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ORIGINAL ARTICLE

Combination of maintenance hemodialysis with hemoperfusion: A safe and effective model of artificial kidney

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ABSTRACT

Objective: *To investigate whether the combination of maintenance hemodialysis (MHD) with hemoperfusion (HP) could improve the clearance rate of middle and large molecule uremic toxins so as to improve the quality of life of MHD patients and reduce their mortality rate.*

Methods: *This study was a prospective, randomized, controlled clinical trial. 100 MHD patients were selected and then randomly divided into two groups after four weeks of run-in period. Group 1 received HD alone 2 times a week and the combined treatment of HD with HP (HD+HP) once a week, whereas Group 2 was given HD alone 3 times a week. This study was followed up for a mean of 2 years. The primary outcome was the death of patients. Secondary end points included normal clinical data, leptin, high sensitive C-reactive protein (hsCRP), interleukin-6 (IL-6), β_2 microglobulin (β_2-MG), immunoreactive parathyroid hormone (iPTH), tumor necrosis factor-α (TNF-α) and the index of dimensions of Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36 Chinese Edition).*

Results: *At the end of the two-year observation, the serum concentration of leptin, hsCRP, iPTH, IL-6, β_2-MG and TNF-α, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiothoracic ratio, left ventricular mass index (LVMI), the EPO doses and the types of antihypertensive drugs used were lower with Group 1 than with Group 2 ($p<0.05$); Group 1 had higher hemoglobin (Hb), ejection fraction (EF), and body mass index (BMI) ($p<0.05$). No statistical difference between the two groups was observed in terms of serum albumin, serum iron (SI), total iron binding capacity (TIBC), cardiac output (CO), Kt/V, early/atrial mitral inflow velocities (E/A) ($p>0.05$). Besides, the SF-36 indicated that the total score of overall dimentions of Group 1 was higher than Group 2 ($p<0.05$) and the quality of life of Group 1 was evidently better than Group 2. The Kaplan-Meier Survival Curves for the 2-year observation period showed that patients in Group 1 had obvious survival advantage while Log-rank test results showed $p<0.05$. No serious adverse incidents occurred during the HD+HP treatment.*

Conclusions: *HD+HP was superior to HD in regularly eliminating middle and large molecule uremic toxins accumulated in the body. These findings suggest a potential role for HD+HP in the treatment to improve the quality of life and survival rate of MHD patients.*

KEY WORDS: *Hemoperfusion, Maintenance hemodialysis, Middle and large molecule uremic toxins, Artificial kidney*

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INTRODUCTION

Some of the conditions which occur in maintenance hemodialysis (MHD) patients with a high incidence, resulting in a decline in their quality of life, include malnutrition, insulin resistance, pathological changes in the peripheral nervous system, renal osteodystrophy, left ventricular hypertrophy, refractory hypertension, chronic systemic inflammation, and accelerated deterioration of residual renal function. Studies have shown that the occurrence of mid- and long-term uremic complications is related to the low clearance rate of middle and large molecule uremic toxins when hemodialysis (HD) alone is adopted. As the toxic components of uremic toxins and their corresponding biological effects become increasingly clear, blood purification treatment that aims to remove these toxins has developed from a stage of life-sustaining to improving the quality of life and enabling the patients to return to society as a normal person. Clinical applications of various models of extracorporeal blood purification technology (1, 2) show the clearance rates of middle and large molecule uremic toxins for these models take place in the following order: HD + hemoperfusion (HP) > HP > bio-artificial kidney > hemodiafiltration (HDF) > hemofiltration (HF) > HD.

In China and other developing countries, due to the low level of economic development, low-flux dialysis is the main means of extracorporeal blood purification therapy. But it can hardly remove the middle and large molecule uremic toxins and protein-bound toxins; as a result, the patients suffer from long-term complications and poor quality of life. However, with HP, whose requirements for extracorporeal blood purification equipment are relatively low, most

TABLE I - BASELINE CLINICAL CHARACTERISTICS OF GROUP 1 VERSUS GROUP 2 MHD PATIENTS

Baseline clinical characteristics	Group 1 (n=51)	Group 2 (n=49)	P
Male/female	28/23	26/23	1.000[b]
Age (years	53.54±13.82	51.4±12.52	0.4196[a]
Diseases caused by renal failure (%)			
cGN	20(39.22%)	22(44.90%)	0.6857[b]
DM	14(27.45%)	13(26.53%)	1.000[b]
HBP	9(17.65%)	8(16.33%)	1.000[b]
ADPKD	3(5.88%)	4(8.16%)	0.7124[b]
Unknown	5(9.80%)	2(4.08%)	0.4367[b]
Vascular access for dialysis (%)			
Arteriovenous fistula	51(100%)	49(100%)	-
BMI (kg/m^2)	23.1 ± 1.4	22.8 ± 3.6	0.5813[a]
Complications (%)			
CAD	5(9.80%)	4(8.16%)	1.0000[b]
Congestive heart failure	8(15.69%)	10(20.41%)	0.6083[b]
Peripheral vascular disease	3(5.88%)	5(10.20%)	0.4829[b]
Stroke	1(1.96%)	2(4.08%)	0.6136[b]
COPD	2 (3.92%)	3 (6.12%)	0.6747[b]
Dialysis age months	21.0±11.8	25.8±13.5	0.0617[a]
SBP (mmHg)	153.6± 45.7	155.1± 49.2	0.8747[a]
DBP(mmHg)	89.7± 27.1	87.1± 29.1	0.6447[a]
Laboratory data			
Albumin (g/dL)	3.5±0.5	3.4±0.6	0.3667[a]
Ca^{2+} (mg/dL)	8.3±0.8	8.4±0.9	0.5580[a]
P^{3+} (mg/dL)	4.7±1.6	4.8±1.5	0.7480[a]
iPTH (pg/dL)	254.56±158.07	279.23±165.36	0.4474[a]
Hb (g/L)	82.3 ± 16.2	85.2 ± 19.8	0.4239[a]
spKt/V	1.43±0.19	1.46±0.18	0.4200[a]

BMI = weight/height^2; CAD = Coronary artery disease; COPD = Chronic obstructive pulmonary disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; Alb = serum albumin; Ca^{2+} = serum calcium; P^{3+} = serum phosphorus; iPTH = immunoreactive parathyroid hormone; Hb=Hemoglobin spKt/V(3)=-Ln(R-0.008×T)+(4-3.5×R)×UF/BW; R = the ratio between urea concentration after dialysis and before dialysis; T = dialysis time; UF = weight loss value of patient after dialysis; BW = patient's weight after dialysis; Ln = natural logarithm); [a] two-sample t-test; [b] Fisher's exact test.

blood purification centers can afford to adopt the model artficial kidney therapy of HD combined with HP. In January 2007, Xinhua Hospital included an HP apparatus as an item covered by the national health insurance for the first time in China and became the first to conduct research on MHD patients with the treatment of HD combined with HP and to explore the efficacy and safety of maintenance HP.

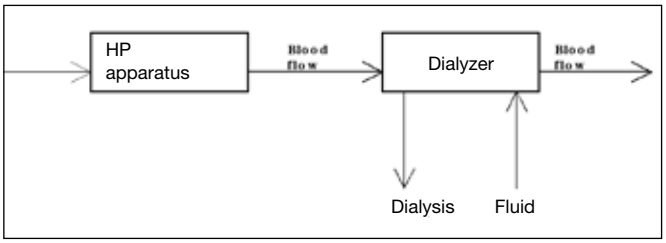

Fig. 1 - *Flow chart of HD+HP.*

SUBJECTS AND METHODS

Subjects

In February 2007, 100 patients (all Chinese) were selected as the subjects for research in the blood purification center of Xinhua Hospital, among whom 54 were male and 46 female, all aged between 38 and 61 years. The patient selection criteria were a relatively stable clinical condition; having gone through conventional HD for 6 to 30 months; no contraindications for HP; average urine volume below 500 ml/day; HD access via autogenous arteriovenous fistula; no malignant tumor. Table I details the baseline clinical characteristics of the two groups of patients.

METHODS

One hundred patients were randomly divided into 2 groups on the basis of the random number table: group 1 received maintenance HD+HP; group 2 received HD alone. During the test period, each patient underwent routine symptomatic treatment of uremia.

Group 1 patients received MHD alone 2 times a week and the HD+HP once a week. Group1 were treated with polysulfone dialyzers (Rexeed 15L; Asahi Kasei Corporation, Tokyo, Japan) and a neutral macroporous resin apparatus (HA-130; Zhuhai Li Zhu Group, Biological Material Co., Ltd., Xiangzhou, Zhuhai, Guangdong, China). The apparatus was compounded in series with the dialyzer (Fig. 1, detail in the flow chart of HD+HP). Two steps were involved during the HD+HP treatment: the first step was HD+HP treatment for two hours, then when the HP apparatus became saturated it was removed (during this process the blood flow rate was between 150 to 200 ml/min). For the next two hours, the blood went through the dialyzer alone (this time the blood flow rate returned to 250 ml/min). Group 2 received HD alone, 3 times a week, 4 hours per session. For the two groups of patients in our study, the average blood flow rate was 250 ml/min when they received HD alone. Both groups used bicarbonate dialysate with a flow rate of 500 ml/min. Ultrafiltration of each patient depended on the clinical condition of the water balance. The low-molecular-weight heparin dose was adjusted, based on clinical bleeding and clotting in the pipeline.

Before using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; Chinese Edition), the investigators were rigorously trained. The patients were interviewed personally and asked to fill out the list of SF-36 questions by themselves. In the event the patients were unable to fill out the list, the investigator wrote down what they said. No investigator or relatives of the patients were allowed to answer the SF-36 questions for the patients.

Collection of clinical data

Clinical data including name, gender, age, BMI, comorbid conditions, course of ESRD, duration of dialysis, SBP, DBP, HR, blood routine, liver function, kidney function, spKt/V, SI, TIBC, EPO doses, chest X-ray, and ultrasonic cardiogram of regular MHD patients can be obtained from the Renal Registry Network of the Quality Control Center of Hemodialysis in Shanghai, whose data has been used for international comparison in the annual report of the United States Renal Data System (USRDS) since 2007. The ultrasonic cardiogram for each patient was conducted by the same experienced doctor every three months; and every three months, the quality of life of each patient was scored using the SF-36. These measurements were averaged as the basis for analysis. Records were kept on the occurrence of cacoethic incidents, time and cause of patients missing the interview, and the patients' death.

Detection of cytokines

Samples were taken every three months during the period of this study. The serum cytokine levels of leptin, IL-6, β_2-MG and TNF-α were measured by enzyme-linked immunosorbent assay (ELISA), while hsCRP and iPTH were measured by Latex-enhanced immunoturbidimetric assay and radioimmunoassay, respectively, strictly observing the manufacturer's instructions. The kits used for detection of cytokines was obtained from American Biosource Company (San Diego, CA, USA).

Data analysis

All measurement data were expressed as mean ± SD. The significance of mean differences between group 1 and group 2 was assessed with the two-sample t test, and the differences in enumeration data were tested with Fisher's exact test. All p values were two-tailed, and p values less than 0.05 were considered to indicate statistical significance. Analyses were conducted using SAS 9.1.3 software package (SAS Institute Inc., Cary, NC, USA).

Event curves were based on Kaplan-Meier analysis, and significance was assessed by means of the log-rank test.

RESULTS

During the 2-year observation period, 4 patients from group 1 missed the interview: 3 of them had successful kidney transplants and 1 transferred to other hospitals for HD. Five patients from group 2 missed the interview: 2 had successful kidney transplants, while the other 2 transferred to other hospitals for HD. One other patient switched to peritoneal dialysis.

When the 4-week run-in period was over, statistical analysis indicated that the baseline values of two groups were similar in their demographic characteristics (age, gender) and that their percentage of diseases caused by renal failure, vascular access for dialysis, complications, duration of dialysis, SBP, DBP, HR and BMI, and their clinical laboratory data (see Tab. II for details, p>0.05, respectively). At the

TABLE II - GENERAL PHYSIOLOGICAL AND LABORATORY VARIABLES OF GROUP 1 VERSUS GROUP 2 DURING THE STUDY PERIOD

Variable	Group 1 n=51)	Group 1 n=41)	Group 2 (n=49)	†P 0years	Group 2 (n=30)	§P 2 years
	0 years	2 years	0 years		2 years	
SBP (mmHg)	153.6± 45.7	136.2± 28.6	155.1± 49.2	0.8747	159.5± 60.8	0.0348
DBP (mmHg)	89.7± 27.1	71.4± 15.6	87.1± 29.1	0.6447	90.6± 32.4	0.0015
HR (time/min)	76.8± 18.9	71.1± 9.8	74.9± 21.3	0.6378	79.1± 19.8	0.0281
Cardiothoracic ratio	0.46± 0.042	0.42± 0.028	0.45± 0.058	0.3244	0.48± 0.052	<.0001
EF (%)	64.7 ± 9.1	72.4 ± 6.8	66.1 ± 7.3	0.3993	62.5 ± 10.5	<.0001
CO (L/min)	5.89 ± 1.20	5.81 ± 0.96	5.77 ± 1.33	0.6365	5.83 ± 1.55	0.9468
E/A	0.92 ± 0.32	0.88 ± 0.29	0.83 ± 0.17	0.0839	0.85 ± 0.20	0.6273
LVMI (g/m^2)	102.99 ± 12.39	101.38 ± 14.95	105.99 ± 13.48	0.2491	175.61 ± 51.88	<.0001
Hb (g/L)	82.3 ± 16.2	105.7 ± 17.7	85.2 ± 19.8	0.4239	83.9 ± 14.4	<.0001
EPO (U/weekly)	3861.35±123.41	3232.91±109.15	3916.67±163.57	0.585	4729.66±208.12	<.0001
SI (μmol/L)	12.4±4.41	12.5±5.07	12.5±4.89	0.9146	12.6±5.44	0.9368
TIBC (μmol/L)	50.97±13.00	51.08±13.73	50.83±7.41	0.9477	52.11±15.61	0.7691
Alb (g/dL)	3.5 ± 0.5	3.6 ± 0.7	3.4 ± 0.6	0.1214	3.5 ± 0.8	0.0869
BMI (kg/m^2)	23.1 ± 1.4	25.6 ± 6.9	22.8 ± 3.6	0.5813	21.5 ± 5.5	0.009
Types of antihypertensive drugs	2.6± 0.5	1.3± 0.4	2.4± 0.9	0.1705	2.7± 0.6	<.0001
spKt/V	1.43±0.19	1.41±0.22	1.46±0.18	0.42	1.43±0.31	0.7513

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; EF = ejection fraction; CO = cardiac output; E/A = early/atrial mitral inflow velocities; LVMI = left ventricular mass index; Hb = hemoglobin; SI = serum iron; TIBC = total iron binding capacity; Alb = serum albumin; BMI = body mass index; †*P*: Group 1 vs. Group 2 (T=0 years) ; §*P*: Group 1 vs. Group 2 (T=2 years).

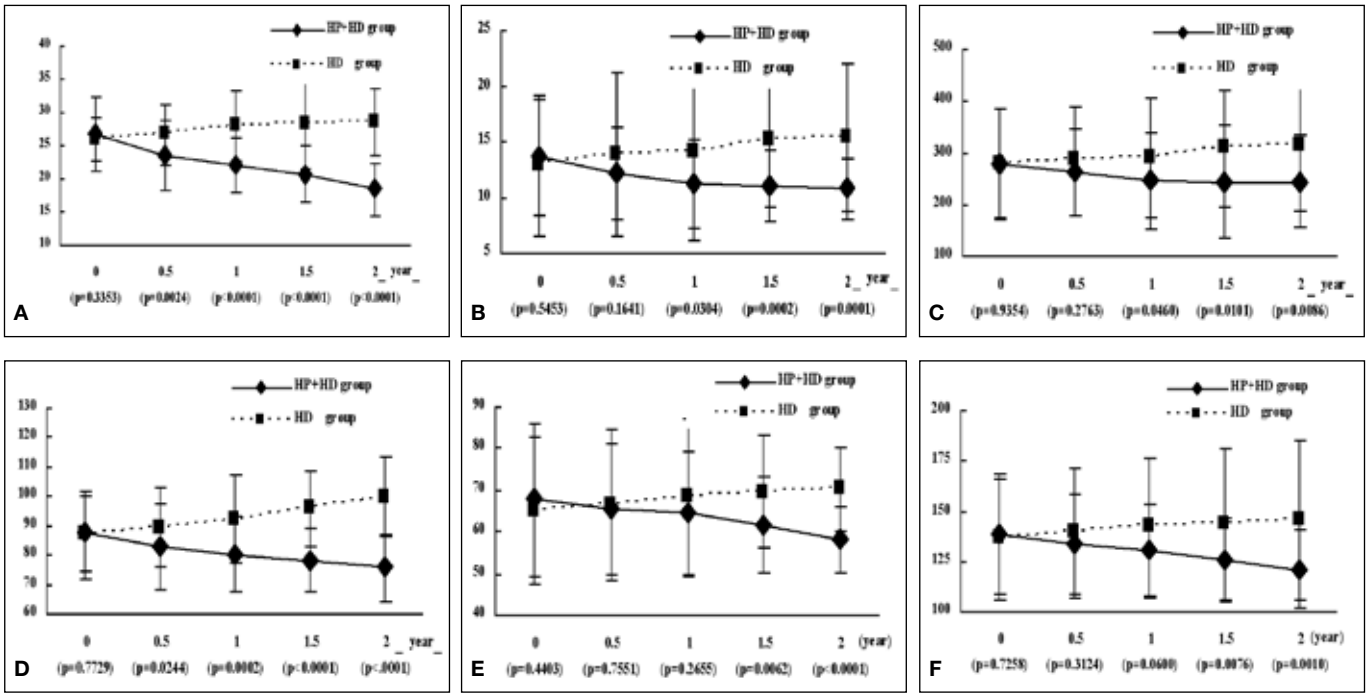

Fig. 2 - *Change trend of serum concentration of leptin, hsCRP, iPTH, IL-6, β_2-MG, and TNF-α during the 2-year observation period. Square and diamond represent mean; vertical line represents standard deviation.*

end of the 2-year observation period, SBP, DBP, HR, cardiothoracic ratio, LVMI, EPO doses and types of antihypertensive drug used in group 1 were lower than in group 2 (136.2±28.6 vs. 159.5±60.8; 71.4±15.6 vs. 90.6±32.4; 71.1±9.8 vs. 79.1±19.8; 0.42±0.028 vs. 0.48±0.052; 101.38±14.95 vs. 175.61±51.88; 3232.91±109.15 vs. 4729.66±208.12; 1.3±0.4 vs. 2.7±0.6, P < 0.05 respectively). Group 1 had evidently higher values of hemoglobin and EF than Group 2 (105.7±17.7 vs. 83.9±14.4; 72.4±6.8 vs. 62.5±10.5; p<0.01, respectively). However, no statistical difference was found between the two groups in serum albumin, CO, E/A, SI, TIBC and Kt/V (3.6±0.7 vs. 3.5±0.8; 5.81±0.96 vs. 5.83±1.55; 0.88±0.29 vs. 0.85±0.20; 12.5±5.07 vs. 12.6±5.44; 51.08±13.73 vs. 52.11±15.61; 1.41±0.22 vs. 1.43±0.31; p>0.05, respectively, see Tab. II).

In this study, at the end of the run-in period the baseline serum concentration levels of each patient's leptin, hsCRP, iPTH, IL-6, β_2-MG and TNF-α were tested. According to the statistical analysis of two-sample t test, the baseline values of the two groups of patients were similar (for both p>0.05). Yet during the observation period the serum concentrations of the six types of toxins mentioned previously remained lower in group 1 than in group 2. At the end of the 2-year observation period, the serum concentration levels of leptin, hsCRP, iPTH, IL-6, β_2-MG, TNF-α of group 1 dropped by 31.34%, 20.58%, 12.77%, 13.47%, 13.88%, and 12.56%, respectively, whereas these concentration levels of group 2 patients rose by 10.04%, 19.38%, 12.67%, 14.86%, 8.32%, and 6.67%, respectively. The comparison of the two groups of patients at the end of the 2-year observation period had statistical significance (18.4±3.9 vs. 28.5±5.1; 10.8±2.7 vs. 15.4±6.6; 243.9±89.9 vs. 313.1±125.7; 75.8±11.4 vs. 99.7±13.4; 58.3±7.9 vs. 70.3±10.1, 121.1±19.6 vs. 145.5±39.4, P <0.01 respectively). Figure 2 details the change trend of the six types of toxins during the 2-year observation period.

During the 2-year observation period, every 3 months the quality of life of each surviving patient was assessed using the SF-36. Overall, the results of this study show that compared with normal people in China, MHD patients scored significantly lower in the various dimentions of SF-36 (normal people score 100 in each domain of the SF-36). At the end of the 2-year observation period, it was found that the 2 groups showed no statistical difference in the dimentions of physical functioning, physical role and social function, but significant statistical difference in the domains of bo-

dily pain, general health, vitality, emotional role and mental health (64.62±27.54 vs. 44.31±21.45; 48.48±18.29 vs. 42.43±11.78; 56.82±21.59 vs. 49.36±20.11; 54.88±15.19 vs. 51.16±12.22; 65.09±20.24 vs. 55.23±21.47, $p<0.05$, respectively). In terms of total score, the two groups also had a statistically significant difference (59.76±19.46 vs. 41.09±15.52, $p<0.05$, see Tab. III).

During the 2-year observation period, a total of 6 patients from group 1 died (a mortality rate of 12.77%), whereas from group 2 a total of 14 patients died (a mortality rate of 31.82%). During the period, records were made about the time and cause of each patient's death and the Kaplan-Meier survival curve was drawn accordingly (see Fig. 3). Log-rank test results showed that in comparison group 1 had a significant survival advantage ($p<0.01$).

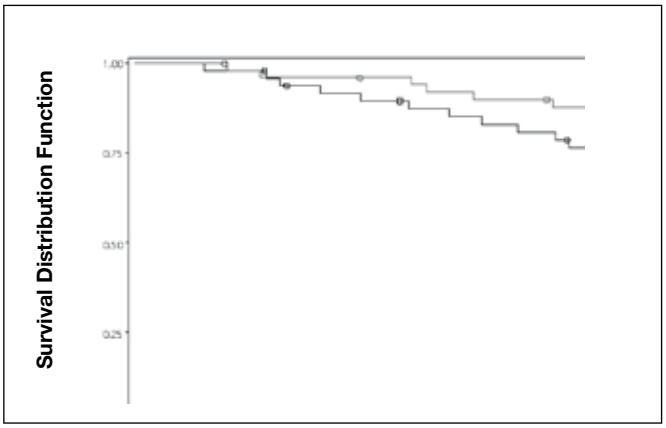

Fig. 3 - *Survival curve of the two groups of patients during the study period; log-rank test results indicated p<0.01.*

Safety issue

Three patients from group 1 suffered low blood pressure at the beginning of the HD+HP treatment but regained normal blood pressure after the blood flow was slowed and 200 mL of normal saline was perfused. Itching and rash occurred over the whole body of 2 patients from the same group when receiving HD+HP treatment but these symptoms were alleviated through intravenous injection of dexamethasone 5 mg. Hemorrhagic spots appeared on the inside of the forearms of 2 patients from the group. Considering it resulted from over-anticoagulation of the 2 patients due to the regular dosage of heparin in HP, the dosage of heparin was adjusted according to ACT and no more hemorrhagic spots appeared. During the study, no other adverse events such as a significant decrease of leukocyte or platelets occurred to group 1 patients.

TABLE III - SF-36 SCORES OF GROUP 1 VERSUS GROUP 2 AFTER TWO YEARS

Dimension	Group 1 n=41 2 years	Group 2 n=30 2 years	P
PF	58.48±20.05	57.32±19.45	0.8028
RF	38.64±21.84	36.56±19.43	0.6703
BP	64.62±27.54	44.31±21.45	0.0009
GH	48.48±18.29	40.43±10.78	0.0415
VT	56.82±21.59	49.36±20.11	0.0321
SF	58.69±15.74	55.35±12.57	0.0641
RE	56.88±15.19	51.16±12.22	0.0257
MH	65.09±20.24	55.23±21.47	0.0463
Total score	59.76±19.46	41.09±15.52	0.0069

PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT= vitality; SF = social functioning; RE = role-emotional; MH = mental health.

DISCUSSION

Uremic toxins are the major causes of uremic symptoms, metabolic disorders, and uremic complications. In addition to urea nitrogen and creatinine, middle and large molecule substance, protein-bound small molecules, short-chain amino acids and cytokines are at play in the pathological process of the complications of MHD patients. An increasing number of studies have confirmed that an increase of advanced glycation endoproducts (AGEs) and homocysteine (Hcy) is the independent risk factor for heart disease, accumulation of leptin is the cause of malnutrition and loss of appetite of ESRD patients (4), β_2-MG accumulation leads to amyloid change and carpal tunnel syndrome (5), the accumulation of iPTH results in renal osteodystrophy and ectopic calcification (6), renin accumulation leads to resistant hypertension, and the accumulation of cytokines such as IL-6 and IL-1 results in chronic systemic inflammation, while more and more studies show that such inflammation is related to atherosclerosis and malnutrition. Many of these complications are irreversible and cannot be alleviated even after renal transplantation, which poses a challenge to the long-term survival of patients on dialysis. For this reason, these cytokines have been one of our targets for

the treatment of MHD patients. In this study, 6 of them were chosen as objects of our observation.

With the failure of monoclonal antibodis or other anti-cytokine factor treatments, the expectation has grown that these cytokines should be removed (7). Before the 1980s, low-flux dialysis was the main technology for extracorporeal blood purification in uremia treatment, which could hardly remove the middle and large molecule toxins and protein-bound toxins. The patients consequently led a life of poor quality with long-term complications. After the 1980s, with developments in the research of dialyzer membranes and dialysis machines, high-flux dialysis and online -HDF were applied. The latter was especially efficient at clearing the middle and large molecule substances (8, 9). However, the rate of clearance of middle and large molecule toxins and protein-bound toxins by taking these measures could not match the rate these toxins grew inside the body. On the other hand, molecular interception using high-flux dialyzer reached 60 KD, so membrane permeability could not be increased any further, otherwise plasma albumin and visible components would be removed. Therefore, large-size and high-affinity blood adsorbent was introduced into the blood purification therapy for uremic patients. Winchester pointed out that middle and large molecule substances displayed a multicompartmental distribution, which made them hard to be removed with traditional HD, but they could be removed to varying degrees by the use of high-flux dialyzers (10, 11). HDF was superior to HD, while HP was more effective than HD and HDF in removing middle and large molecule substances. For this reason we assumed that HD+HP would be the ideal choice for uremic toxin removal as a model for a hybrid artificial kidney.

Vanholder et al reported the removal of leptin by HD+HP, stating that they found a single treatment could reduce the leptin concentration by 32% and continuous treatment for 3 weeks could reduce the concentration by 37% (12, 13). Combined with HD for one session, the Betasorb TM500 device (Renal Tech International, Monmouth Junction, NJ, usa) could remove a 2-day accumulation of β_2-MG; when this treatment was carried out 3 times a week, β_2-MG levels nearly approached physiological ones (14). The same device also worked well in the removal of middle and large molecules such as IL-6, TNF, and AGEs. The pre-test of our study also found HD+HP could effectively remove leptin, hsCRP, β_2-MG, IL-6, iPTH and TNF-α, while a single treatment could reach a clearance rate of 20.73~35.42%, which was consistent with reports of other scholars. Meanwhile, the pre-test revealed the middle and large molecules such as leptin, hsCRP, β_2-MG, IL-6, iPTH and TNF-α returned to their original level of serum concentration about 7 days after the single treatment.

Therefore, in the present study once-a-week maintenance HP combined with regular HD was adopted so that middle and large molecule toxins in MHD patients could be cleared steadily and controlled at a lower level with the dialysis age. In our study, at the end of the 2-year observation, the serum concentration levels of leptin, hsCRP, iPTH, IL-6, β2-MG, TNF-α of group 1 dropped by 31.34%, 20.58%, 12.77%, 13.47%, 13.88%, and 12.56%, respectively, whereas these concentration levels of group 2 patients rose by 10.04%, 19.38%, 12.67%, 14.86%, 8.32%, and 6.67%, respectively. This indicates that for those who received HD + HP treatment, the serum concentrations of these 6 types of toxins declined to varying degrees (although remaining higher than in healthy people), while for those receiving HD alone, they instead continously rose. Our study also showed that group 1 had a higher total score of quality of life assessed with SF-36 and alower mortality rate than group 2 ($p<0.05$, respectively). Therefore, we assume that the better clinical prognosis of group 1 may be clinically related to the continuous drop in the 6 types of toxins after they received HD+HP treatment.

The aim of this study was to investigate the efficacy and safety of the model of artificial kidney of HD+HP treatment rather than the HP apparatus (HA-130, Zhuhai Li Zhu Group, Biological Material Co., Ltd., Xiangzhou, Zhuhai, Guangdong, China) in this study. The choice of HP apparatus varing with clinical studies might have something to do with the national health insurance policies as well as the financial capacity and clinical condition of patients. With different apparatuses we are very likely to get different reports about the clearance rate of the above 6 types of toxins. So we believe the above 6 types of toxins would drop more drastically and the patients would get a better clinical prognosis by using an HP apparatus with better capacity for large-size molecules and high-affinity.

In addition, we assume the prognosis of group 1 patients not only depends on the concentrations of the 6 types of toxins but also on their better blood pressure, heart rate,

Hb, LVMI, EF, BMI, and so forth. For example, the better control of blood pressure and heart rate can reduce the incidence of cardiovascular and cerebrovascular events of MHD patients, thereby reducing their mortality. In addition, HP may also clear those toxins whose chemical structures and corresponding functions are still unclear at present, thereby helping to improve the prognosis of MHD patients.

In addition, by using rH-EPO, maintenance HD combined with HP not only ensured the thorough clearance of small molecule toxins, but was also able to remove the medium and large molecule toxins, which would help alleviate the systemic inflammation of uremic patients and increase the effect of the treatment of uremic anemia more effective than HD alone (15). One of the most important causes for uremic anemia is the decrease in the production of EPO by renal interstitial cells. Another important cause is that uremic patients have had systemic inflammatory response syndrome (SIRS) for a long time. The functional iron deficiency of patients in an inflammatory state can cause the decline of reticulocyte hemoglobin content (CHr), which will in turn lead to lower responsiveness of EPO (16, 17). In addition, medium and large molecule toxins such as hsCRP, iPTH, IL-6, and TNF-α accumulated in the patient's body will directly inhibit the maturation of erythrocytes.

These statements explain our results: during the 2-year follow-up, group1 showed a higher hemoglobin level than group 2; group1 used a lower dosage of rh-EPO than group 2 (since with reduced toxins present in body, less EPO is needed); there was no statistical difference in iron metabolism between the two groups (each patient was checked for iron metabolism and received intravenous iron treatment periodically.)

In this study, the adsorbents for the HA130 HP apparatus are neutral resin, whose adsorption capacity depends primarily on the molecular sieve effect of the three-dimensional network structure and the affinity between the resin molecular group and the adsorbed material as well as electric gravitation between molecular groups. They could therefore selectively adsorb those middle and large molecule uremic toxins (such as parathyroid hormone, β_2-MG, leptin, renin and angiotensin, cytokines, etc.) and protein-bound toxins (such as homocysteine, indole sulfate, spermine, cresol, etc.). In the one-time use of resin adsorption column during the treatment, no pyrogen reaction or blood cell decrease occurred, suggesting its good biocompatibility. During the 2-year observation period, 2 patients developed hypotension, but after receiving rehydration therapy (saline 200 mL) their blood pressure returned to normal, which might be related to an increase in the patients' blood volume *in vitro*. One-time use of resin adsorption column cascaded plus dialyzer could both increase blood cells and serum proteins as blood concentrated after dialysis dehydration. No other adverse event or side effect was observed. As HP could neither clear excess water in the uremic patient's body, nor regulate electrolyte and acid-base balance, normally it was not advised to be employed alone. However, when HP was combined with HD, the complementary use of the two different methods of blood purification was able to fully remove the metabolites, toxins, and pathogenic factors as well as regulate water, electrolyte, and acid-base balance in patients, rapidly improving the patients' sleep and appetite while alleviating itchy skin symptoms, which in turn would prevent the recent and long-term complications in patients, improve quality of life, and prolong life (18).

In conclusion, the combination of maintenance HD with HP can remove uremic toxins more fully and effectively. In spite of the fact that active control of complications is a thorny task, this study suggests that this model of artificial kidney may be an important means for improving the quality of life of MHD patients and the rate of their mid- and long-term survival.

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