Int J Clin Exp Med 2018;11(10):11161-11168
www.ijcem.com /ISSN:1940-5901/IJCEM0078239

Original Article

Application value of hemoperfusion adjuvant therapy in maintenance hemodialysis and its influence on inflammatory response in patients

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Received April 20, 2018; Accepted June 28, 2018; Epub October 15, 2018; Published October 30, 2018

Abstract: Objective: The aim of this study was to investigate the application value of hemoperfusion (HP) adjuvant therapy in maintenance hemodialysis (HD) and its influence on inflammatory response, nutritional status, bone metabolism, and calcium-phosphorus metabolism. Methods: A total of 120 patients undergoing maintenance HD in Affiliated Hospital of Beihua University, from March 2014 to January 2017, were selected and divided into an experimental group (n=60) and control group (n=60) using a random number table. Patients in the control group were only treated with HD, while those in the experimental group, based on treatment in control group, were treated with HP. Changes in related indexes regarding inflammatory response, nutritional status, bone metabolism, and calcium-phosphorus metabolism were detected and compared between the two groups of patients. Pruritus in the two groups was statistically analyzed and compared. Results: Levels of interleukin-6, high-sensitivity C-reactive protein, and tumor necrosis factor-α, in both groups, were significantly decreased at 6 months after treatment compared with those before treatment (all $P<0.01$). These levels were significantly lower in the experimental group than the control group, showing significant differences (all $P<0.01$). Levels of transferring, hemoglobin, prealbumin, and albumin, in both groups, were significantly increased at 6 months after treatment compared with those before treatment (all $P<0.01$). These levels were significantly higher in the experimental group than the control group, showing significant differences (all $P<0.01$). Moreover, levels of procollagen type I N-terminal propeptide, bone gla protein, osteoprotegerin, and fibroblast growth factor-23, in both groups, were remarkably decreased at 6 months after treatment compared with those before treatment (all $P<0.01$). These levels were remarkably lower in the experimental group than the control group, showing significant differences (all $P<0.05$). Levels of blood P and immunoreactive parathyroid hormone, in both groups, were also remarkably decreased at 6 months after treatment compared with those before treatment. These levels were remarkably lower in the experimental group than the control group (all $P<0.01$). However, levels of blood Ca were obviously increased and higher in the experimental group than the control group, showing significant differences (all $P<0.01$). Moreover, pruritus rates in the experimental group after treatment were significantly reduced compared to the control group ($P<0.05$). Conclusion: HP, combined with HD, can effectively alleviate clinical symptoms of patients, reduce inflammatory response in the body, and correct calcium-phosphorus metabolism disorders in the treatment of patients receiving maintenance HD. These positive effects contribute to the stability of patient nutritional status and bone metabolism. This treatment method is also safe and reliable.

Keywords: Hemoperfusion, hemodialysis, maintenance hemodialysis, inflammation, nutrition, bone metabolism, curative effects

Introduction

Maintenance hemodialysis (HD) is a viable means of clinical treatment of end-stage renal disease, mainly replacing renal function via blood purification [1-3]. It has been found that there is micro-inflammation in most patients undergoing maintenance HD. In HD, a widely-used method, middle- and macro-molecule toxins gradually deposit and accumulate in the body with the extension of dialysis time, exacerbating the micro-inflammatory state, leading to continuous deterioration of disease, and increasing long-term mortality risk [4, 5]. With continuous improvement in medical technology, toxin hemoperfusion (HP) has played an important role in maintenance HD, effectively eliminating middle- and large-molecular substances and binding to proteins with significant curative effects. Some scholars have applied HP, combined with HD, in the treatment of patients receiving maintenance HD. Results have demonstrated that it can greatly enhance blood purification effects and exert positive effects on the prognosis of patients [6]. Previous studies have mostly focused on the influence of HP, combined with HD, in one aspect. Its comprehensive influence remains unclear. This study aimed to further investigate the application value of HP adjuvant therapy in maintenance HD and its comprehensive influence on inflammatory response, nutritional status, bone metabolism, and calcium-phosphorus metabolism.

Materials and methods

General data

A total of 120 patients undergoing maintenance HD in Affiliated Hospital of Beihua University, from March 2014 to January 2017, were enrolled into this study. All patients were divided into an experimental group (n=60) and control group (n=60) using a random number table.

Inclusion criteria: (1) Patients in stable condition; (2) Patients with normal immune system; (3) Patients not taking drugs affecting calcium-phosphorus metabolism in the past one month; (4) Patients without contraindications in this study; (5) Patients without malignant tumors; (6) Patients with no blood transfusion history in the past 3 months; and (7) Patients with complete clinical data.

Exclusion criteria: (1) Patients accompanied with severe organic diseases in the heart, liver, or kidneys; (2) Patients with severe malnutrition; (3) Patients quitting midway; (4) Patients with poor compliance; and (5) Patients with acute or chronic infections.

This study was approved by the Medical Ethics Committee of Affiliated Hospital of Beihua University. All participants and their families signed the informed consent form.

Methods

All enrolled patients were first given erythropoietin (subcutaneous injection of recombinant human erythropoietin, 100-150 U/kg, twice a week), supplemented by iron supplements (iron proteinsuccinylate oral solution, orally, 15 mL/time, twice a day), calcium acetate (calcium acetate capsules, orally, 0.6 g/time, twice a day), and folic acid (folic acid tablets, orally, 0.4 mg/time, once a day). They also received other conventional therapies [7]. Patients in the control group, based on the above treatment, were treated with HD using a hemodialysis machine (Braun, German). F15 hollow fiber dialyzer was used as the dialyzer and sodium bicarbonate solution as dialysate. Dialysate flow rate was set at 500 mL/min and blood flow rate at 200-250 mL/min for maintenance HD (3 times a week, 4 hours/time) [8].

HP was combined with HD for the experimental group. Patients were first treated with HP for 2 hours, followed by HD for 2 hours. A middle-sized macroporous resin perfusion apparatus was connected to the front end of the dialyzer of extracorporeal circulation pipeline of hemodialysis machine in series with the rated volume of 65 mL and body surface area of 1,000-1,500 m^2/g. After conventional pre-flushing of the pipeline, dialyzer, and perfusion apparatus, HP was performed. Blood flow rate was set at 200-220 mL/min. After 2 hours, the saturated perfusion apparatus was removed via air blood returning, followed by routine HD for 2 hours. HP combined with HD was performed once every 2 weeks [9].

Observation indexes

Major observation indexes included inflammatory factors, nutritional status, and calcium-phosphate metabolism. Afterward, 3 mL of 24-hour fasting elbow venous blood was drawn from patients in both groups in the morning before treatment and at 6 months after treatment. Blood specimens were centrifuged at 3,500 rpm for 5 minutes to isolate the serum. The serum was stored to be detected. (1) Inflammatory response: changes in levels of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and tumor necrosis factor-α (TNF-α) were detected and compared between the two groups of patients via enzyme-linked immunosorbent assay (ELISA) using kits purchased from Nanjing Jiancheng Bioengineering Institute, in strict accordance with instructions. (2) Nutritional status: changes in levels of transferring (TRF), hemoglobin (Hb), prealbumin (PA), and albumin (Alb) were detected and compared between the two groups of patients

Table 1. Comparison of clinical data between the two groups of patients

Group	Experimental group (n=60)	Control group (n=60)	t/χ²	P
Gender (case)			0.301	0.583
Male	33	30		
Female	27	30		
Age (year)	45.81±5.03	45.76±5.01	0.055	0.957
Average duration of disease (year)	4.91±0.68	5.02±0.64	0.912	0.363
Classification of disease (case)			0.351	0.896
Hypertensive nephropathy	11	10		
Chronic glomerulonephritis	12	10		
Kidney calculi	13	14		
Diabetic Nephropathy	15	16		
Other	9	10		

using the full-automatic biochemical analyzer. (3) Determination of calcium-phosphorus metabolism: blood Ca and blood P in both groups were routinely detected using the full-automatic biochemical analyzer and changes in serum immunoreactive parathyroid hormone (iPTH) were detected via immunoluminometric assay using a kit purchased from Tianjin Tianshuo Biological Products Co., Ltd.

Secondary observation indexes included bone metabolism and pruritus. (1) Determination of bone metabolism: changes in levels of procollagen type I N-terminal propeptide (PINP), bone gla protein (BGP), osteoprotegerin (OPG), and fibroblast growth factor-23 (FGF-23) were detected and compared between the two groups of patients. Levels of PINP, BGP, and OPG were detected via immunoluminometric assay using kits purchased from Roche. FGF-23 was determined via human FGF-23 (C-terminal) ELISA using a kit from Biowen, Canada. (2) Pruritus of patients in both groups was evaluated: significant remission or disappearance of pruritus (remarkably effective), slight remission of pruritus (effective), and no improvement or exacerbation of pruritus (ineffective) [10]. Improvement rate = (number of remarkably effective cases + number of effective cases)/number of total cases * 100%.

Statistical methods

SPSS 20.0 software was used for statistical analysis of research data. Measurement data are presented as mean ± standard deviation ($\bar{x}$ ± sd). Paired t-test was used for measurement data in line with normal distribution in intra-group comparisons before and after treatment. Independent t-test was adopted for measurement data in line with normal distribution between the two groups. Data are expressed as t. Enumeration data are presented as percentage (%). Chi-square test and Fisher's exact test were used, with data expressed as Chi-square. P<0.05 suggests that differences are statistically significant.

Results

Comparison of clinical data between the two groups of patients

Statistical analyses of major baseline clinical data, such as gender, age, and classification of disease, revealed that there were no significant differences between the two groups of patients (all P>0.05) and comparative analysis could continue to be performed between the two groups (**Table 1**).

Comparison of inflammatory index levels between the two groups of patients before and after treatment

Levels of each inflammatory index had no statistically significant differences before treatment between the two groups of patients (all P>0.05). Levels of IL-6, hs-CRP, and TNF-α, in both groups, at 6 months after treatment were all significantly decreased compared with before treatment (all P<0.01). These levels were significantly lower in the experimental group than the control group, showing significant differences (all P<0.01) as shown in **Table 2**.

Comparison of nutritional status index levels between the two groups of patients before and after treatment

Levels of each nutritional status index had no statistically significant differences before treatment between the two groups of patients (all P>0.05). Levels of TRF, Hb, PA, and Alb, in both groups, at 6 months after treatment were all significantly increased compared with those before treatment (all P<0.01). These levels were significantly higher in the experimental group than the control group, displaying signifi-

Table 2. Comparison of inflammatory index levels between the two groups of patients before and after treatment ($\overline{x}$ ± sd)

Group	IL-6 (ng/L)	hs-CRP (ng/L)	TNF-α (ng/L)
Experimental group (n=60)			
Before treatment	101.10±8.59	15.08±2.55	198.51±26.34
6 months after treatment	54.27±7.65	6.31±1.74	80.45±10.42
t	31.536	22.005	32.284
P	<0.001	<0.001	<0.001
Control group (n=60)			
Before treatment	101.75±8.52	15.07±2.47	197.91±26.28
6 months after treatment	83.97±7.64	9.80±1.58	101.33±10.45
t	12.035	13.922	26.452
P	<0.001	<0.001	<0.001
t value of two group after treatment	21.278	11.502	10.960
P value of two group after treatment	<0.001	<0.001	<0.001

Note: IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor.

Table 3. Comparison of nutritional status index levels between the two groups of patients before and after treatment ($\overline{x}$ ± sd)

Group	TRF (g/L)	Hb (g/L)	PA (mg/L)	Alb (g/L)
Experimental group (n=60)	1.19±0.30	88.37±8.71	241.55±41.16	36.45±4.10
Before treatment	2.01±0.28	103.58±8.41	320.59±40.08	45.67±5.82
6 months after treatment	5.478	9.731	10.657	10.032
t	<0.001	<0.001	<0.001	<0.001
P				
Control group (n=60)				
Before treatment	1.18±0.25	88.29±8.65	241.47±41.18	36.44±4.09
6 months after treatment	1.59±0.27	94.71±8.36	287.65±39.77	40.32±5.76
t	8.631	4.134	6.249	4.254
P	<0.001	<0.001	<0.001	<0.001
t value of two group after treatment	8.364	5.794	4.519	5.061
P value of two group after treatment	<0.001	<0.001	<0.001	<0.001

Note: TRF, transferring; Hb, hemoglobin; PA, prealbumin; Alb, albumin.

cant differences (all P<0.01) as shown in **Table 3**.

Comparison of bone metabolism index levels between the two groups of patients before and after treatment

No statistically significant differences were found in levels of each bone metabolism index before treatment between the two groups of patients (all P>0.05). Levels of PINP, BGP, OPG, and FGF-23, in both groups, at 6 months after treatment were remarkably decreased compared with those before treatment (all P<0.01). These levels were remarkably lower in the experimental group than the control group, showing significant differences (all P<0.05) as shown in **Table 4**.

Comparison of calcium-phosphorus metabolism index levels between the two groups of patients before and after treatment

There were no statistically significant differences in levels of each calcium-phosphorus metabolism index before treatment between the two groups of patients (all P>0.05). Levels of blood P and iPTH, in both groups, were obviously decreased at 6 months after treatment compared with those before treatment. They were obviously lower in the experimental group than the control group (all P<0.01). However,

Table 4. Comparison of bone metabolism index levels between the two groups of patients before and after treatment ($\overline{x}$ ± sd)

Group	PINP (mg/mL)	BGP (mg/mL)	OPG (mg/mL)	FGF-23 (mg/mL)
Experimental group (n=60)				
Before treatment	155.20±31.97	187.52±41.71	318.87±42.06	350.38±50.19
6 months after treatment	105.44±25.09	101.52±35.49	99.86±35.41	106.46±22.30
t	8.912	12.164	30.855	34.402
P	<0.001	<0.001	<0.001	<0.001
Control group (n=60)				
Before treatment	155.19±31.86	186.46±40.93	318.85±42.03	350.42±50.17
6 months after treatment	116.43±23.12	125.71±34.50	146.76±36.04	164.83±23.01
t	7.627	8.791	24.076	26.045
P	<0.001	<0.001	<0.001	<0.001
t value of two group after treatment	2.495	3.786	7.190	14.110
P value of two group after treatment	0.014	<0.001	<0.001	<0.001

Note: PINP, procollagen type I N-terminal propeptide; BGP, bone gla protein; OPG, osteoprotegerin; FGF-23, fibroblast growth factor-23.

Table 5. Comparison of calcium-phosphorus metabolism index levels between the two groups of patients before and after treatment ($\overline{x}$ ± sd)

Group	Blood calcium (mmol/L)	Blood phosphorus (mmol/L)	iPTH (ng/L)
Experimental group (n=60)			
Before treatment	2.17±0.20	2.18±0.49	687.86±47.06
6 months after treatment	3.09±0.19	1.30±0.25	298.65±38.73
t	25.833	12.391	49.465
P	<0.001	<0.001	<0.001
Control group (n=60)			
Before treatment	2.15±0.21	2.17±0.52	687.95±48.89
6 months after treatment	2.38±0.22	1.84±0.23	593.44±39.67
t	5.858	4.496	11.628
P	<0.001	<0.001	<0.001
t value of two group after treatment	18.919	12.313	41.187
P value of two group after treatment	<0.001	<0.001	<0.001

Note: iPTH, immunoreactive parathyroid hormone.

Table 6. Comparison of improvement in pruritus between the two groups of patients

Group	Remarkably effective	Effective	Ineffective	Improvement rate
Experimental group (n=60)	26	31	3	57 (95.00)
Control group (n=60)	20	30	10	50 (83.33)
χ^2				4.227
P				0.040

levels of blood Ca were significantly increased (all P<0.01) and obviously higher in the experimental group than the control group, showing significant differences (all P<0.01) as shown in **Table 5**.

Comparison of improvement in pruritus between the two groups of patients

The improvement rate of pruritus in the experimental group was significantly increased compared with that in the control group, displaying statistically significant differences (P<0.05) as shown in **Table 6**.

Discussion

Many studies have confirmed that the micro-inflammatory state can aggravate the condition of patients receiving maintenance HD, a major factor increasing the mortality risk of patients [11]. Abnormal release of IL-6, hs-CRP, and TNF-α, main inflammatory factors in the body, can lead to the micro-inflammatory state in the body. Early micro-inflammatory state has no significant clinical manifestations.

However, it can result in anemia, malnutrition, and cardiovascular and cerebrovascular diseases in patients with progression of the disease, further deteriorating their condition. At the same time, some scholars have reported that long-term application of HD will make products and various endotoxins in the dialysate flow into the blood circulation through the dialysis membrane, thereby aggravating inflammatory response [12]. Results of this study revealed that levels of IL-6, hs-CRP, and TNF-α, in both groups, were significantly decreased at 6 months after treatment compared with those before treatment, with significant differences between the two groups, suggesting that HP combined with HD can effectively inhibit inflammatory response and play an important role in recovery. A possible reason is that, on one hand, HD exerts decisive effects in removing excess water in the body, maintaining acid-base and electrolyte balance. On the other hand, HD cannot completely remove middle- and large-sized molecular substances, whereas HP can efficiently eliminate middle- and large-sized molecular substances, endogenous toxins, and protein-binding toxins through the extracorporeal circulation system, thereby alleviating inflammatory response effectively. The above results are in accord with related research [13].

Some studies have demonstrated that, due to systemic chronic inflammatory response, the appetite of patients receiving maintenance HD declines and protein synthesis rates decrease significantly, resulting in malnutrition [14, 15]. In addition, some scholars have reported that micro-inflammation is closely related to the nutritional status of the body, clearly reflected by TRF, Hb, PA, and Alb [16]. Results of this study showed that levels of TRF, Hb, PA, and Alb, in both groups, were remarkably elevated at 6 months after treatment compared with those before treatment. There were significant differences between the two groups, indicating that the nutritional status of patients was significantly improved after receiving HD combined with HP. HP removes large- and medium-sized molecular substances, thus, patient appetites are effectively improved, more energy is taken in, and protein synthesis is accelerated. Moreover, reduced inflammatory response can effectively promote the division and proliferation of erythroid progenitor cells in the body, significantly shorten the time of erythrocyte maturation, and further increase concentrations of Hb, maintaining good nutritional status of patients. Results of this present study were in accord with related reports [17].

Calcium-phosphorus metabolism disorder is a common clinical manifestation in patients with end-stage renal disease, whose metabolic pathway is mainly regulated by the PTH-Vd axis. Renal secretion function in patients requiring maintenance HD is severely damaged, so expression of iPTH is high. Moreover, hyperphosphatemia can also cause an abnormal increase in iPTH, leading to clinical symptoms in patients, such as pruritus and lowered blood Ca concentrations [18]. At the same time, PINP, BGP, OPG, and FGF-23 are sensitive indexes reflecting bone metabolism status. In cases of abnormally high expression of blood P, FGF-23 can be rapidly synthesized, thus inhibiting secretion of Vd, significantly increasing levels of iPTH. PINP is a reliable index of bone metabolism. Lower levels indicate higher bone mineral density. Furthermore, BGP can better reflect bone metabolism rates in the body, showing positive correlation [19]. This present study manifested that levels of blood P and iPTH, in both groups, were decreased remarkably at 6 months after treatment compared with those before treatment, while levels of blood Ca were increased remarkably. Additionally, levels of PINP, BGP, OPG, and FGF-23, in both groups, were obviously decreased at 6 months after treatment compared with those before treatment and the improvement rate of pruritus in the experimental group was obviously higher than that in the control group. These results indicate that HD combined with HP can effectively correct calcium-phosphorus metabolism and bone metabolism disorders in the body and effectively reduce the incidence rate of pruritus. The possible reason behind this is that combined application of HD and HP can remove excessive blood P in the body and maintain normal blood Ca concentrations, thereby effectively keeping normal levels of iPTH, inhibiting progression of the disease, and restoring calcium-phosphorus metabolism and bone metabolism status. Similar results have been found related reports [20]. However, for this study, the sample size was quite small and research time was relatively short. Therefore, future in-depth studies with larger sample sizes are needed to further optimize the therapeutic regimen.

In conclusion, HP combined with HD can effectively improve blood purification effects, alleviate inflammatory response in the body, correct bone metabolism and calcium-phosphorus metabolism disorders, and improve the nutritional status in patients receiving maintenance HD. This treatment method has definite curative effects and is worthy of clinical application.

Disclosure of conflict of interest

None.

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