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Original Article

Hemodialysis plus hemoperfusion on uremia and micro-inflammatory state

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Abstract: Objective: To explore the effect of hemodialysis combined with hemoperfusion on renal function, dialysis efficacy and micro-inflammatory state in uremia patients. Methods: Eighty patients with maintenance hemodialysis were randomly divided into observation group (hemodialysis plus hemoperfusion) and control group (hemodialysis), with 40 patients in each group. Serum creatinine, blood urea nitrogen, glomerular filtration rate, hemoglobin, serum albumin, blood calcium, serum inorganic phosphorus, parathyroid hormone, β2 microglobulin, inflammatory factors and quality of life were compared before treatment and after 3-month treatment. Results: Patients in observation group had decreased blood urea nitrogen and serum creatinine, increased glomerular filtration rate, hemoglobin and serum albumin, reduced serum inorganic phosphorus, parathyroid hormone and β2 microglobulin, elevated blood calcium, lower C-reactive protein, interleukin-6 and tumor necrosis factor-α, and better quality of life (reflected in the improved physiological function, role physical, social function, role emotional and bodily pain) compared with control group after treatment (all $P<0.05$). Conclusion: Hemodialysis combined with hemoperfusion can effectively eliminate toxic substances and inflammatory factors and improve the nutritional status and quality of life of patients, which is worthy of popularization in clinic.

Keywords: Hemodialysis, hemoperfusion, uremia, clinical efficacy, micro-inflammatory state

Introduction

As the economy improves, the number of patients suffered from chronic kidney disease increases year by year, with the morbidity rate up to 11% [1]. With the increase of morbidity rate, the number of patients with end-stage renal disease (ESRD) rises, thereupon, various complications occur, especially water and electrolyte disturbance, toxin retention, and anemia [2, 3]. The major therapy for ESRD in clinic is hemodialysis, peritoneal dialysis or kidney transplantation [4]. Over 2 million people need ESRD replacement therapy every year in the world, and the way to treat ESRD in China is mainly maintenance hemodialysis [5].

Hemodialysis is a process of removing toxins and excessive fluid from the body by dispersion, convection and adsorption to maintain acid-base balance in the human body; the method is to lead patients' blood into the hemofiltration equipment for blood purification and then infuse back into the body [6-8]. Hemodialysis is a conventional renal replacement therapy, which can efficiently remove micromolecule urotoxins such as urea, creatinine and uric acid, improve water-sodium retention, and adjust the electrolyte balance. It is easy to operate, and has good safety [9, 10]. However, hemodialysis therapy has some shortcomings; for example, it is not easy to eliminate macromolecular substances with high liposolubility and protein binding, such as parathyroid hormone and β2 microglobulin [11-13]. Long-term toxin retention can lead to the occurrence of complications, thereby influencing patients' quality of life, and injuring other visceral organs [6, 14, 15]. Hemoperfusion has begun to apply in clinical practice in view of the shortcomings of hemodialysis. Hemoperfusion can not only remove creatinine, uric acid and other micromolecule substances, but also well eliminate protein-bound macromolecular substances, such as parathyroid hormone and β2 microglobulin [16, 17]. Nevertheless, hemoperfusion has a lower elimination capacity to micromolecule substances than hemodialysis and is unable to rectify acidosis and electrolyte disturbance [18].

Therefore, hemodialysis combined with hemoperfusion is used for the treatment of ESRD in clinical practice, and the combination can effectively eliminate toxic substances, improve renal function and enhance the efficacy of dialysis [19, 20]. Recent study has shown that ESRD patients have been chronically in the micro-inflammatory state, and the improvement of micro-inflammatory state can boost the efficacy of dialysis [21]. However, there are few clinical researches about the improvement of micro-inflammatory state by hemodialysis combined with hemoperfusion. In this study, randomized controlled trial was conducted to explore the clinical efficacy of hemodialysis combined with hemoperfusion in ESRD patients and its effect on micro-inflammatory state, providing more support for clinical application.

Materials and methods

General data

Eighty patients received maintenance hemodialysis in the Department of Intensive Care Unit in The First Hospital of Jilin University from March 2016 to March 2019 were selected and divided, according to the random number table method, into two groups with 40 patients in each group: observation group (hemodialysis plus hemoperfusion) and control group (hemodialysis). All patients were 40-80 years old, with an average age of 62.5±8.2 years old.

Informed consent has been obtained from all individuals included in this study. The research has been approved by the Ethics Committee of The First Hospital of Jilin University.

Inclusive and exclusive criteria

Inclusion criteria: Diagnosis of ESRD according to the diagnostic criteria of ESRD in *Internal Medicine (Version 14)*; patients over 18 years old. Exclusion criteria: Patients suffered from infection for the near term; patients with severe malnutrition, tumor, etc.; patients with mental disease or cerebrovascular disease that could not comply with treatment; patients administrated with glucocorticoids or immunosuppressive agents recently.

Methods

Basic treatment protocol: Patients in the two groups were treated for decompression, adjusted for acid-base imbalance and maintained for electrolyte balance and given high-quality low protein, low salt, low fat, and low phosphorous diet.

Hemodialysis was performed by using hemodialysis equipment (Fresenius 4008s, Germany) and low-flux hollow fiber dialyzer (Fresenius FX10, Germany) in addition to basic treatment protocol in control group. The dialysate flow rate was set as 500 ml/min, blood flow volume 200-250 ml/min, and dialysis duration 4 h/time. A regular hemodialysis was performed three times per week for 3 months.

Hemodialysis twice per week, hemodialysis + hemoperfusion once per week and hemoperfusion (Jafron HA130, Zhuhai, China) once a week were carried out in observation group in addition to basic treatment protocol. Hemodialysis protocol was the same as that in control group. Hemodialysis + hemoperfusion protocol: Hemodialysis combined with hemoperfusion was conducted for 2 h followed by hemodialysis for 2 h. The dialysate flow rate was set at 500 ml/min, and blood flow volume was set at 200-250 ml/min. The treatment was performed for 3 months.

Outcome measurements

Main outcome measurements: Serum creatinine, blood urea nitrogen, glomerular filtration rate, hemoglobin, serum albumin, blood calcium and serum inorganic phosphorus were detected before and after dialysis by using Beckman automatic biochemical analyzer (Beckman, Germany). Parathyroid hormone (iPTH), β2 microglobulin (β2-MG) and inflammatory factors including interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) were measured using enzyme linked immunosorbent assay (kits from Beijing Tianyu Hengtai Technology Co., Ltd., China) before and after dialysis.

Secondary outcome measurements: The MOS 36-item short-form health survey (SF-36) was used for scoring the quality of life in terms of general health, mental health, physiological function, role physical, social function, role

Table 1. General data and baseline data comparison ($\overline{x}\pm$sd, n (%))

	Observation group (n=40)	Control group (n=40)	χ^2/t	P
Male/Female	26/14	28/12	0.228	0.633
Age (years)	57.7±14.0	57.8±13.5	0.041	0.968
Systolic pressure (mmHg)	152.18±7.19	152.05±8.20	0.072	0.943
Diastolic pressure (mmHg)	88.18±7.19	88.20±7.82	0.015	0.988
Triglyceride (mmol/l)	1.77±0.64	1.78±0.64	0.052	0.958
Total cholesterol (mmol/l)	5.56±0.76	5.60±0.78	0.217	0.829
HDL (mmol/l)	1.07±0.35	1.11±0.33	0.624	0.534
LDL (mmol/l)	3.82±0.84	3.95±0.68	0.759	0.450
Hemoglobin (g/l)	102.52±10.46	103.45±9.73	0.409	0.683
ALB (g/l)	35.78±4.76	35.81±4.86	0.033	0.974
BMI (kg/m^2)	17.07±1.80	17.14±2.50	0.138	0.890
Blood glucose (mmol/l)	5.86±0.42	5.87±0.42	0.027	0.979
Pre-dialysis BUN (mmol/l)	27.97±0.64	27.98±0.64	0.052	0.958
Pre-dialysis SCr (μmol/l)	692.86±218.55	687.85±224.95	0.101	0.920
Cause				
Diabetic nephropathy	14 (35.0%)	15 (37.5%)	0.801	0.977
Chronic glomerulonephritis	11 (27.5%)	13 (32.5%)		
Hypertensive nephrosclerosis	8 (20.0%)	7 (17.5%)		
Tubulointerstitial lesion	2 (5.0%)	2 (5.0%)		
Obstructive nephropathy	2 (5.0%)	1 (2.5%)		
Polycystic kidney and others	3 (7.5%)	2 (5.0%)		

Note: HDL: high-density lipoprotein; LDL: low-density lipoprotein; BMI: body mass index; BUN: blood urea nitrogen; SCr: serum creatinine; ALB: serum albumin.

emotional, bodily pain and vitality [22]. Each item was scored 0-100.

Statistical analysis

SPSS 17.0 software was used. Continuous variables were expressed as mean ± standard deviation ($\overline{x}\pm$sd). The variables conformed to normal distribution and homoscedasticity were analyzed by paired t test for comparison before and after treatment and by independent sample t test for comparison between groups; the variables that did not conform to normal distribution and homoscedasticity were analyzed by rank sum test. The enumeration data were shown as % and analyzed by Pearson chi-square test and Fisher's exact test. There was a significant difference at P<0.05.

Results

General data and baseline data comparison

There were no differences in general data and baseline data between the two groups (all P>0.05, **Table 1**).

Renal function, hemoglobin and serum albumin comparison before and after dialysis

Blood urea nitrogen, serum creatinine and glomerular filtration rate were improved after treatment in the two groups compared with those before treatment (all P<0.05). Hemoglobin and serum albumin were increased after treatment in observation group compared with those before treatment (all P<0.05). Blood urea nitrogen and serum creatinine were decreased, and glomerular filtration rate, hemoglobin and serum albumin were increased in observation group after treatment as compared to control group (all P<0.05, **Table 2**).

Blood calcium, serum inorganic phosphorus, iPTH and β2-MG comparison before and after dialysis

Blood calcium, serum inorganic phosphorus, iPTH and β2-MG were improved after treatment in observation group compared with those before treatment (all P<0.05); serum inorganic phosphorus and β2-MG were improved after treatment in control group compared with

Table 2. Renal function, hemoglobin and serum albumin comparison before and after dialysis ($\overline{x}$±sd)

	Observation group Pre-dialysis	Control group Pre-dialysis	Observation group Post-dialysis	Control group Post-dialysis	t	P
BUN (mmol/l)	27.97±0.64	27.98±0.64	10.81±4.01[a]	14.82±4.74[a]	4.091	<0.001
SCr (μmol/l)	692.86±218.55	687.85±224.95	327.21±65.58[a]	367.44±58.65[a]	2.891	0.005
GFR (ml/min)	27.69±7.18	27.51±7.11	40.92±7.25[a]	34.31±6.01[a]	4.436	<0.001
Hemoglobin (g/l)	102.52±10.46	103.45±9.73	104.10±7.33[a]	100.05±9.03	2.205	0.031
ALB (g/l)	35.78±4.76	35.81±4.86	39.66±4.94[a]	36.27±5.00	3.052	0.003

Note: Compared with pre-dialysis, [a]P<0.05. BUN: blood urea nitrogen; SCr: serum creatinine; GFR: glomerular filtration rate; ALB: serum albumin.

Table 3. Blood calcium, serum inorganic phosphorus, iPTH and β2-MG comparison before and after dialysis ($\overline{x}$±sd)

	Observation group Pre-dialysis	Control group Pre-dialysis	Observation group Post-dialysis	Control group Post-dialysis	t	P
Blood calcium (mmol/l)	2.23±0.22	2.22±0.21	2.37±0.17[a]	2.21±0.19	3.939	<0.001
PHOS (mmol/l)	2.12±0.20	2.13±0.23	1.64±0.11[a]	1.89±0.12[a]	9.681	<0.001
iPTH (pg/ml)	356.48±136.05	360.96±144.40	298.90±107.02[a]	361.62±129.34	2.382	0.020
β2-MG (g/l)	5.88±0.75	5.97±0.85	1.87±0.19[a]	3.39±0.67[a]	13.823	<0.001

Note: Compared with pre-dialysis, [a]P<0.05. PHOS: serum inorganic phosphorus; iPTH: parathyroid hormone; β2-MG: β2 microglobulin.

Table 4. Inflammatory factors comparison before and after dialysis ($\overline{x}$±sd)

	Observation group Pre-dialysis	Control group Pre-dialysis	t	P	Observation group Post-dialysis	Control group Post-dialysis	t	P
CRP (mg/l)	23.71±2.84	23.94±3.52	0.298	0.766	7.81±2.28[a]	13.82±2.28[a]	9.709	<0.001
IL-6 (ng/l)	188.12±1.31	188.55±1.38	1.437	0.155	121.19±5.31[a]	154.87±5.56[a]	27.716	<0.001
TNF-α (ng/l)	55.29±7.31	56.48±6.34	0.757	0.451	22.42±1.89[a]	33.74±2.27[a]	24.469	<0.001

Note: Compared with pre-dialysis within the group, [a]P<0.05. CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α.

those before treatment (both P<0.05). Serum inorganic phosphorus, iPTH and β2-MG were decreased, and blood calcium was increased in observation group after treatment as compared to control group (all P<0.05, **Table 3**).

Inflammatory factors comparison before and after dialysis

CRP, IL-6 and TNF-α were decreased after treatment in the two groups compared with those before treatment (all P<0.05). CRP, IL-6 and TNF-α after treatment were lower in observation group than those in control group (all P<0.05, **Table 4**).

Quality of life comparison after 3-month treatment

Patients in observation group had better quality of life after 3-month treatment compared with control group, reflecting in the improved physiological function, role physical, social function, role emotional and bodily pain (all P<0.05). There were no significant differences in general health, mental health and vitality between the two groups (all P>0.05, **Table 5** and **Figure 1**).

Discussion

The combination of hemodialysis and hemoperfusion in the treatment of ESRD can improve the therapeutic effect and maintain homeostasis, which has been widely used [23]. Creatinine is the metabolites of the muscles, and normally most creatinine is metabolized by the kidney and excreted from the urine; when the glomerular filtration rate decreases, creatinine excreted in the urine reduced, resulting in increased serum creatinine [24]. Blood urea nitrogen is

Table 5. Quality of life comparison after 3-month treatment ($\overline{x}\pm sd$)

	Observation group Pre-treatment	Control group Pre-treatment	t	P	Observation group Post-treatment	Control group Post-treatment	t	P
GH	72.25±4.34	72.26±4.01	0.107	0.874	75.10±3.28	75.19±3.29	0.119	0.906
MH	69.41±3.01	69.26±2.94	1.147	0.684	71.50±3.34	70.22±2.85	1.084	0.750
PF	60.95±3.04	61.36±3.01	0.362	0.451	80.05±2.81[a]	64.19±3.17	23.203	<0.001
RP	60.41±6.13	59.21±6.24	1.248	0.532	76.73±6.46[a]	65.85±6.15[a]	7.764	<0.001
SF	58.23±5.21	57.36±5.84	1.458	0.421	75.35±5.46[a]	63.35±5.46[a]	9.627	<0.001
RE	60.58±5.69	59.67±5.95	1.541	0.436	79.65±6.22[a]	66.81±9.87[a]	6.878	<0.001
BP	44.62±4.26	44.26±4.21	0.159	0.789	57.18±4.03[a]	52.14±4.28[a]	5.139	<0.001
VT	69.69±3.54	70.14±3.47	1.145	0.694	71.50±3.34	70.22±2.85	1.804	0.750

Note: Compared with pre-dialysis within the group, [a]P<0.05. GH: general health; MH: mental health; PF: physiological function; RP: role physical; SF: social function; RE: role emotional; BP: bodily pain; VT: vitality.

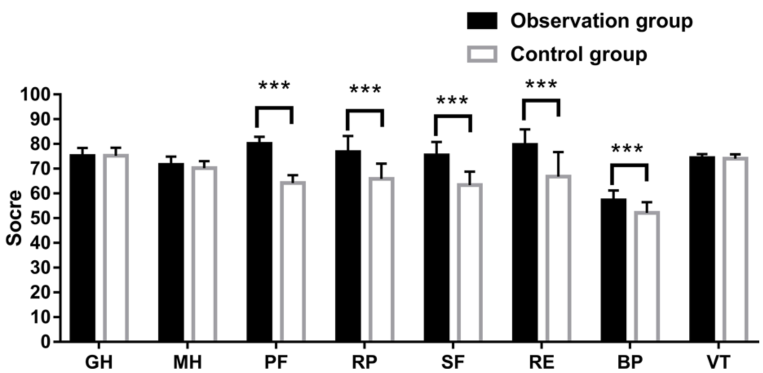

Figure 1. Quality of life comparison after 3-month treatment. Compared with control group, ***P<0.001. GH: general health; MH: mental health; PF: physiological function; RP: role physical; SF: social function; RE: role emotional; BP: bodily pain; VT: vitality.

the end product of protein metabolism; when the glomerular filtration rate drops to half, blood urea nitrogen rises rapidly. Therefore, serum creatinine, blood urea nitrogen and glomerular filtration rate are commonly used in clinical evaluation of renal function. In this study, the improvement of serum creatinine, blood urea nitrogen and glomerular filtration rate and the elimination of iPTH and β2-MG by hemodialysis + hemoperfusion were better than those by hemodialysis. Previous studies also showed that the clearance of macromolecules by hemodialysis + hemoperfusion was significantly superior to that by hemodialysis, improving clinical efficacy [25, 26].

Oxidative stress exists in ESRD patients, under which multiple inflammatory factors are secreted, aggravating the inflammatory state in the body [21]. Hemodialysis + hemoperfusion can effectively remove inflammatory factors in addition to improving renal function, thus improving the micro-inflammatory state in patients [27, 28]. In this study, we found that the clearance of CRP, IL-6 and TNF-α by hemodialysis + hemoperfusion was better than that by hemodialysis. Another study has reported that hemodialysis + hemoperfusion can eliminate inflammatory mediators, reduce oxidative stress response, improve oxidative stress state, and lower the loss of nutrition, thereby improving anemia [8]. In this study, we found that hemodialysis + hemoperfusion could increase serum albumin and hemoglobin, which was associated with the improvement of nutritional status after the clearance of inflammatory factors.

As science and technology evolve, patients' attitudes are changing, and "preventive treatment of disease" is getting more and more attention. Many clinical studies are assessed by using the quality of life rating scale, and the most popular one is the SF-36 quality of life questionnaire [22]. In this study, hemodialysis + hemoperfusion could more effectively eliminate macromolecular toxin and inflammatory factors, improve renal function and the nutritional status, recover bodily functions, and relieve physical discomfort to some extent such as pruritus and bone pain. Therefore, patients in observation group had better quality of life after 3-month treatment compared with the control group, which was consistent with results in a previous study [29].

Shortcomings and outlook: There was small sample size in this study, and the further expanded sample size is needed to conduct multi-center randomized controlled study. The follow-up time was short, which should be further prolonged to observe the clinical efficacy of hemodialysis + hemoperfusion.

In summary, hemodialysis + hemoperfusion can effectively eliminate toxic substances and inflammatory factors and improve the nutritional status and quality of life of patients, which is worth further popularizing and applying.

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Disclosure of conflict of interest

None.

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