Blood Purification

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Randomized Control Study on Hemoperfusion Combined with Hemodialysis versus Standard Hemodialysis: Effects on Middle-Molecular-Weight Toxins and Uremic Pruritus

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Abstract
Introduction: Classic hemodialysis schedules present inadequate middle-molecular-weight toxin clearance due to limitations of membrane-based separation processes. Accumulation of uremic retention solutes may result in specific symptoms (e.g., pruritus) and may affect clinical outcome and patient's quality of life. Hemoperfusion (HP) is a blood purification modality based on adsorption that can overcome such limitations, and thus, it may be interesting to test the efficacy of at least one session per week of HP combined with hemodialysis. This is a randomized, open-label trial, controlled, multicenter clinical study to investigate the effect of long-term HP combined with hemodialysis on middle-molecular-weight toxins and uremic pruritus in maintenance hemodialysis (MHD) patients. ***Methods:*** 438 MHD patients from 37 HD centers in China with end-stage kidney disease (63.9% males, mean age 51 years) suffering from chronic intractable pruritus were enrolled in the study. Eligible patients were randomized into four groups: low-flux hemodialysis (LFHD), high-flux hemodialysis (HFHD), HP + LFHD, and HP + HFHD at a 1:1:1:1 ratio. Beta-2 microglobulin (β2M) and parathyroid hormone (PTH) were measured at baseline, 3–6, and 12 months. At the same time points, the pruritus score was evaluated. The primary outcome was the reduction of β2M and PTH, while the secondary outcome was the reduction of the pruritus score. ***Results:*** In the two groups HP + LFHD and HP + HFHD, there was a significant decrease of β2M and PTH levels after 12 months compared to the control groups. No significant differences were noted between HP + LFHD and HP + HFHD. Pruritus score reduction was 63% in the HP + LFHD group and 51% in the HP + HFHD group, respectively. ***Conclusion:*** The long-term HP + HD can reduce β2M and PTH levels and improve pruritus in MHD patients independently on the use of high- or low-flux dialyzers, showing that the results are linked to the effect of adsorption.

Introduction

The hemodialysis (HD) treatment is intended to clear the uremic toxins accumulated in the patients with end-stage kidney disease (ESKD). However, due to limitations imposed by membrane permeability, a significant amount of uremic molecules with medium-high molecular weight such as beta-2 microglobulin (β2M) and parathyroid hormone (PTH) can still accumulate in dialysis patients [1] being associated with specific complications such as dialysis-related amyloidosis, malnutrition, uremic pruritus (UP) [2–7] cardiovascular disease [8–11], and mortality [12–16].

Although high-flux HD (HFHD) and hemodiafiltration (HDF) display increased middle molecule clearance compared to low-flux HD (LFHD) [17–23], clinical outcomes are still unsatisfactory [24, 25]. Hemoperfusion (HP) expands the capacity of removal of uremic toxins using adsorption as a main mechanism. Previous studies showed that HP combined with HD (HP + HD) can increase the clearance of middle-molecular-weight toxins and improve symptoms such as UP [26–29]. A meta-analysis suggested that HP + HD may improve clinical outcomes, life expectancy and quality of life [30]. These observations require further evidence, and in particular, it should be clarified if HP + LFHD and HP + HFHD present comparable effects. The purpose of this study was to investigate the long-term effects of once weekly HP + LFHD or HP + HFHD compared to standard LFHD and HFHD in terms of β2M/PTH levels and UP in ESKD patients undergoing regular dialysis (maintenance hemodialysis [MHD]).

Methods

Study Design

This is an open-label prospective, randomized, controlled, multicenter clinical study. Thirty-seven HD centers from 20 provinces in China participated in the study. The primary efficacy hypothesis was the positive effect of the intervention (HP + LFHD or HP + HFHD) versus standard treatments (LFHD and HFHD) on UP and middle-molecular-weight toxins clearance in MHD patients and a noninferiority effect of HP + LFHD compared to HFHD on the same targets.

The study was sponsored by the National Clinical Research Center for Kidney Diseases of the Chinese PLA General Hospital. The Giant Med-Pharma Service Group undertook the quality supervision of this study. The Medical Statistics Department of Peking University First Hospital processed and analyzed the data. The study was conducted in accordance with all local laws, good clinical practice guidelines, and the Declaration of Helsinki. The study protocol was approved by the independent Ethics Committees of each study site. All patients provided written informed consent before their enrollment in the study. This trial was registered with ClinicalTrials.gov, No. NCT02461953.

Eligible patients were enrolled at each study site according to inclusion, exclusion, and withdrawal criteria shown in Table 1. After signing informed consent, all patients were first treated with LFHD for 8 weeks as a washout period. After the washout period, the eligible patients were randomized into four groups: LFHD, HFHD, HP + LFHD, and HP + HFHD at a 1:1:1:1 ratio. A com-

Table 1. The inclusion, exclusion, and withdrawal criteria

Inclusion criteria
1. Males or females, aged ≥18 years
2. HD duration >3 months
3. Regular HD, three times a week, 4 h per session
4. PTH ≥300 pg/mL
5. Written informed consent signed
Exclusion criteria
1. Allergic to HD dialyzer or HP apparatus
2. PLT $<60 \times 10^9$/L
3. Blood flow <200 mL/min
4. Serum albumin <30 g/L
5. Kt/V <1.2
6. PTH >800 pg/mL
7. HDF
8. Coagulation disorder and severe bleeding tendency, with active bleeding
9. Severe hypotension and severe cardiopulmonary insufficiency
10. Under other drug trials
11. Acute infection, severe heart, lung, liver, nervous diseases, and malignant tumors
Withdrawal criteria
1. Obvious adverse events such as organ bleeding and subcutaneous purpura were observed during the treatment
2. Coagulation function was significantly prolonged ≥ normal value more than 1 times or thrombocytopenia $<60 \times 10^9$/L
3. Failed to undergo blood purification treatment
4. Violated the study requirements
5. Accorded to the requirements of patients, investigators, or sponsors
6. The ethics committee decided to discontinue the trial

HD, hemodialysis; HP, hemoperfusion; PTH, parathyroid hormone; PLT, platelets.

puter-generated permuted block randomization was used, with a block size of four and stratified by study site. After the patients entered the washout period, treating physicians from centers referred to a central random system, and the CRO monitoring company issued a random number to the eligible patients. The treatment assignment was not masked to the patients and local physicians, while the investigators who evaluated results were blinded to randomized groups.

Procedures

After the 8-week washout period and subsequent randomization, a 12-month observation period was scheduled for each group (all patients were treated three times a week at 4 h per session). A detailed protocol for each group is shown in Table 2. Polysulfone dialyzers (various brands) with a surface area of 1.3–1.6 m^2 were utilized in all patients. Low-flux and high-flux dialyzers were defined by an ultrafiltration rate <20 mL/h·mm Hg and >40 mL/h·mm Hg, respectively. For HP, the HA130 cartridge (Jafron Biomedical, Zuhai, China) was utilized and placed in series with the hemodialyzer. Dialysis prescription was as follows: dialysis time = 4 h, average blood flow rate = 250 mL/min, average dialysate flow rate = 500 mL/min, bicarbonate dialysate, calcium ion concentration: 1.25–1.5 mmol/L. During the study, routine medication therapy (i.e., anemia and hypertension) remained unchanged unless a different prescription was required according to patient needs.

Venous blood samples were collected before the first dialysis of the week at baseline, 3rd, 6th, and 12th months. Blood routine and biochemical tests were measured at each study site. The β2M (Siemens; scatter turbidimetry) and iPTH (Roche Elecsys) were centrally measured at the leading study site, after being locally centrifuged (10 min at 3,000 rpm) and transported in a cold chain under −80°C conditions.

At each follow-up point, patients were evaluated for the pruritus score assessed using Duo's Modified Itching Rating Scale [31]. The assessment method was subject to a uniform scale, and the patients were assessed by trained medical professionals at each center. Safety monitoring was made by recording any treatment or device-related adverse event (AE).

Study End Points

The primary end point was the reduction ratio of middle-molecular-weight toxins calculated as (β2M or PTH baseline value – 12th-month value)/baseline value × 100%. The secondary outcome measure was the reduction ratio of the pruritus score, calculated as the primary outcome. Safety indicators included blood routine and biochemical tests at each visit point to determine possible effect on the studied subjects.

Statistical Analysis

The sample size was calculated separately for noninferior and superior efficacy hypothesis. All hypothetical bounds were 5%,

Table 2. Treatment modalities representing the four studied groups

Group	Dialyzer ultrafiltration rate	Dialyzer membrane	Dialyzer surface area, m^2	HP
LFHD	<20 mL/h·mm Hg	Polysulfone	1.3~1.6	No HP
HFHD	>40 mL/h·mm Hg	Polysulfone	1.3~1.6	No HP
HP + LFHD	<20 mL/h·mm Hg	Polysulfone	1.3~1.6	Once HP per week combined with LFHD for 2 h, followed by LFHD for 2 h.
HP + HFHD	>40 mL/h·mm Hg	Polysulfone	1.3~1.6	Once HP per week combined with HFHD for 2 h, followed by HFHD for 2 h.

LFHD, low-flux hemodialysis; HFHD, high-flux hemodialysis; HP, hemoperfusion.

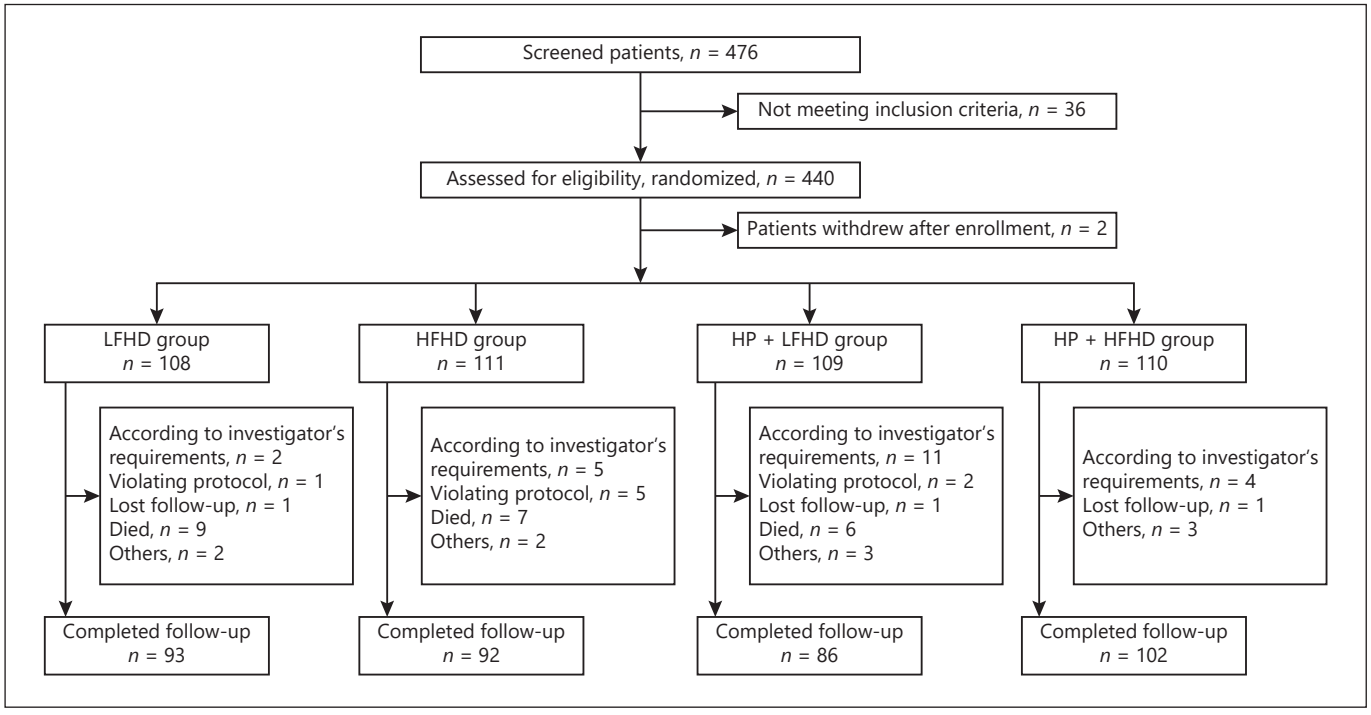

Fig. 1. The flow of patients through the study. LFHD, low-flux hemodialysis; HFHD, high-flux hemodialysis; HP, hemoperfusion.

with α = 0.05 at a two-sided test; the power of β was 0.8 and calculated using a single β2M clearance rate. According to laboratory data, HFHD was 49.8 ± 7.4%, and HP + HFHD was 58.3 ± 5.3%. For conservative projections, 7.4% was used as the sample size to estimate the standard deviation. Therefore, 36 patients were required in each group for the noninferiority efficacy, and 72 patients were required in each group for the superiority efficacy, respectively. Therefore, the maximum sample size required was selected and expanded to 100 pairs considered by the shedding and exclusion factors.

The intergroup analysis was performed on the primary outcome (reduction ratios of 12-month β2M or PTH) and the secondary outcome (reduction ratios of 12-month pruritus score), while intragroup analysis was performed on the β2M or PTH at the follow-up time points for 3rd, 6th, and 12th months, respectively, or pruritus scores at different time points before and after. All analyses were based on the efficacy full analysis set–intention to treat population, which included all patients who had undergone randomization and had baseline and at least one post-baseline observation indicator. Less than 10% of the subjects entering the FAS set were absent from the indicators; the last observation carry-over method was used to fill the data. For the noninferior and superior test, the superiority margin was 5%, and the noninferiority margin was −5%. For the quantitative data subject to a normal distribution, ANOVA was used for the comparison between groups, and *t* test was used to compare different intragroup time points before and after. The Wilcoxon or Kruskal-Wallis rank-sum test was used for that was not subject to normal distribution. χ^2 was used to compare qualitative data.

If the primary efficacy was achieved, further analysis would be performed to determine the effect of HP on the reduction ratios of β2M or PTH, respectively, and to determine whether there was an

Table 3. General characteristics of patients at baseline

	LFHD (*N* = 108)	HFHD (*N* = 111)	HP + LFHD (*N* = 109)	HP + HFHD (*N* = 110)	Total
Sex, male, *n* (%)	60 (55.6)	77 (69.4)	67 (61.5)	76 (69.1)	280 (63.9)
Age, years	54±14	50±13	49±13	49±12	51±13
BMI, kg/m^2	22±3	23±4	23±4	23±4	23±4
Dry weight, kg	59.4±11.8	65.3±14.2	62.8±12.8	64.8±14.1	63.12±13.43
BP, mm Hg	145/84	144/84	145/85	143/83	144/84
Duration of dialysis, years	2.69 (1.64, 4.90)	2.38 (1.24, 4.69)	3.18 (1.28, 5.63)	3.35 (2.02, 5.89)	2.99 (1.35, 5.19)
Access, *n* (%)					
Arteriovenous fistula	89 (82.4)	100 (90.1)	89 (81.7)	98 (89.1)	376 (85.8)
Central venous catheter	19 (17.6)	11 (9.9)	18 (16.5)	11 (10)	59 (13.5)
Other	0 (0)	0 (0)	2 (1.8)	1 (0.9)	3 (0.7)
Urea, mmol/L	25.7±7.1	25.2±6.4	24.9±5.9	26.5±6.7	25.55±6.52
Creatinine, μmol/L	954±272	1,022±265	1,009±298	1,046±299	1,007.60±284.97
Kt/V	1.45±0.40	1.45±0.39	1.47±0.39	1.55±0.91	1.48±0.57
Albumin, g/L	40±4	40±4	41±4	40±4	40±4
Hemoglobin, g/L	108±15	106±16	107±15	111±14	108±15
PLT, 10^9/L	173±59	182±63	176±54	184±61	178.94±59.57
Serum potassium, mmol/L	5.05±1.24	4.98±0.81	5.01±0.93	5.16±1.00	5.05±1.01
Serum sodium, mmol/L	138±3	139±3	138±4	138±4	138.32±3.53
Serum calcium, mmol/L	2.12±0.39	2.13±0.33	2.15±0.37	2.19±0.36	2.15±0.36
Serum phosphorus, mmol/L	1.88±0.64	2.00±0.66	2.06±0.56	2.19±0.63	2.03±0.63
β2M, mg/dL	3.93±1.24	3.55±1.41	4.46±1.45	4.08±1.34	4.00±1.40
PTH, pg/mL	373 (219, 489)	311 (217, 457)	386 (252, 520)	417 (284, 581)	405 (243, 513)

LFHD, low-flux hemodialysis; HFHD, high-flux hemodialysis; HP, hemoperfusion; β2M, β2-microglobulin; PTH,parathyroid hormone; BMI, body mass index; BP, blood pressure; PLT, platelets.

interaction between HP and flux of the HD dialyzer. The method was to construct a general linear model with the 12th month β2M (or PTH) relative to baseline reduction ratios as a dependent variable and baseline β2M (or PTH), flux of the dialyzer, HP or not, and flux of the dialyzer +HP (interaction term) as independent variables.

All analyses were performed in SAS version 9.4. p value <0.05 was considered statistically significant.

Results

Patient Enrollment and Baseline General Conditions

438 patients were enrolled between June 8, 2015, and December 31, 2017, of whom 108 were randomly assigned to the LFHD group, 111 to the HFHD group, 109 to the HP + LFHD group, and 110 to the HP + HFHD group. Of the enrolled participants, 8 patients violated the protocol, 22 patients died, 3 patients were lost follow-up, and 32 patients withdrew from the study for other reasons. Finally, 354 patients completed the 12-month follow-up, 93 (86.1%) patients in LFHD group, 92 (82.9%) patients in the HFHD group, 86 (78.9%) patients in the HP + LFHD group, and 102 (92.7%) patients in the HP + HFHD group. The flow of patients through the study is shown in Figure 1. Baseline characteristics of the eligible study population are shown in Table 3. 63.9% were males, with an average age of 51 years.

Effect of Middle-Molecular-Weight Toxins (PTH and β2M)

The average baseline level of β2M was 4.00 ± 1.40 mg/dL. In the LFHD group, there were no significant changes between any of the three follow-up time points compared with the baseline. In the HP + LFHD group, the levels of the 6th and 12th month decreased significantly. In the HFHD group and HP + HFHD group, β2M levels significantly decreased at the three follow-up time points from baseline (Fig. 2; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525225). The 12-month reduction ratios (Fig. 3; online suppl. Table 2) showed statistical significance between the LFHD group and the HP + LFHD group (p < 0.001), HFHD group, and HP + HFHD group (p < 0.001), but there was no statistical significance between the HP + LFHD group and HFHD group. The results of primary efficacy showed that (Fig. 4; online suppl. Table 3) the 12-month reduction

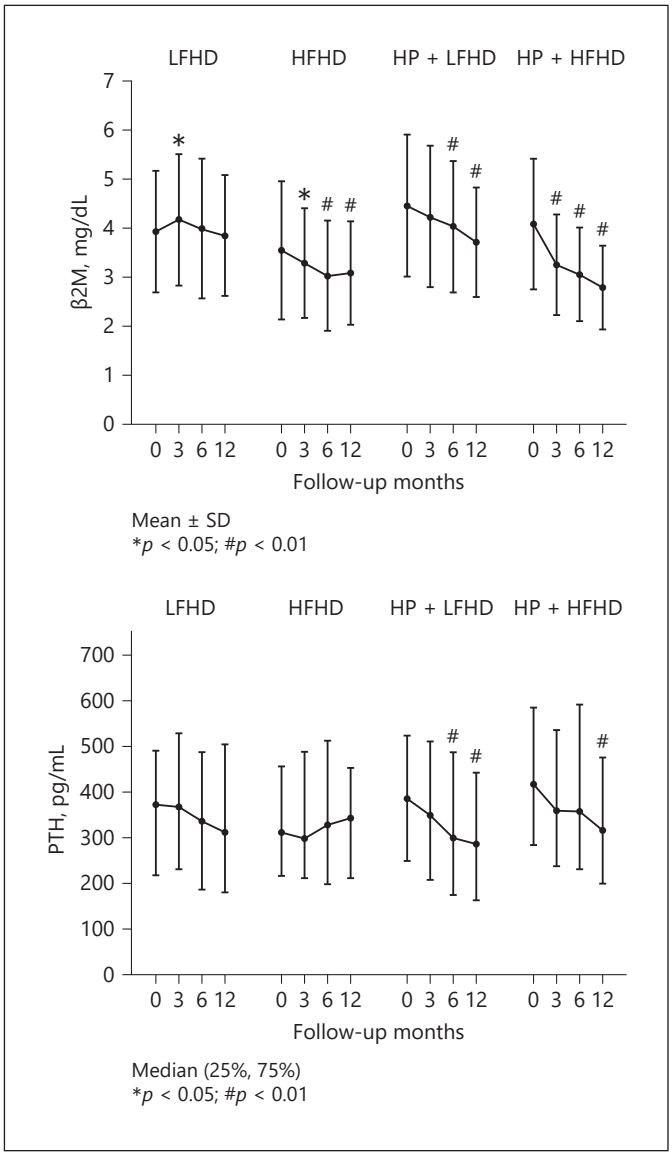

Fig. 2. β2M and PTH: levels at the 3rd, 6th, 12th months and intragroup analysis, compared with baseline values within the groups. LFHD, low-flux hemodialysis; HFHD, high-flux hemodialysis; HP, hemoperfusion; β2M, β2-microglobulin; PTH, parathyroid hormone. $^{*}p < 0.05$, $^{\#}p < 0.01$.

ratios of β2M in the HP + LFHD group were noninferior to those of the HFHD group (8.22 [−1.3, 17.8], $p = 0.007$), the HP + LFHD group was superior to the LFHD group (15.9 [7.0, 24.95], $p = 0.017$), and the HP + HFHD group was superior to the HFHD group (22.2 [12.6, 31.9], $p < 0.001$).

The average level of baseline PTH was 405 (243, 513) pg/mL. In the LFHD group and HFHD group, there were no significant changes between the three follow-up time points and the baseline values. In the HP + LFHD group, there was a significant decrease at 6th and 12th months compared with the baseline values. In the HP + HFHD group, the levels at all three time points decreased from baseline, but statistical significance was only reached at 12 months (Fig. 2; online suppl. Table 1). The 12-month reduction ratios (Fig. 3; online suppl. Table 2) showed a significant difference between the HP + LFHD group and the HFHD group ($p < 0.001$), the HP + LFHD group, and the LFHD group ($p < 0.001$), the HFHD group and HP + HFHD group ($p < 0.001$). The results of primary efficacy showed that (Fig. 4; online suppl. Table 3) the reduction ratios of 12-month PTH in the HP + LFHD group were noninferior to those of the HFHD group (difference between groups 32.0 [17.5, 46.5], $p < 0.001$); the HP + LFHD group was superior to the LFHD group (difference between groups, 23.7 [8.4, 39.1], $p = 0.017$), but there was no statistical significance between the HP + HFHD group and HFHD group (difference between groups, 21.0 [4.4, 37.6], $p = 0.059$).

Table 4. Factorial analysis on the reduction ratios of the 12-month β2M (PTH) and the fluxes of HD dialyzer and HP

	β2M		PTH	
	parameter estimation	*p* value	parameter estimation	*p* value
Baseline	14.42	<0.001	0.06	<0.001
HFHD	13.21	<0.001	−5.89	0.456
HP	8.28	0.038	22.04	0.006
HP*HFHD	6.22	0.262	−7.85	0.484

β2M, β2-microglobulin; PTH, parathyroid hormone; HD, hemodialysis; HFHD, high-flux hemodialysis; HP, hemoperfusion.

Factorial Analysis of Flux of the HD Dialyzer and HP

Twelfth month β2M or PTH reduction ratios were used as a dependent variable, and baseline β2M (or PTH), flux of the dialyzer, HP or not, and flux of the dialyzer +HP (interaction term) as dependent variables to construct a general linear model for factorial analysis. The results (Table 4) showed that HFHD increased the reduction ratios at 12 months of β2M by 13.21%, and HP increased it by 8.28%. The effect of the two factors on the reduction ratios at 12 months of β2M was statistically significant, while the effect of both factors combined interactively was no significant. HFHD declined the reduction ratios at the 12 months of PTH by 5.89%, but there was no statistical significance. However, HP increased it by

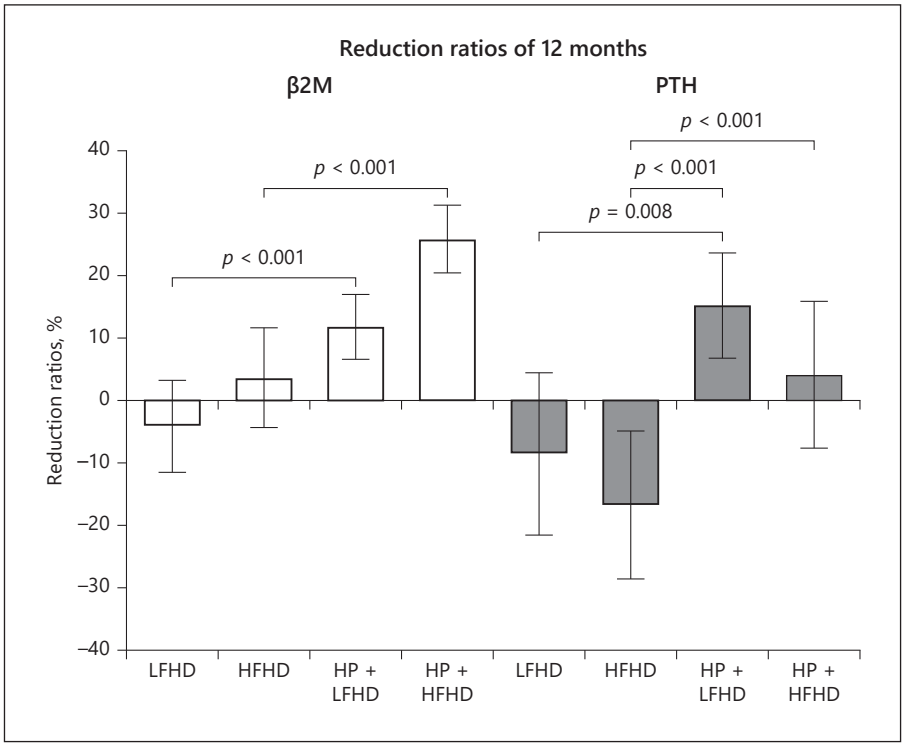

Fig. 3. Reduction ratios of β2M and PTH: intergroups analysis. LFHD, low-flux hemodialysis; HFHD, high-flux hemodialysis; HP, hemoperfusion; β2M, β2-microglobulin; PTH, parathyroid hormone.

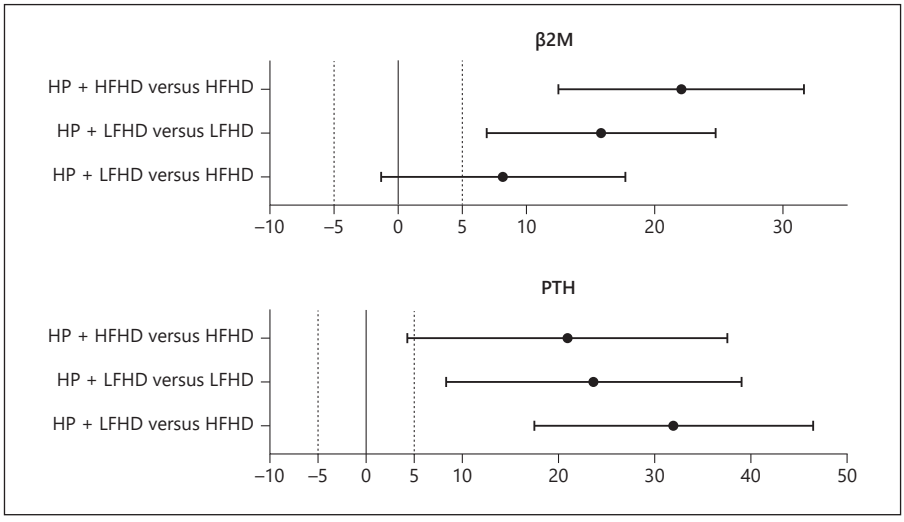

Fig. 4. Reduction ratios of β2M and PTH: efficiency test. LFHD, low-flux hemodialysis; HFHD, high-flux hemodialysis; HP, hemoperfusion; β2M, β2-microglobulin; PTH, parathyroid hormone.

22.04% on average, and it was statistically significant. The effect of both combined interactively was not statistically significant.

Improvement of Pruritus

The UP scores of the LFHD group and HFHD group were higher than those of the baseline, and there were statistical differences at 12 months. The scores decrease at each time point, and there were statistical differences in the HP + LFHD group and HP + HFHD group, respectively (online suppl. Table 4). The 12-month UP score reduction ratios (Fig. 5; online suppl. Table 5) were 63% (55, 71) and 51% (40, 62) in the HP + LFHD group and HP + HFHD group, respectively, while −75% (109, −41) and −92% (−165, −19) in the LFHD group and HFHD group, respectively. The comparison be-

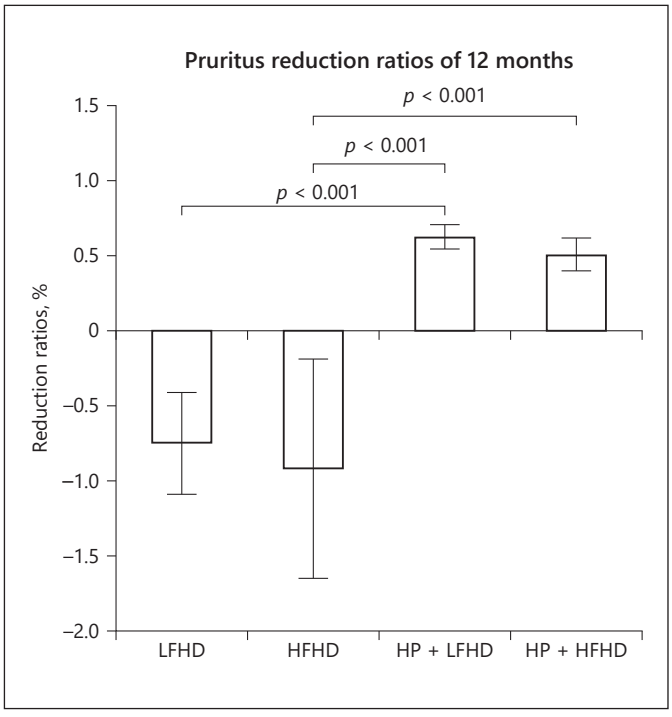

Fig. 5. Reduction ratios of pruritus: intergroups analysis. LFHD, low-flux hemodialysis; HFHD, high-flux hemodialysis; HP, hemoperfusion.

tween groups showed that there was statistical significance between the HFHD group and HP + LFHD group ($p < 0.001$), LFHD group and HP + LFHD group ($p < 0.001$), HFHD group and HP + HFHD group ($p < 0.001$).

Safety Evaluation

After 12 months of treatment, blood values were compared with the baseline level. There were no statistical differences between the clinical indicators including PLT, urea, SCr, ALB, K, Na, Ca, while the levels of Hb and P presented significant changes among the four groups. There was no difference in the incidence of AE in the four groups during the study period. AEs ranged from 1.80% to 7.27% of all sessions. The most common AEs were hypotension and coagulation disorders. The rate of hospitalization in 12 months ranged from 9.09% to 16.67%. The results showed that there was no statistical significance in the number of hospitalized patients among the four groups. No clinical or technical events resulted specifically correlated to the additional use of HP cartridge in the HP + LFHD and HP + HFHD groups.

Discussion

The purpose of the study was to evaluate the long-term effect of HD combined once weekly with HP on middle-molecular-weight toxins and UP in MHD patients. To our knowledge, this is the largest prospective clinical study on HD combined with HP. The logic behind the study and the four group randomization is to elucidate if HFHD is superior to LFHD and if HP + LFHD is noninferior to HFHD and to HP + HFHD. In this view, the importance of the contribution of adsorption can be demonstrated, and new therapeutic options can be proposed. The choice to use HP once weekly depends on the calculation of medium-large solute kinetics in the body where inter-compartmental transport is much slower than that of small solutes (urea and creatinine). At the same time, particular attention to the costs of various techniques may suggest to combine cost/benefits in the most efficient way. Patients were followed up for 12 months, and our results indicate that HP + LFHD was noninferior to HFHD, while HP + HFHD was superior to HP + LFHD and HFHD.

These results are of particular importance since according to the Chinese National Renal Data System [32], 61.9% of dialyzers were low-flux in the last years. LFHD is unable to clear middle-molecular-weight toxins, while HFHD and HDF, less commonly utilized, are reported to present a better performance [17–23]. However, previous studies have identified the HP + HD was superior to HD in terms of middle and large uremic toxin elimination [26, 27]. These findings have suggested a potential role for once HP + HD per week in the treatment to improve clinical conditions possibly associated with middle-large toxin accumulation.

Several toxins are retained in uremia, and some specific complications are known to be associated with their retention and increased levels in blood [1]. In order to make the meaning of the study generalizable, we decided to evaluate the clearing efficiency of different schedules for multiple indicators. As both β2M and PTH are considered classic middle-molecular-weight uremic toxins [15, 33, 34], they were selected as marker molecules for this study.

As prespecified in the statistical analysis plan, for the patients in the intention-to-treat, we performed an intragroup analysis of β2M levels at different time points (3, 6, and 12 months). The results showed that both HP + HFHD and HFHD were associated with a reduced β2M level, while LFHD alone could not reduce the β2M level. Conversely, HP + LFHD displayed a significant reduction

capacity. The β2M reduction ratio analysis at 12 months showed that both HP + LFHD and HP + HFHD were significantly superior to LFHD and HFHD, respectively. The results of the validity analysis further confirmed that the effect of HP + LFHD on β2M was noninferior to HFHD, while HP + LFHD and HP + HFHD were, respectively, superior to LFHD and HFHD alone. Our results confirmed previous findings [20]. In particular, we may draw the conclusion that once weekly HP associated to LFHD or HFHD can adequately control β2M in ESKD patients on MHD. Not all patients can receive high-volume HDF, and not all healthcare systems in the world can afford complex therapies such as On-Line HDF. Patients may not have vascular access capabilities for high blood flows, and regional dialysis programs may not supply expensive procedures. For this reason, one might speculate that the use of low-flux dialyzers can be still adequate if once weekly HP is coupled with the dialysis session in a simplified extracorporeal circuit. The cost benefit calculation may be in favor to this solution in which the cost of one sorbent cartridge is distributed over a week period and the three dialysis sessions. Similar considerations may emerge for PTH and for other uremia retention products in the middle- to large-molecular-weight range.

UP is a common complication in chronic dialysis that seriously affects patients' quality of life. Inadequate clearance of uremic toxins has been identified as its main cause. In fact, UP is often observed in patients with high levels of PTH and β2M [35]. In our study, PTH levels in HP + LFHD and HP + HFHD were reduced at different time points, while levels remained unchanged in LFHD and HFHD. The 12-month PTH reduction ratios in subgroup analysis showed that HP + LFHD and HP + HFHD significantly improved blood levels compared with LFHD and HFHD. Furthermore, HP + LFHD significantly improved PTH reduction ratios compared to HFHD. The validity analysis confirmed such results. Although previous studies suggested that HFHD is able to clear PTH to some extent, we may speculate that it cannot effectively reduce PTH levels, and high-dose medications may be continuously required [36–39].

The main component of HP is resin, which has the clearing effect of β2M and PTH because of the direct adsorption of resin to middle-molecular uremic toxins. However, to determine whether the ultrafiltration volume of the HD dialyzer will affect its clearing effect, we conducted further factorial analysis on the flux of dialyzer combined with HP. The results indicate that the effect of adsorption (HP) is independent on the convective component of the treatment.

While biochemical parameters are objective parameters, UP improvement could be, at least in part, due to subjective factors. In fact, the impossibility to blind patients to the technique represent a limitation, and we cannot rule out a "intervention" psychological effect.

This study has several other limitations. Numerous uremic toxins, such as advanced glycation endoproducts, homocysteine, and leptin, play a role in uremia, and therefore, more marker molecules should be studied in future trials. Furthermore, while we are aware that pharmacological therapy might affect PTH levels, we tried to maintain original prescription unchanged as far as possible. In most cases, medications were scaled down possibly multiplying and enhancing the HP effect.

Conclusion

Long-term combination of HP with HD can significantly reduce β2M and PTH levels and improve pruritus in MHD patients. The effect of HP + LFHD was noninferior to HP + HFHD. These results open a new pathway toward adequate/optimal blood purification in ESKD patients. Not only the addition of adsorption could reduce complications due to uremia retention products but also it could be a possible way to prevent such complications if timely applied in MHD.

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Statement of Ethics

The study was conducted in accordance with all local laws, Good Clinical Practice guidelines, and the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of Chinese PLA General Hospital, approval number (2014 [011]). All patients provided written informed consent before enrolling in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Xiangmei Chen, Xuefeng Sun, and Guangyan Cai conceived and designed study. Delong Zhao wrote the first draft of this manuscript. Delong Zhao, Yuanda Wang, and Yong Wang developed the CRFs and reviewed original data. Xiangmei Chen and Xuefeng Sun reviewed the manuscript. Yuanda Wang, Yong Wang, Aili Jiang, Ning Cao, Yani He, Junxia Wang, Zhiyong Guo, Wenhu Liu, Wei Shi, Lirong Hao, Jinyu Li, Wenge Li, Caili Wang, Jianqin Wang, Hongli Lin, Wei Shi, Lihua Wang, Hongli Jiang, Guohua Ding, Yun Li, Wenbo Hu, Hua Yue, Jian Liu, Xiaoping Yang, Yibin Yang, Guohui Liu, Hong Li, Yuefei Xiao, Niansong Wang, Gengru Jiang, Guoying Ma, Jie Wang, Ying Li, Rongshan Li, Qian Li, Shiren Sun, Jundong Jiao, and Chunsheng Xi represented the collaborating coordinating centers responsible for their centers' participation in the trial.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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