



# Effect of hemodialysis in combined with hemoperfusion on the toxin clearance rate and carotid intima in patients with uremia

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## ABSTRACT

**Objective:** To explore the effect of hemodialysis (HD) in combined with hemoperfusion (HP) on the toxin clearance rate and carotid intima in patients with uremia. **Methods:** A total of 40 patients with uremia who were admitted in our hospital from May, 2015 to February, 2017 were included in the study and randomized into the control group ( $n=20$ ) and the study group ( $n=20$ ). The patients in the two groups were given routine HD treatment. On the above basis, the patients in the study group were given HP treatment, continuously for 3 months. The toxin content, clearance rate, and serum inflammatory cytokines before and after treatment in the two groups were detected and compared. The ultrasound diagnostic apparatus was used to detect the carotid IMT before and after treatment in the two groups. **Results:** Scr and BUN after treatment in the two groups, and PTH and  $\beta$  2-MG contents in the study group were significantly reduced when compared with before treatment. PTH and  $\beta$  2-MG contents after treatment in the study group were significantly lower than those in the control group, while PTH and  $\beta$  2-MG clearance rate was significantly higher than that in the control group. The serum MDA, hs-CRP, IL-6, and TNF- $\alpha$  levels after treatment in the two groups were significantly reduced when compared with before treatment. The serum hs-CRP, IL-6, and TNF- $\alpha$  levels after treatment in the study group were significantly lower than those in the control group. IMT and plaque area after treatment in the control group were significantly increased when compared with before treatment, while IMT and plaque area in the study group were not significantly changed. The plaque area after treatment in the study group was significantly less than that in the control group. **Conclusions:** HD in combined with HP can significantly enhance the toxin clearance rate of large molecules in patients with uremia, alleviate the inflammatory reaction, and meanwhile effectively delay the occurrence of atherosclerosis and other cardiovascular complications.

## 1. Introduction

Hemodialysis (HD) is a main means in the treatment of progressive chronic renal failure, i.e. uremia, can improve the long-term water-sodium retention, acid-base imbalance, vitamin metabolic disorder, and enhance the survival rate; however, long-term HD can elevate

the occurrence rate of refractory hypertension, dialysis related amyloidosis, renal osteopathy, and cardiovascular complications[1,2]. Some researches demonstrate that[3] the occurrence of various complications in patients with uremia has a certain correlation with invalid clearance of large molecule toxin by HD. Hemoperfusion (HP) can clear the endogenous and exogenous toxin through bringing the blood into the solid adsorbent, effectively eliminate the middle and large molecule toxin, and alleviate the micro-inflammation state [4]. The study is aimed to explore the effect of HD in combined with HP on the toxin clearance rate and carotid intima in patients with uremia.

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## 2. Materials and methods

### 2.1. Clinical materials

A total of 40 patients with uremia who were admitted in our hospital from May, 2015 to February, 2017 were included in the study. Inclusion criteria: (1) those who were in accordance with the diagnostic criteria of uremia (KDIGO, 2012)[5]; (2) those who had a stable condition with more than 3-month HD; (3) those who were aged from 35 to 80 years old; (4) those whose urine volume was less than 400 mL; (5) those who had signed the informed consents. Those who were merged with liver function damage, acute and chronic infection history, malignant tumor, and active rheumatic disease were excluded from the study.

The patients were randomized into the control group ( $n=20$ ) and the study group ( $n=20$ ). In the control group, 14 were male, and 6 were female; with an average age of ( $44.4\pm 3.6$ ) years old, and average course of ( $6.8\pm 3.4$ ) years; 7 had chronic glomerulonephritis, 5 had glomerular arteriosclerosis, 3 had diabetic nephropathy, 3 had chronic interstitial nephritis, and 2 had chronic pyelonephritis. In the study group, 13 were male, and 7 were female; with an average age of ( $43.9\pm 3.5$ ) years old, and average course of ( $6.7\pm 2.6$ ) years; 7 had chronic glomerulonephritis, 6 had glomerular arteriosclerosis, 4 had diabetic nephropathy, 2 had chronic interstitial nephritis, and 1 had chronic pyelonephritis. The comparison of gender, age, course, and primary disease between the two groups was not statistically significant ( $P>0.05$ ), and it was comparable.

### 2.2. Methods

The patients in the two groups were performed with routine HD, 3 times/week, 4-5 h/time, blood flow volume of 240 mL/min, bicarbonate dialysate with flow volume of about 500 mL/min, temperature of 36.5-37.5 °C, blood pump blood volume of about 220-280 mL/min. SWS4000A hemodialysis machine and B16P polysulfone membrane dialyzer were adopted. The patients in the study group were given HD and HP, 2 times/week for HD, and 1 time/week for HP. MG150 resin blood perfusion apparatus was adopted for HP. First, HP was given for 2 h, then the absorption column was removed, and finally HD was given for 2 h. The

patients in the two groups were continuously treated for 3 months, and received basic treatments during the treatment process. Low-molecular-weight heparin sodium or low-molecular-weight calcium was adopted in the anticoagulation treatment, calcium dobesilate 0.5 g/time, tid, and calcitriol 0.25 µg/time, qh. Meanwhile, it should pay attention to the diet control.

### 2.3. Observation indicators

A volume of 4 mL morning fasting venous blood before and after treatment was collected, centrifuged at 3 000 rpm for 15 min, and preserved at -80 °C for detection after the serum was separated. The full automatic biochemical analyzer was used to detect Scr, BUN, PTH, and β 2-MG contents. Kt/V was used to detect the dialysis sufficiency degree.  $Kt/V = -\ln(R - 0.008t) + (4 - 3.5R) UF/W$ . The spectrophotometry was used to detect the plasma MDA level. The immunoturbidimetry was used to detect hs-CRP level. ELISA was used to detect IL-6 and TNF-α level. The two-dimensional and color Doppler ultrasound diagnostic apparatus was used to detect IMT, and the plaque area was measured.

### 2.4. Statistical analysis

SPSS 22.0 software was used for the statistical analysis. The measurement data were expressed as mean ± SD, t test was used for homogeneity of variance, and non-parametric test was used for heterogeneity of variance.  $P<0.05$  was regarded as statistically significant.

## 3. Results

### 3.1. Comparison of the toxin clearance rate before and after treatment between the two groups

The comparison of Scr, PTH, BUN, and β 2-MG levels before treatment between the two groups was not statistically significant ( $P>0.05$ ). Scr and BUN after treatment in the two groups, and PTH and β 2-MG contents in the study group were significantly reduced when compared with before treatment ( $P<0.01$ ). PTH and β 2-MG contents after treatment in the study group were significantly lower

**Table 1.**

Comparison of the toxin clearance rate before and after treatment between the two groups.

Groups	n	Scr(µmol/L)			PTH(pg/mL)			BUN(mmol/L)			β 2-MG(mg/L)		
		Before treatment	After treatment	Clearance rate (%)	Before treatment	After treatment	Clearance rate (%)	Before treatment	After treatment	Clearance rate (%)	Before treatment	After treatment	Clearance rate (%)
Study group	20	952.9±105.6	469.6±90.7**	50.4±10.6	721.5±135.7	354.6±95.8**##	50.8±11.5##	25.9±5.6	10.7±3.9**	58.6±5.2	40.6±8.5	17.5±6.3***	56.7±6.4##
Control group	20	922.5±103.8	491.3±96.1**	46.7±9.8	706.9±145.2	689.6±136.7	2.4±5.1	24.8±5.2	11.0±3.4**	55.8±5.1	39.4±8.2	38.7±7.6	1.7±3.2

\*\* $P<0.01$ , when compared with before treatment; ## $P<0.01$ , when compared with the control group.

**Table 2.**

Comparison of the serum inflammatory indicators before and after treatment between the two groups.

Groups	n	MDA( $\mu\text{mol/L}$ )		hs-CRP( $\text{mg/L}$ )		IL-6( $\text{ng/L}$ )		TNF- $\alpha$ ( $\text{ng/L}$ )	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	20	5.7 $\pm$ 2.5	3.6 $\pm$ 2.2**	9.3 $\pm$ 1.2	6.1 $\pm$ 1.2**	168.5 $\pm$ 25.3	122.2 $\pm$ 17.5***	12.2 $\pm$ 6.2	6.9 $\pm$ 2.1***
Control group	20	5.5 $\pm$ 2.2	4.1 $\pm$ 2.1*	9.3 $\pm$ 1.2	8.5 $\pm$ 1.1*	172.7 $\pm$ 23.2	157.2 $\pm$ 20.5*	12.3 $\pm$ 6.1	8.8 $\pm$ 2.9**

\* $P$ <0.05, \*\* $P$ <0.01, when compared with before treatment; # $P$ <0.05, ## $P$ <0.01, when compared with the control group.

**Table 3.**

Comparison of IMT and plaque area before and after treatment between the two groups.

Groups	n	IMT(mm)		Plaque area ( $\text{mm}^2$ )	
		Before treatment	After treatment	Before treatment	After treatment
Study group	20	0.95 $\pm$ 0.23	0.93 $\pm$ 0.24	24.16 $\pm$ 9.58	24.33 $\pm$ 9.66##
Control group	20	0.90 $\pm$ 0.25	1.07 $\pm$ 0.26*	21.52 $\pm$ 10.23	36.24 $\pm$ 16.02**

\* $P$ <0.05, \*\* $P$ <0.01, when compared with before treatment; ## $P$ <0.01, when compared with the control group.

than those in the control group, while PTH and  $\beta$  2-MG clearance rate was significantly higher than that in the control group ( $P$ <0.01) (Table 1).

### 3.2. Comparison of the serum inflammatory indicators before and after treatment between the two groups

The comparison of serum inflammatory cytokines before treatment between the two groups was not statistically significant ( $P$ >0.05). The serum MDA, hs-CRP, IL-6, and TNF- $\alpha$  levels after treatment in the two groups were significantly reduced when compared with before treatment ( $P$ <0.05 or  $P$ <0.01). The serum hs-CRP, IL-6, and TNF- $\alpha$  levels after treatment in the study group were significantly lower than those in the control group ( $P$ <0.05 or  $P$ <0.01) (Table 2).

### 3.3. Comparison of IMT and plaque area before and after treatment between the two groups

The comparison of IMT and plaque area before treatment between the two groups was not statistically significant ( $P$ >0.05). IMT and plaque area after treatment in the control group were significantly increased when compared with before treatment ( $P$ <0.05 or  $P$ <0.01), while IMT and plaque area in the study group were not significantly changed ( $P$ >0.05). The plaque area after treatment in the study group was significantly less than that in the control group ( $P$ <0.01) (Table 3).

## 4. Discussion

The maintenance HD is a main method in the treatment of uremia, can imitate partial renal function, and reach the goal of improving the clinical symptoms and extending the survival time through eliminating in vivo toxin and correcting electrolyte disturbance. However, HD can effectively eliminate the small molecule toxin, such as BUN and Scr with molecular weight less than 500 Kkd, and

has a limitedness in removing the middle and large molecule toxin of PTH and  $\beta$  2-MG; therefore long-term accumulation of toxins can cause the neurological and circulatory system abnormality, resulting in the occurrence of various severe complications and high death rate[6]. High-flux HD is widely applied in the clinic in 1980s, with molecule interception reaching 60000 KD; however, its clearance of middle and large molecule toxin is still less than their accumulation amount inside; therefore, various complications still exist[7]. HP, as a special blood purification method, can effectively eliminate the exogenous toxin and endogenous metabolic products through bringing the blood outside under the effect of fixed adsorbent of activated carbon according to absorption affinity chromatography theory to reach the final goal of blood purification. Some researches demonstrate that[8] HP can eliminate PTH,  $\beta$  2-MG, and other middle and large molecule toxins, and phenol, guanidine, benzpyrole, and other middle molecule substances, but has a lower rate in eliminating water, electrolyte, and BUN; therefore, HP cannot be uniquely applied in dialysis in patients with uremia, so that HP is usually combined with HD in the clinic to reach the goal of effectively eliminating the toxins and alleviating the clinical symptoms.

$\beta$  2-MG is a single stranded polypeptide molecular protein with relative molecular weight of 11800, and is mainly produced by platelet, multi-nucleation leukocytes and peripheral blood lymphocytes.  $\beta$  2-MG can freely pass the glomerular capillary wall, most of which is absorbed and resolved by the kidney. In patients with uremia,  $\beta$  2-MG content can reach 20-50 mg/L, farther higher than the normal value. Some researches demonstrate that[9] the dialysis mode and micro-inflammation environment in patients with uremia can accelerate the production of  $\beta$  2-MG, which is accumulated in various organs and skeleton to form the amyloid fiber, resulting in organic and tissue damage, and is also a common complication; therefore, the content of  $\beta$  2-MG can be applied to estimate the sufficiency of dialysis. It is reported that[10]  $\beta$  2-MG content is closely associated with the death rate in patients with uremia, and patients can achieve a higher survival rate when  $\beta$  2-

MG content is less than 27.5 mg/L. PTH is a polypeptide secreted by parathyroid gland cells with molecular weight of 9400. Uremia patients are usually merged with hyperparathyroidism, resulting in the elevation of PTH content, and bone metabolic disorder. Meanwhile, PTH can destroy the integrity of red blood cells, act on the white blood cells, inhibit the immunoreaction and myocardial cell energy metabolism, and cause the reduction of immunological function and the occurrence of myocardial hypertrophy and heart failure, with multiple systems involved. The results in the study showed that Scr and BUN after treatment in the two groups, and PTH and  $\beta$  2-MG contents in the study group were significantly reduced when compared with before treatment ( $P < 0.01$ ); PTH and  $\beta$  2-MG contents after treatment in the study group were significantly lower than those in the control group, while PTH and  $\beta$  2-MG clearance rate was significantly higher than that in the control group ( $P < 0.01$ ), indicating that HD in combined with HP can preferably eliminate the small, middle, and large molecule toxins, improve the electrolyte disturbance and acid-base imbalance, and alleviate the clinical symptoms, which is consistent with the results reported by Li[11]. HD in combined with HP can eliminate the toxins and excessive water, and alleviate the bad effects, but due to the proteins and glycosylation end-products formed by degradation of glucose in dialysate, and the weakened gut barrier, the endotoxin absorption is increased. Long-term dialysis can facilitate the patients in a micro-inflammation state, while the cardiovascular disease and malnutrition caused by the micro-inflammation state are the high risk factors for the high case fatality rate in patients with uremia[12]. Some researches demonstrate that[13] the myocardial cells and vascular endothelial cells are in a severe pathological change state in patients with uremia, and the risk factors of cardiovascular events are increased with the disease progression. In the study, the serum MDA, hs-CRP, IL-6, and TNF- $\alpha$  before and after treatment were detected, and two-dimensional and color Doppler ultrasound diagnostic apparatus was used to detect IMT to estimate the inflammatory state and atherosclerosis degree. The results in the study showed that the serum MDA, hs-CRP, IL-6, and TNF- $\alpha$  levels after treatment in the two groups were significantly reduced when compared with before treatment ( $P < 0.05$  or  $P < 0.01$ ); the serum hs-CRP, IL-6, and TNF- $\alpha$  levels after treatment in the study group were significantly lower than those in the control group ( $P < 0.05$  or  $P < 0.01$ ); IMT and plaque area after treatment in the control group were significantly increased when compared with before treatment ( $P < 0.05$  or  $P < 0.01$ ), while IMT and plaque area in the study group were not significantly changed ( $P > 0.05$ ); the plaque area after treatment in the study group was significantly less than that in the control group ( $P < 0.01$ ), indicating that HD in combined with HP can preferably inhibit the inflammatory reaction degree, delay the progression of atherosclerosis, and has a significant advantage in preventing the occurrence of cardiovascular complications.

In conclusion, HD in combined with HP can not only eliminate water and small molecular substances in patients with uremia, but also significantly enhance the toxin clearance rate of large molecules, alleviate the inflammatory reaction, and improve the dialysis quality, and meanwhile can effectively delay the occurrence of atherosclerosis and other cardiovascular complications, and is an effective therapeutic scheme in improving the long-term survival rate.

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