT are two important indices for the evaluation of iron metabolism, SF can reflect iron storage and the TSAT reaction cycle can reflect the available iron level. A previous study has shown that Shengxuening tablet can improve the content of serum iron and the saturation of transferrin of anemia rats, increase SF, and reduce transferrin as well as soluble transferrin receptor, suggesting that Shengxuening tablet is effective for improving iron storage and transportation, and promoting hemoglobin synthesis (15).

Micro-inflammatory state is a common low-level immune inflammation of MHD patients, which is closely related to cardiovascular complications, malnutrition and renal anemia and may seriously affect the prognosis of patients (16). CRP and SOD are important indices for the detection of the micro-inflammatory state of MHD patients. Iron therapy, especially intravenous iron, has been found to increase free iron and induce the peroxidation of lipid and protein, aggravate the microinflammation, and result in increased SOD and CRP (17-20). SOD, as an antioxidant enzyme representative, can remove oxygen-free radicals and block the damage caused by free radicals, thereby reflecting the level of oxidative stress (18-20).

The results of this study showed that 3 months later, Hb, Hct, SF and TSAT of the observation group were significantly higher than those of the control group. After 6 months, the above indices of the observation group further decreased while the improvement of control group was not obvious, and differences became increased. The consumption of rHuEPO of the observation group was significantly less than that of the control group and the total effective rate was significantly higher than the control group ($p < 0.05$). In conclusion, Shengxuening tablets combined with rHuEPO was safe and effective for the treatment of renal anemia of MHD patients.

Table III. Comparison of rHuEPO dosage and total efficiency

Group	rHuEPO dosage U/(kg·w)	Excellence ^a	Effective ^b	Ineffective	Total efficiency
Control (n=34)	106.5±26.6	7	10	17	17 (50.0)
Observation (n=38)	82.4±21.3	13	15	10	28 (73.7)
T (χ^2)	5.926 ^c				4.295 ^d
P-value	0.015				0.038

^aAnemia was significantly improved, Hb increased by ≥ 30 g/l, Hct increased by $\geq 10\%$; ^banemia was improved, Hb increased by 15-30 g/l, Hct increased by 5-10%; other cases were ineffective. rHuEPO, recombinant human erythropoietin. ^cT test, ^d χ^2 test.

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