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Original Article

Traditional Chinese medicine enema combined with high flux hemodialysis improves inflammation and stress response in patients with uremia

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Abstract: Objective: This study aimed to investigate the therapeutic effect of traditional Chinese medicine (TCM) enema combined with high flux hemodialysis in patients with uremia and its improvement of inflammation and oxidative stress response. Methods: Ninety patients with uremia in our hospital were randomly divided into study group and control group with 45 cases in each group. The study group was treated with TCM enema combined with high flux hemodialysis, while the control group was treated with high flux hemodialysis alone. The therapeutic effect and the incidence of adverse reactions were observed in the two groups. The levels of serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA) and superoxide dismutase (SOD) were measured by the enzyme-linked immunosorbent assay (ELISA) before and after treatment in the two groups. The levels of serum urea nitrogen (BUN), serum uric acid (SUA), serum creatinine (SCr) were measured by automatic biochemical analyzer before and after treatment in the two groups. Results: The effective rate of treatment in the study group was higher than that in the control group (P<0.05). The levels of serum CRP, TNF-α, BUN, SUA, SCr, and MDA in the two groups after treatment were decreased as compared with those before treatment (P<0.05), while the level of SOD was significantly increased (P<0.001). After treatment, the levels of CRP, TNF-α, serum BUN, SUA, SCr, and MDA in the study group were significantly lower than those in the control group (P<0.01), and the level of SOD was significantly increased (P<0.001). Conclusion: TCM enema combined with high flux hemodialysis can improve the therapeutic effect of uremia and reduce inflammation and oxidative stress response.

Keywords: Uremia, traditional Chinese medicine enema, high flux hemodialysis, inflammation, oxidative stress response

Introduction

Uremia is the end-stage of renal failure. Chronic renal diseases can cause gradual failure and loss of renal function and accumulation of toxins in human body, resulting in system dysfunction [1]. Anemia, repeated infections, malnutrition and metabolic disorders are found in the patients with uremia. If the patients are not treated in time, they may have complications such as heart failure and atherosclerosis, which eventually lead to death of patients [2].

Hemodialysis is the preferred treatment scheme for patients with uremia. However, conventional hemodialysis is difficult to effectively remove macromolecules in the blood, and is easy to cause chronic complications such as malnutrition and inflammation. High flux hemodialysis has the characteristics of high toxin clearance rate [3]. Although it can reduce the long-term complications, the therapeutic effect is limited [4]. In recent years, traditional Chinese medicine (TCM) plays an important role in the treatment of chronic renal diseases. TCM enema therapy is an external treatment of TCM based on the decocting method, which is one of the important methods to treat chronic renal diseases [5]. The previous studies have shown that uremia toxins could cause immune system disorders and micro-inflammation state, and hemodialysis itself could cause inflammatory state [6, 7]. During the long-term hemodialysis, chronic inflammation can induce the increased production of reactive oxygen species (ROS) in the patients with uremia, which cannot be effectively balanced by the antioxidant system. Finally, the oxidative stress state is aggravated, leading to the release of

inflammatory cytokines in large amounts [8]. Inflammation is a key factor leading to malnutrition and vascular diseases in hemodialysis patients. The dialysis disequilibrium syndrome could lead to higher morbidity and mortality [9]. Therefore, it is very important to reduce inflammation and stress response of the patients with uremia during hemodialysis. Studies have shown that high-throughput hemodialysis has a good clinical effect on uremia pruritus, and can inhibit the inflammatory response of dialysis patients [10].

However, there are few studies on the application of this technique combined with TCM enema for treatment. In this study, TCM enema combined with high flux hemodialysis was used to treat uremia, and the therapeutic effect and its effect on inflammation and oxidative stress response were explored.

Materials and methods

General data

Ninety patients with uremia in our hospital were randomly divided into study group and control group with 45 cases in each group. There were 21 males and 24 females in the study group, aged from 35 to 61 years old, with the average age of 47.8±8.4 years old. There were 18 males and 27 females in the control group, aged from 34 to 59 years old, with the average age of 46.7±8.1 years old. This study has been approved by Ethics Committee of Shengli Hospital. The subjects and their families signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria: patients meeting the diagnostic criteria of uremia [11]; patients who did not use immunosuppressive agents; patients meeting the criteria of hemodialysis: patients with blood urea nitrogen (BUN) ≥ 28.6 mmol/L or serum creatinine (SCr) ≥ 707.2 mmol/L; patients aged between 34-61 years old.

Exclusion criteria: patients who used the immunosuppressive agents or anti-inflammatory drugs recently; patients with the allergic history of cardiopulmonary bypass filters and pipes; patients with severe cardiopulmonary dysfunction, malignant tumors, recent infections, connective tissue diseases, autoimmune diseases, infectious diseases, cardiovascular and cerebrovascular diseases; patients with cognitive dysfunction and mental disorders; patients who didn't cooperate with this study.

Treatment scheme

The control group was treated with high flux hemodialysis by Swabs Dialog + hemodialysis machine (Swabs Medical International Trade Co., Ltd., Shanghai, China) and FX80 high flux dialyzer (Fresenius Medical Care AG & Co. KGaA). The dialysis fluid was bicarbonate, the dialysis blood flow was 250-300 mL/min, and the dialysis fluid flow was 600 mL/min. The dialysis was carried out 4 h each time, three times a week. The study group was treated with TCM enema combined with high flux hemodialysis [12]. The ingredients of TCM were as follows: *Astragalus propinquus Schischkin* 20 g, *Angelica sinensis Diels* 12 g, *Salvia miltiorrhiza Bge.* 15 g, *Ophiopogon japonicus Ker-Gawl.* 12 g, *Ostrea gigas Thunberg* 25 g, *Rheum officinale* 15 g, and *Radix paeoniae rubra* 10 g. 400 mL of water was added and boiled to 200 mL. The decoction was taken for enema, once a day, once an hour, one month as a course, three courses in total.

Evaluation of therapeutic effect

After 3 months of treatment, the therapeutic effects of the two groups were observed. Evaluation criteria [13]: Markedly effective: the clinical symptoms and signs are completely disappeared or markedly improved, and the decrease of SCr level is less than 30%. Effective: the clinical symptoms and signs are disappeared or markedly alleviated, and the decrease of SCr level is less than 20%. Ineffective: the clinical symptoms and signs remained unchanged or even worse, and BUN and SCR levels are increased. Total effective rate = (Markedly effective + effective)/Total number of cases in the group × 100%. The incidence of adverse reactions during treatment was observed. The adverse reactions included hypotension, hypoglycemia, disequilibrium syndrome and muscle spasm.

Index detection

Before treatment and 3 months after treatment, 5 mL of venous blood was extracted and placed in vacuum blood collection tubes with-

out anticoagulant, and the serum was separated by centrifugation. The levels of serum BUN, SUA and SCr were measured by DXC600 automatic biochemical analyzer (Beckman Coulter Inc., Chaska, MN, USA). The operation process was carried out strictly in accordance with the instructions.

The enzyme-linked immunosorbent assay (ELISA) [14] was used to detect the levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), superoxide dismutase (SOD) in serum (Zhenyu Biotechnology Co., Ltd., Shanghai, China, Lot. No.: CSB-E16524h-1, CSB-EQ023955HU-1, CEA597Ge-1, and SES134Hu-1). The standard well, sample well and blank control well (without sample and enzyme-linked reagent) were set up. 50 μL of standard diluted twice was added into the standard well. 50 μL of sample was added into the sample well. The diluted antibody was added into each well, and then incubated for 2 h. The solution in each well was discarded and the samples were washed five times and patted dry. 100 μL of diluted streptavidin labeled by horseradish peroxidase was added into each well, and then incubated for 45 min. The solution in each well was discarded and the samples were washed five times and patted dry. 100 μL of TMB solution was added into each well, and then incubated for 5 min away from light. Finally, 100 μL of stop solution was added. The absorbance (OD) of each well was measured sequentially at 450 nm using HBS-1096C Pro ELISA analyzer (DeTie Laboratory Equipment Co., Ltd., Nanjing, China). The levels of CRP, TNF-α, MDA and SOD were calculated.

Statistical methods

SPSS 19.0 (Chembio Medical Co., Ltd., Shanghai, China) was used for statistical analysis. The measurement data were expressed as means ± standard deviation (x ± SD). The measurement data between the two groups were compared by Independent-sample t-test, and the measurement data in the two groups before and after treatment were compared by paired t-test. The enumeration data were expressed as number of cases/percentage [n (%)]. The enumeration data between the two groups were compared by *Chi*-square test. When the theoretical frequency was less than 5, the continuity correction *Chi*-square test was used. $P<0.05$ indicates that the difference was statistically significant.

Results

General information

There were no obvious differences in general clinical data of gender, age, body mass index (BMI), course of disease, type of primary disease, dialysis time, degree of anemia, smoking history, drinking history, residence, total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL), and low density lipoprotein (LDL) between the two groups (**Table 1**).

Levels of serum CRP and TNF-α are decreased in both groups

After treatment, the levels of CRP and TNF-α in the two groups were lower than those before treatment ($P<0.05$). After treatment, the levels of CRP and TNF-α in the study group were significantly lower than those in the control group ($P<0.01$) (**Table 2**).

Levels of serum MDA and SOD are decreased and increased respectively in both groups

After treatment, the serum MDA level in the two groups was decreased as compared with that before treatment ($P<0.001$), and the serum SOD level was significantly increased than that before treatment ($P<0.001$). After treatment, the serum MDA level in the study group was decreased ($P<0.001$) as compared with that in the control group, and the serum SOD level was significantly increased than that in the control group ($P<0.001$) (**Table 3**).

Levels of BUN, SUA and SCr in serum are decreased in both groups

After treatment, the levels of BUN, SUA and SCr in the two groups were significantly lower than those before treatment ($P<0.001$). After treatment, the levels of BUN, SUA and SCr in the study group were remarkably lower than those in the control group ($P<0.001$) (**Table 4**).

Therapeutic effect is better in the study group

In the study group, 29 cases were markedly effective, 13 cases were effective, 3 cases were ineffective, and the effective rate was 93.33%. In the control group, the corresponding data were 16, 19, 10, and 77.78%. The

Table 1. General data of the study group and the control group [n (%)]/(mean ± SD)

Item	Study group (n=45)	Control group (n=45)	t/χ^2 value	*P* value
Gender			0.407	0.523
Male	21 (46.67)	18 (40.00)		
Female	24 (53.33)	27 (60.00)		
Age (years old)	47.8±8.4	46.7±8.1	0.632	0.529
BMI (kg/m^2)	20.37±2.16	21.15±2.31	1.654	0.102
Course of disease (year)	1.2±0.5	1.1±0.7	0.780	0.438
Types of primary diseases			0.867	0.648
Diabetic nephropathy	7 (15.56)	9 (20.00)		
Chronic glomerulonephritis	29 (64.44)	30 (66.67)		
hypertensive renal atherosclerosis	9 (20.00)	6 (13.13)		
Dialysis time (month)	22.6±1.8	22.3±1.5	0.859	0.393
Degree of anemia			0.547	0.761
Mild	14 (31.11)	13 (28.89)		
Severe	24 (53.33)	27 (60.00)		
Severe	7 (15.56)	5 (11.11)		
Smoking history			0.865	0.352
Yes	11 (24.44)	15 (33.33)		
No	34 (75.56)	30 (66.67)		
Drinking history			0.403	0.525
Yes	22 (48.89)	19 (42.22)		
No	23 (51.11)	26 (57.78)		
Residence			0.450	0.502
City	39 (86.67)	41 (91.11)		
Town	6 (13.33)	4 (8.89)		
TC (mmol/L)	4.21±1.12	4.16±1.07	0.216	0.829
TG (mmol/L)	1.48±0.63	1.39±0.74	0.621	0.536
HDL (mmol/L)	1.03±0.48	1.08±0.45	0.510	0.612
LDL (mmol/L)	2.31±0.76	2.19±0.73	0.764	0.447

Table 2. Comparison of the levels of serum CRP and TNF-α between the study group and the control group before and after treatment (mean ± SD)

Group	n	CRP (mg/L)		t value	*P* value	TNF-α (ng/L)		t value	*P* value
		before treatment	after treatment			before treatment	after treatment		
Study group	45	7.56±2.62	4.51±1.64	6.619	<0.001	41.13±8.96	30.62±8.34	5.760	<0.001
Control group	45	7.33±2.84	6.25±2.09	2.055	0.043	40.82±8.01	36.14±7.95	2.782	0.007
t value	-	0.399	4.394	-	-	0.173	3.214	-	-
P value	-	0.691	<0.001	-	-	0.863	0.002	-	-

effective rate of treatment in the study group was significantly higher than that in the control group ($P<0.05$) (**Table 5**).

Incidence of adverse reactions

The study group had 1 case of hypotension, 2 cases of muscle spasm, and no hypoglycemia and disequilibrium syndrome. The incidence of adverse reactions was 6.67%. The control group had 3 cases of hypotension, 2 cases of hypoglycemia, 1 case of disequilibrium syndrome and 1 case of muscle spasm. There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$) (**Table 6**).

Table 3. Comparison of the levels of serum MDA and SOD between the study group and the control group before and after treatment (x ± SD)

Group	n	MDA (nmol/L)		t value	*P* value	SOD (IU/mL)		t value	*P* value
		before treatment	after treatment			before treatment	after treatment		
Study group	45	5.50±0.34	4.34±0.38	15.260	<0.001	62.48±6.59	87.41±5.84	18.990	<0.001
Control group	45	5.54±0.61	4.96±0.52	4.854	<0.001	64.52±5.76	80.49±5.36	13.620	<0.001
t value	-	0.384	6.458	-	-	1.564	5.856	-	-
P value	-	0.702	<0.001	-	-	0.122	<0.001	-	-

Table 4. Comparison of the levels of serum BUN, SUA and SCr in the two groups before and after treatment (mean ± SD)

Item	Study group (n=45)	Control group (n=45)	t value	*P* value
BUN (mmol/L)				
Before treatment	28.46±3.18	28.07±3.29	0.572	0.569
After treatment	8.13±1.72	10.83±1.97	6.926	<0.001
t value	37.720	30.160	-	-
P value	<0.001	<0.001	-	-
SUA (mmol/L)				
Before treatment	692.31±26.28	697.27±25.49	0.909	0.366
After treatment	361.27±17.62	392.08±21.37	7.462	<0.001
t value	70.190	61.550	-	-
P value	<0.001	<0.001	-	-
SCr (μmol/L)				
Before treatment	881.25±43.26	876.62±43.58	0.506	0.614
After treatment	314.81±17.59	334.95±19.27	5.178	<0.001
t value	81.370	76.260	-	-
P value	<0.001	<0.001	-	-

Table 5. Comparisons of effective rate of treatment between the study group and the control group [n (%)]

Group	n	Markedly effective	Effective	Ineffective	Effective rate (%)
Study group	45	29 (64.44)	13 (28.89)	3 (6.67)	93.33
Control group	45	16 (35.56)	19 (42.22)	10 (22.22)	77.78
χ^2 value	-	-	-	-	4.406
P value	-	-	-	-	0.036

Discussion

Although conventional hemodialysis can relieve the clinical symptoms of patients, it has certain limitations in the clearance of toxins and is easy to cause poisoning [15, 16]. High flux hemodialysis can absorb macromolecules in blood, effectively cleanse toxins and reduce the incidence of adverse reactions, but its clinical efficacy is still limited [17].

As the renal clearance capability of patients with uremia is weak, the accumulation of toxins can cause the release of the inflammatory factors. The inflammatory factors can interact with oxidative stress response and exert physiological and pathological effects together [23]. CRP and TNF-α are a kind of important pro-inflammatory cytokines, which can not only act on the tissues, but also mediate a variety of inflammatory mediators, thus causing the deterioration of renal diseases, and both of them are significantly increased in hemodialysis patients [24, 25]. MDA is a degradation product of lipid peroxide. The level of MDA reflects the status of lipid peroxidation. The higher the level of MDA is, the more intense the peroxidation reaction will be [26]. As an important enzyme, SOD can eradicate

Table 6. Comparison of the incidence of adverse reactions between the study group and the control group [n (%)]

Group	n	Hypotension	Hypoglycemia	Disequilibrium syndrome	Muscle spasm	Incidence rate (%)
Study group	45	1 (2.22)	0 (0.00)	0 (0.00)	2 (4.44)	6.67
Control group	45	3 (6.67)	2 (4.44)	1 (2.22)	1 (2.22)	15.56
χ^2 value	-	1.047	2.045	1.011	0.345	1.800
P value	-	0.306	0.153	0.315	0.557	0.180

the oxygen free radicals, which can protect tissues and cells and reduce the damage caused by oxygen free radicals [27]. After treatment, the levels of CRP, TNF-α and MDA in the study group were lower than those in the control group, and the level of SOD was higher, which suggested that TCM enema combined with high flux hemodialysis can alleviate inflammation and oxidative stress response in the patients with uremia. In the study of Lu et al. [28], *Rheum officinale* enemas can improve tubulointerstitial fibrosis in 5/6Nx rats by reducing toxin overload, oxidative stress and inflammatory damage of kidney. *Rheum officinale* enema can regulate immune function, improve endocrine function, correct gastrointestinal dysfunction, decrease the levels of molecular substances in blood, reduce the accumulation of toxins in the body, thus reduce inflammatory reaction and oxidative stress response and improve the hemodialysis effect [29, 30].

In recent years, TCM enema in the treatment of uremia has made great progress [18, 19]. TCM enema can preserve the decoction in the rectum or the colon. Zou et al. [20] reported that TCM enema combined with hemodialysis in the treatment of chronic renal failure can accelerate intestinal absorption kinetics. In this study, the patients were treated with TCM enema combined with hemodialysis. The results revealed that the effective rate of treatment in the study group was higher than that in the control group. After treatment, the levels of BUN, SUA and SCr in the study group were lower than those in the control group, which indicated that TCM enema combined with high flux hemodialysis has better therapeutic effect, and does not increase the incidence of adverse reactions. In the study of Zou et al. [21], TCM enema combined with conventional hemodialysis can reduce the levels of BUN, SCr, SUA in patients with chronic renal failure, and there was no significant adverse reactions during treatment, which is similar to our study. *Rheum officinale*, as the principal drug of TCM enema, can effectively inhibit the proliferation of mesangial cells [22], make a large amount of nitrogen excretion, improve lipid and protein metabolism, and then improve glomerular filtration rate.

It is confirmed that TCM enema combined with high flux hemodialysis has obvious benefits in the treatment of uremia in this study. However, there are still some deficiencies in this study. The residual renal function and the quality of life of patients have not been observed. These deficiencies need to be improved in future studies.

In conclusion, TCM enema combined with high flux hemodialysis can improve the therapeutic effect of uremia and reduce inflammation and oxidative stress response.

Disclosure of conflict of interest

None.

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