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Correlation of EPO resistance with oxidative stress response and inflammatory response in patients with maintenance hemodialysis

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ABSTRACT

Objective: To study the correlation of erythropoietin (EPO) resistance with oxidative stress response and inflammatory response in patients with maintenance hemodialysis. **Methods:** A total of 184 patients with end-stage renal disease who received maintenance hemodialysis in Shaanxi Provincial People's Hospital between March 2015 and October 2016 were selected as dialysis group, 102 volunteers who received physical examination in Shaanxi Provincial People's Hospital during the same period were selected as control group, the EPO resistance index was assessed, the median was calculated, and serum oxidative stress and inflammatory response indexes were detected. **Results:** Serum T-AOC, SOD and CAT levels in dialysis group were significantly lower than those in control group while MDA, AOPP, IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels were significantly higher than those in control group; serum T-AOC, SOD and CAT levels in patients with high ERI were significantly lower than those in patients with low ERI while MDA, AOPP, IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels were significantly higher than those in patients with low ERI. **Conclusion:** The degree of EPO resistance in patients with maintenance hemodialysis is closely related to the activation of oxidative stress response and inflammatory response.

1. Introduction

Anemia is an important complication in patients with end-stage renal disease during maintenance hemodialysis, recombinant human erythropoietin (rh-EPO) is the common drug for renal anemia, and it can effectively promote the red blood cell maturation and improve the anemia status[1,2]. Nevertheless, some patients with maintenance hemodialysis still have EPO resistance, and conventional doses of rh-EPO can not effectively correct anemia or the rh-EPO dosage needs to be increased to correct anemia[3]. EPO resistance is an important factor affecting the therapeutic effect of renal anemia, but the specific occurrence mechanism is not clear. Oxidative stress and inflammation are the important pathological changes in the process of maintenance hemodialysis, and it is believed that the oxidative stress products and inflammatory mediators can affect the sensitivity of the EPO and participate in the occurrence of EPO resistance. In the following studies, we analyzed the correlation of EPO resistance with oxidative stress response and inflammatory response in patients with maintenance hemodialysis.

2. Research subjects and methods

2.1 General information of research subjects

A total of 184 patients with end-stage renal disease who received maintenance hemodialysis in Shaanxi Provincial People's Hospital between March 2015 and October 2016 were selected as dialysis group, all patients were with renal anemia and received rh-EPO treatment for more than 6 months, and patients with anemia caused by folic acid and vitamin B12 deficiency, and patients who used immune agents and were with history of blood transfusion within recent six months were excluded. 102 volunteers who received physical examination in Shaanxi Provincial People's Hospital during the same period were selected as control group, and all patients were without history of anemia or blood transfusion. Dialysis group

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included 107 men and 77 women that were 39-62 years old; control group included 60 men and 42 women that were 37-58 years old. There was no significant difference in general data between the two groups (P>0.05).

2.2 EPO resistance evaluation

The average monthly rh-EPO dosage and hemoglobin level of the patients were recorded during the treatment, and the EPO resistance index (ERI) = rh-EPO dosage (IU/month)/hemoglobin (g/L).

2.3 Serum oxidative stress and inflammatory response index detection

3-5 mL of cubital venous blood was collected from dialysis group of patients during treatment, 3-5 mL of cubital venous blood was collected from control group of volunteers during physical examination, the blood was centrifuged to get serum, the radioimmunoprecipitation kit was used to determine T-AOC, SOD, CAT, MDA and AOPP levels, and enzyme-linked immunosorbent assay kit was used to determine IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels.

2.4 Statistical methods

SPSS 19.0 software was used to input data, the median of ERI of dialysis group was calculated, patients with ERI < the median were judged as those with lower ERI, and patients with ERI the median was judged as those higher ERI. Differences in measurement data between two groups was by t test and P<0.05 indicated statistical significance in differences.

3. Results

3.1 Oxidative stress in patients with maintenance hemodialysis and its correlation with EPO resistance

Analysis of serum oxidative stress indexes T-AOC (U/mL), SOD (U/mL), CAT (U/mL), MDA (μmol/L) and AOPP (μmol/L) between dialysis group and control group was as follows: serum T-AOC, SOD and CAT levels in dialysis group were significantly lower than those in control group while MDA and AOPP levels were significantly higher than those in control group. Differences in serum T-AOC, SOD, CAT, MDA and AOPP levels were statistically significant between the two groups (P<0.05).

Analysis of serum oxidative stress indexes T-AOC, SOD, CAT, MDA and AOPP between dialysis group of patients with different ERI levels was as follows: serum T-AOC, SOD and CAT levels in patients with high ERI were significantly lower than those in patients with low ERI while MDA and AOPP levels were significantly higher than those in patients with low ERI. Differences in serum T-AOC, SOD, CAT, MDA and AOPP levels were statistically significant between dialysis group of patients with different ERI levels (P<0.05).

3.2 Inflammatory response in patients with maintenance hemodialysis and its correlation with EPO resistance

Analysis of serum inflammatory response indexes IFN-γ (pg/mL), HMGB-1 (pg/mL), ICAM-1 (ng/mL), IL-4 (pg/mL) and IL-10 (pg/mL) between dialysis group and control group was as follows: serum IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels in dialysis group were significantly higher than those in control group. Differences in serum IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels were statistically significant between the two groups (P<0.05).

Analysis of serum inflammatory response indexes IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 between dialysis group of patients with different ERI levels was as follows: serum IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels in patients with high ERI were significantly higher than those in patients with low ERI. Differences in serum IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels were statistically significant between dialysis group of patients with different ERI levels (P<0.05).

4. Discussion

Maintenance hemodialysis is the main therapy for end-stage kidney disease, which can effectively remove toxic metabolites and maintain the electrolyte and acid-base balance in the body,

Table 1.
Comparison of serum oxidative stress indexes between two groups of subjects.

Groups	n	T-AOC	SOD	CAT	MDA	AOPP
Dialysis group	184	20.35±3.52	74.51±9.36	35.51±5.29	11.41±1.45	126.41±15.86
Control group	102	49.58±6.71	128.55±16.71	83.51±9.35	4.59±0.62	50.15±6.72
T		13.298	7.968	12.951	16.496	11.467
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 2.
Comparison of serum oxidative stress indexes between dialysis group of patients with different ERI levels.

ERI level	n	T-AOC	SOD	CAT	MDA	AOPP
High ERI	92	13.41±1.89	57.85±7.82	27.53±3.49	15.41±1.95	163.59±20.35
Low ERI	92	28.12±4.29	93.32±11.29	44.21±6.42	7.09±0.88	79.76±9.57
T		11.395	9.038	9.382	12.672	10.358
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 3.
Comparison of serum inflammatory response indexes between two groups of subjects.

Groups	n	IFN-γ	HMGB-1	ICAM-1	IL-4	IL-10
Dialysis group	184	85.21±9.35	48.50±6.72	456.71±58.62	193.51±22.62	28.45±3.58
Control group	102	38.52±5.57	21.31±3.26	137.78±16.72	113.46±14.57	17.74±2.52
T		13.482	12.039	17.869	8.208	7.725
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 4.
Comparison of serum inflammatory response indexes between dialysis group of patients with different ERI levels.

ERI level	n	IFN-γ	HMGB-1	ICAM-1	IL-4	IL-10
High ERI	92	127.27±16.24	62.82±8.29	646.62±77.25	253.47±35.25	37.61±6.25
Low ERI	92	48.11±5.96	34.27±5.62	272.35±37.92	134.52±17.61	21.25±3.29
T		19.498	9.296	15.461	8.948	8.248
P		<0.05	<0.05	<0.05	<0.05	<0.05

and also significantly improves the outcomes of patients with end-stage kidney disease and prolong the survival time. Nevertheless, the occurrence of anemia during maintenance hemodialysis can adversely affect the condition of end-stage renal disease and increase the mortality of the disease. The occurrence of renal anemia in patients with end-stage renal disease is associated with the inadequate secretion of EPO and the disorder of red blood cell differentiation and maturation, so rh-EPO is the preferred drug for treatment of renal anemia, and it can enhance the bone marrow hematopoiesis and improve the anemia status[4,5]. But in recent years, a growing number of studies have found that there is significant EPO resistance in patients with end-stage renal disease during the maintenance hemodialysis, which is characterized that routine-dose rh-EPO therapy is difficult to effectively correct the anemia or the increased dose of rh-EPO is needed to corrected anemia[6,7]. At present, it is not clear about the mechanism of EPO resistance in patients with end-stage renal disease. Iron reserve difficiency, EPO antibody production, oxidative stress and inflammatory reaction activation, and other pathological phenomena in the process of hemodialysis will affect the biological activities of EPO, which may be involved in the occurrence of EPO resistance.

Oxidative stress reaction is an important pathological change in the process of continuous hemodialysis, and the biological incompatibility of dialysis membrane is the main cause of increased formation of oxygen free radicals and oxidative stress activation[8,9]. In addition, the increase in glycosylation end-product also activates the oxidative stress response in patients with end-stage renal disease caused by diabetic nephropathy[10]. Oxygen free radicals are aggressive to the lipid and protein in biological membrane structure in the body, lipid and protein generate MDA and AOPP respectively after oxidized, and they can also cause the biofilm structure destruction and tissue injury[11,12]. The body has its own antioxidant capacity, which can remove oxygen free radicals through the reduction reaction catalyzed by antioxidant enzymes such as SOD and CAT so as to avoid excessive oxidative damage to the tissue; when oxygen free radicals are continuously produced, antioxidant enzymes are massively consumed and T-AOC significantly reduces[13]. In the study, analysis of the changes in these oxidative stress indicators in patients with maintenance hemodialysis showed that serum T-AOC, SOD and CAT levels in dialysis group were significantly lower than those in control group while MDA and AOPP levels were significantly higher than those in control group. This indicates that there is significant oxidative stress response activation in patients with end-stage renal disease during continuous hemodialysis, the production of oxidative reaction products increases and the antioxidant enzymes are consumed in large quantities. Further analysis of the correlation between EPO resistance and oxidative stress reaction showed that serum T-AOC, SOD and CAT levels in patients with high ERI were significantly lower than those in patients with low ERI while MDA and AOPP levels were significantly higher than those in patients with low ERI. This confirms that the weakening of antioxidant capacity and the increase of oxidative reaction products in patients with continuous hemodialysis can affect EPO sensitivity and cause EPO resistance.

Oxidative stress in the process of continuous hemodialysis will not only directly cause tissue damage through oxidation reaction, but can also activate the secondary inflammatory reaction and increase the secretion of inflammatory mediators to cause tissue damage[14]. In addition, the biological incompatibility of dialysis membrane can also cause inflammatory reaction activation and increase inflammatory mediator secretion. IFN-γ is a pro-inflammatory factor secreted and produced by mononuclear macrophages and Th1 cells, which can mediate the cascade activation of inflammatory response[15]; HMGB-1 is a late inflammatory factor that has the activation effect on mononuclear macrophages, which can promote the cascade secretion of multiple inflammatory mediators[16]; ICAM-1 is a adhesion cytokine that mediates intercellular adhesion, which can promote the inflammatory cells to adhere to the endothelium and infiltrate in inflammatory sites[17]. The inflammatory response activation will cause compensatory secretion of various anti-inflammatory agents and enhance the compensatory anti-inflammatory response, which is characterized by the secretion of various anti-inflammatory factors such as IL-4 and IL-10[18,19]. In the study, analysis of the changes in these inflammatory response

indexes in patients with maintenance hemodialysis showed that serum IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels in dialysis group were significantly higher than those in control group. This indicates that there is significant inflammatory response activation in patients with end-stage renal disease during continuous hemodialysis, and the formation of pro-inflammatory factors and anti-inflammatory factors significantly increase. Further analysis of the correlation between EPO resistance and inflammatory response showed that serum IFN-γ, HMGB-1, ICAM-1, IL-4 and IL-10 levels in patients with high ERI were significantly higher than those in patients with low ERI. This confirms that the activation of inflammatory responses in patients with continuous hemodialysis can affect EPO sensitivity and cause EPO resistance.

The occurrence of EPO resistance in patients with maintenance hemodialysis is closely related to the activation of oxidative stress response and inflammatory response, and the excessive generation of oxidative stress products and inflammatory mediators can affect the EPO sensitivity and cause the EPO resistance.

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