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Original Article

Efficacy of hemodialysis combined with hemofiltration in the treatment of uremia complicated with intractable hypertension

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Abstract: Objective: To explore the efficacy of hemodialysis and hemofiltration in the management of uremia complicated with refractory hypertension (RH). Methods: In this retrospective study, 80 patients with uremia complicated with RH who were admitted to the First People's Hospital of Huoqiu County from March 2019 to March 2022 were included. Patients who received routine hemodialysis were assigned to the control group (C group, n=40), whereas patients received routine hemodialysis and hemofiltration were assigned to the observational group (R group, n=40). The clinical indexes of the two groups were recorded and compared. Differences in diastolic blood pressure, systolic blood pressure, mean pulsating blood pressure, urinary protein, blood urea nitrogen (BUN) and urinary microalbumin, cardiac function parameters and plasma toxic metabolites were observed after one month of treatment. Results: The effective rate of the treatment in the observation group was 97.50%, whereas that for the control group was 75.00%. The observation group showed significantly better improvement of diastolic blood pressure, systolic blood pressure and mean arterial pressure compared with the control group (all $P<0.05$). The levels of urinary microalbumin were lower after treatment than those before treatment. The levels of urinary protein and BUN were higher in the observation group than those in the control group; and the levels of urinary microalbumin were significantly lower in the observation group compared with the levels in the control group (all $P<0.05$). The cardiac parameters of the study cohort were significantly lower after treatment. The levels of plasma toxic metabolites in the observation group were significantly lower after the 12-week treatment. Conclusion: Hemodialysis combined with hemofiltration is effective in the management of uremic patients with refractory hypertension. This treatment strategy effectively reduces blood pressure and average pulsation, improves cardiac function, and promotes the clearance of toxic metabolites. The method is associated with fewer adverse reactions and is safe for clinical applications.

Keywords: Hemodialysis, hemofiltration, uremia, intractable hypertension

Introduction

Hypertension is a global health problem and the main cause of increased mortality among the elderly worldwide. Most hemodialysis patients present with hypertension. Sometimes, the hypertensive patients on regular dialysis still cannot achieve sufficient dialysis volumes [1, 2].

Currently, there are no accurate data on the prevalence of refractory hypertension (RH). The incidence of RH in hypertensive patients without renal disease ranges from 1.9% to 12.8% [3]. A survey conducted from 2003 to 2008 reported that the prevalence of RH among adults in the United States was 12.8% [4]. The prevalence of RH in 9 Central and Eastern European countries was 19.4% [5]. End-stage kidney disease (ESRD), especially in uremia, is complicated with hypertension, which increases the risk of death of these patients [6]. Horowitz et al. reported that the prevalence of hypertension gradually increases with the deterioration of renal function [7]. Georgianos et al. observed that the incidence of RH was 13.6% for patients without chronic kidney disease (CKD), and 28.1% for patients with CKD complicated with RH [8]. Previous findings indicated that cardiovascular disease (CVD) is the risk

factor that affects the prognosis of patients with CKD [9].

Hypertension is an independent risk factor for CVD and is correlated with the quality of life and survival rate of dialysis patients. The incidence of CVD in general population of the same age is 5-8 times lower compared with the incidence among dialysis patients. CVD is the main cause of death of dialysis patients, accounting for 47% of the total number of deaths among this group [10]. Roumeliotis et al. observed that 42% of ESDR patients had RH [11]. The prevalence of hypertension in dialysis patients in China is 74.4-85.2%, the treatment rate is 77.1-94.6%, whereas the standard rate of blood pressure control is only 25.6-59.0% [12, 13]. A previous study reported that about 65% of the patients failed to achieve ideal blood pressure levels after dialysis [14]. The proportion of uremic patients dying from hypertension was approximately 50%, which imposes a huge financial burden on families and social health care and causes significant physical and mental pressure on patients and their families [15].

Maintenance hemodialysis (MHD) is modulated through two main ways, including kidney therapy and hemodialysis. Hemodialysis (HD) is the most used dialysis strategy for uremic patients [16, 17]. More than 90% of uremic patients are treated with HD in US, whereas in Australia and New Zealand, 60% of uremic patients are treated by HD instead of kidney therapy. HD uses the semi-permeable membrane principle to eliminate metabolic wastes from the body through solute exchange. As a result, it maintains a relatively stable internal environment while removing excess fluid, replacing the kidneys to eliminate small molecule toxicants and fluids. The solute is removed by the dispersion principle based on the gradient difference of the solution concentration on both sides of the semi-permeable membrane. The solute gradually accumulates on the side with lower concentration. Solute removal can also be achieved through convection through the pressure gradient on both sides of the semi-permeable membrane, resulting in a gradual increase in water level on the side with low pressure and solute concentration less than the molecular weight intercepted by the membrane. Several studies have shown that a higher molecular weight is associated with a lower clearance rate of HD. HD has poor scavenging ability on medium and large molecular toxins, such as medium and large molecular substances (RA, AngII, ET and PTH), which cannot be removed after effective conventional dialysis. Some patients present with continuous elevated blood pressure after routine hemodialysis, and conventional hemodialysis is not effective in the treatment of RH [18, 19].

Several studies have been conducted to explore the efficacy of conventional HD combined with hemofiltration to determine the efficacy in alleviating RH [20, 21]. Hemofiltration (HF) is an important blood purification method for effective removal of macromolecular toxins. HF further improves the ultrafiltration rate based on basic HD. The method uses a high permeability dialysis filter membrane to effectively filter out large amounts of toxic fluid from the blood and an equal amount of replacement fluid is injected to purify the blood. The goal of this method is to further improve the removal of medium and large molecules of toxins, and effectively remove small molecules of toxins [22]. The filtration function of glomeruli is effectively imitated in HF dialysis, but the reabsorption and secretion of renal tubules cannot be achieved [23]. The method has advantages, such as maintaining stable hemodynamics and effective removal of medium and large molecular toxins with few dialysis-related complications. Moreover, it significantly prolongs the life span of uremic dialysis patients and reduces their mortality. It is imperative to conduct studies to evaluate the curative effect of the hemofiltration in uremic patients with RH.

Materials and methods

General and clinical patient information

In this retrospective study, we included 80 patients with refractory hypertension admitted to the First People's Hospital of Huoqiu Country from March 2019 to March 2022. Subjects who received routine hemodialysis were assigned to the control group, whereas patients who received routine hemodialysis and hemofiltration were assigned to the observation group. The clinical indexes of the two groups were recorded and compared. This study was approved by the Committee on Ethical Issues of the First People's Hospital of Huoqiu County.

Selection of study subjects

Inclusion criteria: 1) patients that underwent "evaluation and treatment of refractory hypertension" [21]; patients that met the diagnostic criteria of uremia. The diagnostic criteria of chronic renal failure and uremia were defined previously [22]; 2) patients with no history of cardiovascular events in the month before the study; 3) patients with complete clinical data; 4) patients that met the conditions of hemodialysis and hemofiltration (the conditions of hemodialysis and hemofiltration were the same for the two groups as follows: the patient was diagnosed as acute and chronic renal failure, no severe heart failure and arrhythmia, no uncontrollable hypotension treated with drugs, and no mental diseases); 5) patients with initial diagnosis and treatment.

Exclusion criteria: 1) patients with other severe organic diseases and malignant tumors; 2) patients with hypoproteinemia and severe anemia; 3) patients with acute trauma or infectious diseases; 4) patients with congestive heart failure; 5) patients with incomplete clinical data.

Methods

Treatment procedures: Hemofiltration therapy: The observation group received hemofiltration therapy conducted using a Diapact CRRT dialysis equipment (German) equipped with Nissan hemofilter (1.3 U) and a corresponding pipeline. The blood flow velocity was set to 200-250 mL/min. The total volume of replacement fluid was adjusted to 35-42 L, and the input speed of the replacement fluid was adjusted to 70-80 mL/min using pre-dilution method. The concentration of sodium ion in the dialysate was adjusted to 140 mmol/L using Delang Bmer16H high-flux dialyzer. The blood flow was set at 250 ml/min for 4 hours. Dialysis was performed 3 times a week for a period of 12 weeks. The Toray TR8000HDF machine (Japan) was used for administration of the replacement fluid. The concentration of the replacement fluid was adjusted regularly according to the condition of the patient. Patients received routine low molecular weight heparin as anticoagulant. A long-term indwelling catheter inserted in the deep vein or autologous arteriovenous fistula was used as vascular pathways. The frequency of treatment was 2-3 times a week, 8-10 h each time for a period of 12 weeks.

Observational indexes

Clinical curative effects: The evaluation criteria after the 12-week treatment were as follows. A relief in blood pressure and renal function by more than 80% indicated very effective; a relief in blood pressure and renal function by 30-79% indicated effective. Renal function improvement by less than 30% or deterioration indicated that the treatment was ineffective. The total effective rate of treatment = [(number of markedly effective cases + effective cases)/ total cases] × 100%.

Detection of blood pressure level and mean pulsating pressure: Standard cuff mercury sphygmomanometer was used to measure blood pressure in the right upper arm of each patient.

Detection of renal function index: EDTA anticoagulation treatment was performed and renal function indexes, including urinary protein, blood urea nitrogen (BUN) and urinary microalbumin, were evaluated. The urinary protein was determined using test strip method, BUN was evaluated by kinetic ultraviolet method, and mALB was determined by radioimmunoassay.

Cardiac function parameters: The two groups of patients underwent color Doppler echocardiography (Wuxi Haiying Electronic Medical System Co., Ltd., model HY6000) after 12 weeks of treatment. In this study, cardiac index (CI), cardiac output (CO), stroke volume (SV), the ratio of early diastolic to late diastolic maximum velocity (Emax A), and the integral ratio of E peak to A peak velocity (EI/AI), were evaluated.

Toxic metabolites: Fasting peripheral venous blood (2 ml) was collected from subjects in the two groups after 12 weeks of treatment, and EDTA (Sichuan Sainuo Fine Chemicals Co., Ltd.) was added as anticoagulant. Blood samples were stored at 4°C for 10 minutes before analysis. The supernatant was collected and the plasma levels of 5-hydroxytryptamine (5-hydroxytryptamine) and canine urine (KYN) were determined through HPLC analysis. The content of beta-2-microglobulin (β2-MG) in the blood sample was determined by latex turbidimetry. The content of parathyroid hormone (PTH) was determined using the chemiluminescence method. The experimental kits were purchased from Sigma (United States).

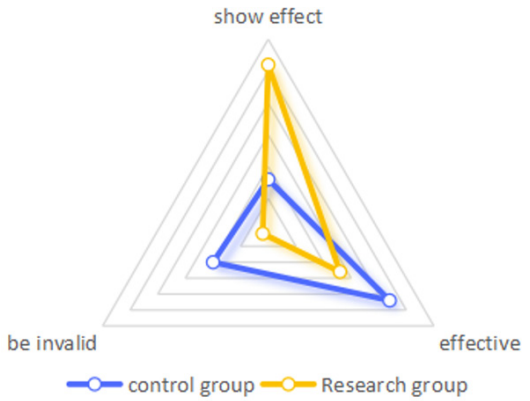

Figure 1. Therapeutic effects between the two groups.

Incidence of adverse reactions: Adverse reactions observed among the subjects included chest tightness, shortness of breath, dizziness and headache, hypotension, nausea and vomiting and muscle spasm.

Statistical analysis

SPSS 20.0 program was adopted for analyzing the data. Diastolic blood pressure, systolic blood pressure, mean pulsating blood pressure, urinary protein, blood urea nitrogen (BUN) and urinary microalbumin, cardiac function parameters and plasma toxic metabolites were measurement data and expressed as mean ± standard deviation ($\bar{x}\pm sd$). A t-test was conducted to explore differences in measurement data between the two groups. Gender and clinical efficacy were count data and expressed as percentage (%). The chi square test was applied to evaluate the differences in count data between the two groups. $P<0.05$ denoted statistical significance.

Results

The general information of the two groups

The records showed that primary diseases in the control group included 13 cases of hypertensive nephropathy, 17 cases of diabetic nephropathy, 2 cases of lupus nephritis, 6 cases of chronic nephritic syndrome, 1 case of polycystic kidney disease, and 1 case of congenital heart defect. The course of hypertension was 5-15 years with an average of 9.21±2.45 years. The course of uremia ranged from 1 to 4 years with an average of 2.12±0.34 years. The education level details of patients in the control group were as follows: 18 cases had primary and junior middle school qualification, 12 cases had senior high school and technical secondary school qualifications and 10 cases had college and above degrees. In the observation group, there were 5 cases of hypertensive nephropathy, 11 cases of diabetic nephropathy, 8 cases of lupus nephritis, 8 cases of chronic glomerulonephritis syndrome, 6 cases of polycystic kidney and 2 cases of others in observation cohort. The course of hypertension in this group was 4-17 years with an average of 9.38±2.45 years. The course of uremia was 1-5 years with an average of 2.20±0.38 years. The education level of subjects in the observation group were as follows: 16 cases with primary and junior high school education level, 13 cases with senior high school and technical secondary school level and 11 cases with junior college or above level. The basic and clinical data did not show significant differences between the two groups (all $P>0.05$).

Differences in therapeutic effects between the two groups

The effective rates for observation and control groups were 97.50% and 75.00%, respectively, indicating significant difference in efficacy ($P<0.05$, **Figure 1**).

Blood pressure and mean arterial pressure

Subjects in the observation group exhibited significantly better alleviation of diastolic blood, systolic blood and mean arterial pressure compared with the control group ($P<0.05$, **Table 1**).

The urinary protein, BUN and mALB levels in the two groups before and after treatment

The levels of urinary protein and BUN were higher after the 12-week therapy than the pretreatment levels. The levels of mALB were lower after the 12-week therapy than the levels observed before treatment. The levels of urinary protein and BUN in the observation group were significantly higher compared with control group, whereas the levels of mALB in the observation group were significantly lower compared with the control group (all $P<0.05$, **Table 2**).

Table 1. Blood pressure and mean arterial pressure of subjects before and after treatment [$\bar{x}$±sd]

Group	N	Systolic blood pressure (mmHg)		Diastolic pressure (mmHg)		Mean arterial pressure (mmHg)	
		Before treatment	After 12 weeks of treatment	Before treatment	After 12 weeks of treatment	Before treatment	After 12 weeks of treatment
C Group	40	180.18±25.17	171.83±16.62[a]	107.36±26.55	102.51±22.03[a]	118.85±6.37	91.83±4.45[a]
R Group	40	179.92±24.86	143.27±15.25[b]	108.21±25.34	89.04±20.01[b]	118.62±6.45	84.23±6.88[b]
t		0.046	8.008	0.146	2.863	0.160	5.866
P		0.963	<0.001	0.884	<0.001	0.873	<0.001

Note: [a]represents the blood pressure and mean arterial pressure of subjects before and after treatment in the control group ([a]P<0.05); [b]represents the blood pressure and mean arterial pressure of subjects before and after treatment in the observation group ([b]P<0.05).

Table 2. The levels of urinary protein, BUN and urinary microalbumin [$\bar{x}$±sd]

Group	N	Urinary protein (g/24 h)		BUN (mmol/L)		Urinary microalbumin (g/L)	
		Before treatment	After 12 weeks of treatment	Before treatment	After 12 weeks of treatment	Before treatment	After 12 weeks of treatment
C Group	40	2.17±0.33	3.77±1.26[a]	2.23±0.15	4.83±1.06[a]	58.13±5.33	43.66±3.54[a]
R Group	40	2.13±0.28	8.76±2.19[b]	2.29±0.18	7.52±1.37[b]	57.46±5.62	28.42±2.17[b]
t		0.584	12.491	1.619	9.822	0.547	23.213
P		0.560	<0.001	0.104	<0.001	0.586	<0.001

Note: [a]denotes P<0.05 in the control group and [b]represents P<0.05 in the observation group. Blood urea nitrogen (BUN).

Table 3. Cardiac function parameters in the two groups [$\bar{x}$±sd]

Group	N	CI (L/min·m)	CO (L/min)	SV (mL)	E/A	EI/AI
C Group	40	2.93±0.34	5.44±0.67	68.46±7.23	1.27±0.18	0.98±0.14
R Group	40	2.19±0.24	4.71±0.56	60.21±6.55	0.93±0.06	0.75±0.08
t		11.246	5.287	5.348	11.333	9.021
P		<0.001	<0.001	<0.001	<0.001	<0.001

cardiac index (CI), cardiac output (CO), stroke volume (SV), and the integral ratio of E peak to A peak velocity (EI/AI).

Cardiac function parameters of the two groups after treatment

There were no differences in the cardiac function parameters, such as CI, CO, SV, E/A and EI/AI between the two groups before treatment. After 12 weeks therapy, the CI, CO, SV, E/A and EI/AI of the observation group were significantly lower than those of the control group (all P<0.05, **Table 3**).

Plasma toxic metabolites of the two groups after treatment

The levels of 5-HT, KYN, β2-MG and PTH in the observation group were significantly lower than those in the control group after 12-week treatment (all P<0.05, **Table 4**).

Adverse reactions in the two groups

The incidence of adverse reactions was 7.50% and 25.00%, in the observation and control groups, respectively (P<0.05, **Figure 2**, **Tables 5** and **6**).

Discussion

Maintenance hemodialysis is a commonly used method for renal replacement therapy in patients with uremia. Previous studies reported that more than 80% of maintenance hemodialysis patients presented with hypertension, and some patients were diagnosed with hypertension after adequate dialysis combined with adequate antihypertensive drug treatment [24]. This type of hypertension is called refractory hypertension. Occurrence of resistant hypertension can significantly increase the risk of cardiovascular events in uremia patients. Cardiovascular events are major risk factors for increased mortality in uremia patients. Currently, clinical awareness of uremia is poor, and the conventional treatment methods used for uremia are not effective. The pathogenesis may be associated with endothelial cell dysfunction, disorders of the renin-angiotensin system, hyperparathyroidism, overexcited sympathetic nerves, use of high amounts of eryth-

Table 4. Levels of plasma toxic metabolites in the two groups [$\bar{x}$±sd]

Group	N	5-HT (mmol/L)	KYN (μmol/L)	β2-MG (mg/L)	PTH (mg/dL)
C Group	40	214.66±25.73	3.72±0.42	24.66±2.93	613.57±70.88
R Group	40	170.33±19.46	2.73±0.31	17.42±1.89	433.76±50.06
t		8.691	11.994	13.133	13.105
P		<0.001	<0.001	<0.001	<0.001

canine urine (KYN), beta-2-microglobulin (β2-MG), parathyroid hormone (PTH).

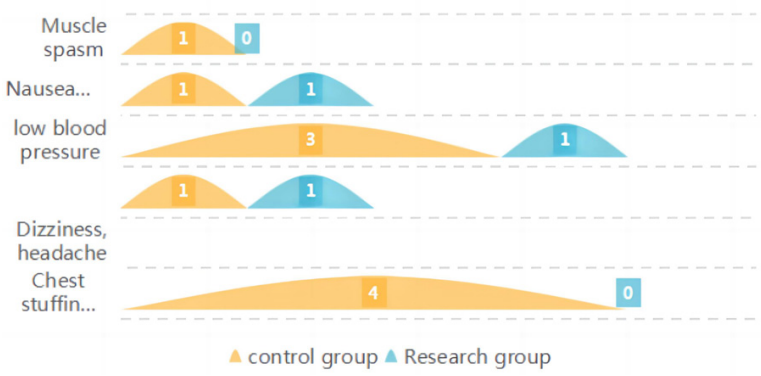

Figure 2. The incidence of adverse reactions in the two groups.

Table 5. Therapeutic effects between the two groups

Group	N	Effective	Show effect	Be invalid	High efficacy
C Group	40	8	22	10	75.0%
R Group	40	26	13	1	97.5%
χ^2					25.290
P					<0.001

ropoietin, excessive volume overload and sodium retention [25]. Hemodialysis mainly relies on the principle of a semipermeable membrane and solute dispersion. The solute moves to the side of low concentration depending on the concentration difference between the solutions on two sides of the semipermeable membrane. On one side, all metabolic wastes are secreted from the body to stabilize the internal environment, and on the other side, excess body fluids are secreted to improve water and sodium retention [26]. However, some hemodialysis patients exhibit persistently elevated blood pressure after dialysis during clinical treatment. The current treatment approaches for hemodialysis patients with uremia have low efficacy [27].

Hemofiltration is a blood purification method which effectively removes medium and large molecules. The method utilizes a high permeability dialysis membrane to filter out several toxins from the blood and improves the ultrafiltration rate by combining it with hemodialysis. The purified blood is returned to circulation and the same amount of replacement fluid is maintained. In addition to improving the filtration rate of medium and large molecule toxins, it eliminates small molecule toxins [28]. In the present study, the observation and control groups had an effective rate of 97.50%, and 75.00%, respectively. This finding indicates that hemodialysis combined with hemofiltration is effective in the treatment of uremia complicated with refractory hypertension. The efficacy of hemodialysis combined with hemofiltration is higher than that of hemodialysis alone. This is mainly because hemodialysis and hemofiltration have complementary advantages and the two methods have a synergistic effect. The method has high clinical application in improving the clinical symptoms and maintaining the physiological indexes of patients effectively.

Previous studies reported that the unique hemofilter could improve sodium and water retention through continuous slow ultrafiltration to ensure physiological dry weight levels in patients [29]. The findings indicate that the clinical effect of hemodialysis combined with hemofiltration is better than hemodialysis alone. This is probably because traditional hemodialysis cannot match the metabolic capacity of filling with the rate of ultrafiltration dehydration [18]. Hemofiltration is a type of ultrafiltration that has a low rate and does not

Table 6. The incidence of adverse reactions in the two groups

Group	N	Dizziness, headache	Nausea and vomiting	Muscle spasm	Chest tightness and shortness of breath	low blood pressure	Total incidence rate
C Group	40	1	1	1	4	3	25.00%
R Group	40	1	1	1	0	0	7.50%
X^2							20.484
P							<0.001

cause excessive changes in hemodynamics but ensures stabilization of the body state. Hemofiltration treatment uses a unique hemofilter, which improves plasma toxicity. In this study, the results indicated that the levels of 5-HT, KYN, β2-MG and PTH were significantly lower in the observation group relative to the control group. This finding indicates that the combination of hemofiltration and hemodialysis can better improve the metabolic capacity of the patient's body to toxic metabolites.

Resistant hypertension is a key risk factor for occurrence of cardiac dysfunction in uremia patients. It is reported that the probability of heart failure in patients with intractable hypertension is more than 3 times higher than that in ordinary hypertensive patients and 10 times higher than that in healthy people [30]. Therefore, high attention should be paid to patients with intractable hypertension during clinical treatment. Long-term water and sodium retention and accumulation of various metabolites in patients with uremia cause damage to cardiomyocytes. Monitoring the cardiac function of patients is a reliable way to evaluate the effect of dialysis treatment [31, 32]. E/A and EI/AI are indicators of diastolic function, whereas CI, CO, and SV are indicators of systolic function. The patients in the observation group had lower CI, CO, SV, E/A levels and EI/AI after undergoing hemodialysis combined with hemodialysis for a month. CI, CO, and SV parameters are associated with the amount of cardiac preload. Dysregulation of water excretion in patients with uremia can induce an increase in circulating blood volume and an increase in cardiac preload. As a result, the levels of CI, CO, and SV increase. Uremic patients may present with increased compensatory cardiac contractility and increased E/A and EI/AI values due to increased circulatory load and enlarged left ventricle [33, 34]. The present results indicate that the cardiac load of uremic patients decreased and the cardiac contractility stabilized after hemodialysis, implying that the probability of long-term congestive heart failure was also significantly reduced.

Dizziness, headache, neck plate tightness, fatigue, palpitation, anorexia, vomiting, edema, and disturbance of consciousness are common symptoms and signs of uremia complicated with intractable hypertension. Circulation to the heart, brain, kidneys, and other vital organs is affected if patients are not treated promptly. Anemia, hypertension, electrolyte disorder, mineral metabolism disorder, renal osteopathy, metabolic acidosis, and other complications can be life-threatening. The findings indicate that hemofiltration combined with hemodialysis can significantly alleviate the adverse symptoms of these patients.

The present study had some limitations. First, only patients admitted to our hospital were included in the study, which limits the generalization of the conclusions. In addition, the sample size was small, and the conclusions should be verified by conducting multicenter, large sample size studies. Moreover, this research is a single-center study, and the findings are subject to some degree of bias. Therefore, the results may differ from those of large-scale multicenter studies from other academic institutes. However, the findings have clinical significance for management of patients with uremia complicated with intractable hypertension and further in-depth investigations should be carried out to verify the findings.

In conclusion, hemodialysis combined with hemofiltration is an effective strategy for treatment of uremia complicated with refractory hypertension. This method effectively controls patients' blood pressure and improves their cardiac function. In addition, it promotes the clearance of toxic metabolites, reduces the risk of adverse reactions and is safe for clinical application.

Disclosure of conflict of interest

None.

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