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Effect of different hemodialysis modalities on hepcidin clearance in patients undergoing maintenance hemodialysis

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Abstract

Introduction: Hepcidin is a master regulator of iron utilization and takes part in the pathophysiology of anemia in maintenance hemodialysis (MHD) patients. Hepcidin is a moderate-molecular-weight substance and partially binds to plasma proteins in the circulation, which theoretically might be removed efficiently by hemoperfusion (HP). This study aimed to compare the effect of different dialysis modalities on hepcidin removal and discuss its effect on the iron and anemia status in MHD patients.

Materials and Methods: In a longitudinal interventional study of 26 stable MHD patients, the serum hepcidin, β2-microglobulin (β2-MG), and intact parathyroid hormone (iPTH) were measured before and after one treatment session of hemodialysis (HD), hemodiafiltration (HDF), HD + HP, and HDF + HP, separately. One-way analysis of variance (ANOVA) was used to identify the effect of dialysis modalities on the intra-dialysis clearance ratios.

Results: The combined dialysis modalities (HD + HP and HDF + HP) achieved greater clearance ratios of serum hepcidin than HD and HDF alone, HD + HP vs. HD (16 ± 15% vs. 4 ± 13%, $p < 0.001$), HDF + HP vs. HDF (18 ± 5% vs. 10 ± 13%, $p = 0.0036$). Similarly, the combined dialysis modalities also performed better than HD and HDF alone in removing β2-MG. There was no significant difference in iPTH clearance among these four modalities, except that HDF + HP achieved a greater clearance ratio than HD. Furthermore, the anemia was improved after the 6-month treatment with regular HD/HDF plus HP, which was indicated by increasing hemoglobin ($p = 0.0004$) and reduction of erythropoiesis-stimulating agents (ESAs) resistance index (ERI) ($p = 0.0431$).

Conclusions: Our findings suggest that the combined dialysis modalities of HD/HDF plus HP could achieve better clearance ratios of hepcidin than HD/HDF alone, thereby, might improve iron utilization, and benefit anemia management in MHD patients. Further studies with larger sample-size patients and longer follow-up duration are still needed.

Ling Sun and Rui-Xue Hua contributed equally to this work.

1 | INTRODUCTION

Anemia is a common complication in patients with end-stage renal disease (ESRD), mainly due to deficiency of erythropoietin and iron. In patients undergoing maintenance hemodialysis (MHD), iron deficiency could be classified into two groups: (1) absolute iron deficiency, which was caused by compromised gastrointestinal iron absorption and increased blood loss; (2) functional iron deficiency, in which, the storage iron was blocked to release from splenic and hepatic macrophages to marrow for erythropoiesis.[1]

Hepcidin, a liver-derived 25-residue peptide (molecular weight [MW] ≈ 2.8 KDa), is a master regulator of iron utilization that causes iron-restricted anemia. Ferroportin (FPN) is the unique cellular iron exporter on the surface of iron-storage cells, pumping iron into circulation, and regulating iron efflux. Hepcidin binds to FPN in enterocytes, macrophages and hepatocytes, occludes iron efflux pathway and induces FPN endocytosis,[2] thereby inhibiting duodenal iron absorption and iron availability from these reticuloendothelial cells.[3] Hepcidin was demonstrated to be influenced by multiple factors, including iron stores, erythropoiesis, hypoxia, inflammation, as well as decreased renal clearance.[4,5]

The hepcidin could bind to plasma proteins in circulation, the binding ratios vary from 3% to 89%. Peslova et al. identified that α2-macroglobulin (α2-MG) was the specific and major hepcidin transporter in blood, the rest was bound to albumin. There was high affinity between hepcidin and α2-MG, whereas hepcidin binding to albumin was nonspecific.[6] Diepeveen et al. found that about 40% of hepcidin exists as protein-binding forms in plasma, with large individual variability. Considering the renal clearance of hepcidin was decreased, and therefore the long-term accumulation of serum hepcidin would potentially promote its protein binding in ESRD patients.[7]

Our previous study found that serum hepcidin was significantly elevated in MHD patients, and the increase of serum hepcidin might be an independent risk factor for all-cause mortality.[8] Strengthening the clearance of hepcidin during dialysis sessions might benefit the anemia management and survival prognosis in MHD patients. Compared with the small molecular (MW < 500 Da), water-soluble and non-protein-bound solutes, such as urea and creatinine, the hepcidin is a medium molecule with partial proportion in protein-bound forms in the circulation. This study aimed to compare the impact of different dialysis modalities on hepcidin removal, and discuss its effect on the iron and anemia status in MHD patients.

2 | MATERIALS AND METHODS

2.1 | Participants

This was a longitudinal interventional study in stable MHD patients from the blood purification center at Xuzhou Central Hospital (Xuzhou, China). The erythropoiesis-stimulating agents (ESAs) and iron supplementation were prescribed for the management of anemia, the drug dose was adjusted once a month, according to the opinion of the senior consultant nephrologist and Chinese Practice Guidelines.[9] Inclusion criteria were as follows: (1) patients with ESRD; (2) ≥ 18 years old; (3) regular blood purification treatment for more than 3 months. Exclusion criteria were as follows: (1) overt infection/inflammation, or malignant diseases; (2) platelet count $<100 \times 10^9$/L or coagulation dysfunction; (3) cerebral hemorrhage or gastrointestinal bleeding in the past 3 months; (4) hospital admission for any reason within the preceding 3 months; (5) refusal to sign written consent.

2.2 | Dialysis modalities

All patients were on conventional hemodialysis (HD) twice a week and online hemodiafiltration (HDF) once a week with each dialysis session of 4 h before the enrolment, then hemoperfusion (HP) were performed using HA130 cartridge (Jafron Biomedical, China) once a week combined with HD or HDF, which were recorded as HD + HP (Figure 1A), and HDF + HP (Figure 1B). HD was performed with polyethersulfone dialyzers with surface area ranging from 1.6 to

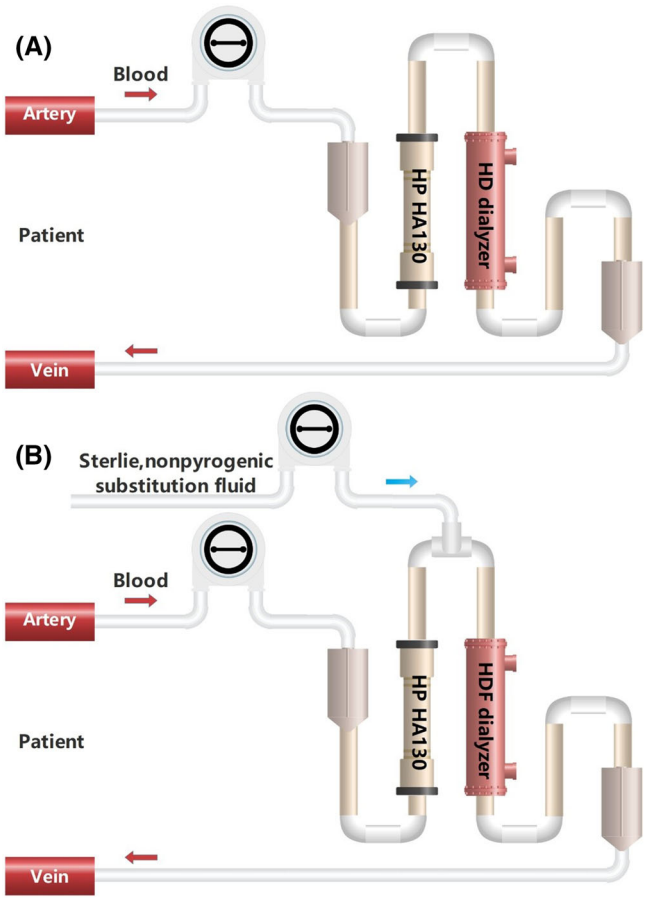

FIGURE 1 (A) The flowchart of hemodialysis (HD) plus hemoperfusion (HP) treatment. (B) The flowchart of hemodiafiltration (HDF) plus HP treatment

1.8 m^2. In online HDF, the pre-dilution substitution volume was set to 60%–70% of total blood volume, using toraysulfone dialyzers with surface area ranging from 1.6 to 1.8 m^2. The composition of dialysate and substitution fluid was the same in all groups: sodium 140 mmol/L, bicarbonate 32 mmol/L, potassium 2.0 mmol/L, calcium 1.5 mmol/L, magnesium 0.5 mmol/L, and no glucose. The blood flow ranged from 240 to 300 ml/min with constant dialysate flow of 500 ml/min. The cohort was established in January 2021. All patients were followed up for 6 months. The protocol was approved by the ethical committee of the Xuzhou Central Hospital (Approval No. XZXY-LJ-20210110-004).

2.3 | Data collection and measurements

Baseline and follow-up demographic and clinical data were recorded. Blood samples were taken at pre-dialysis, and at the end of HD, HDF, HD + HP, and HDF + HP, respectively, from the arterial end of dialysis pathway after turning off ultrafiltration for 2 min. The laboratory measurements were made in a certified laboratory (KingMed Diagnostics, Nanjing, China). The spKt/V was measured by two-point urea modeling based on the reduction of blood urea and weight loss during one single treatment session. The ESAs resistance index (ERI) was calculated by the ratio of weekly ESAs dose to hemoglobin. Serum hepcidin was determined using competitive enzyme-linked immunosorbent assay (ELISA) kits (Cat. CSB-E13062h, Cusabio, China), with coefficient of variation (CV) < 15% in both intra- and inter-assay precision analyses.

The clearance of substances was expressed as the percentage (%) difference between serum concentrations at pre-dialysis (Cpre) and at the end of dialysis session (Cpost). Thus, the clearance ratio was calculated as follows: (Cpre − Cpost)/Cpre × 100%, a positive value indicating a drop of serum concentration during one treatment session. The Cpre and Cpost values were adjusted by total serum protein concentration at Cpre and Cpost.

2.4 | Statistical analysis

Patients' baseline and follow-up data were expressed as proportions, mean (±SD) or medians [interquartile range (IQR)], and analyzed using the paired-samples *t*-test or Wilcoxon matched-pairs signed-rank test for non-normally distributed data. One-way analysis of variance (ANOVA) was used to identify the effect of dialysis modalities on the intra-dialysis clearance. A two-sided *p*-value <0.05 was defined as statistically significant. All statistical analyses were performed using SAS system, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

A total of 26 MHD patients were enrolled in the study, the median age was 54.5 years (range 33 to 87), and 53.8% of the subjects were male (14 males and 12 females), the duration of dialysis treatment was 59 months (range 19 to 132 months).

3.1 | Effect of different dialysis modalities on the clearance of hepcidin

There were no significant differences in spKt/V among these four groups (all $p > 0.05$) (Table 1). After one treatment session, the serum hepcidin decreased from 230.5 ± 38.9 ng/ml to 187.8 ± 32.5 ng/ml, with clearance of 18 ± 5% in HDF + HP group; the serum hepcidin decreased from 218.5 ± 155.4 ng/ml to 197 ± 148.5 ng/ml with clearance of 16 ± 15%, from 236.2 ± 152.2 ng/ml to 209.7 ± 130.5 ng/ml with clearance of 10 ± 13%, and from 275.6 ± 156 ng/ml to 254.7 ± 129.3 ng/ml with clearance of 4 ± 13%, in HD + HP group, HDF group, and HD group, respectively. The HDF + HP achieved the greatest reduction of serum hepcidin, followed by HD + HP and HDF, the smallest reduction was observed in the HD group, of which, there were significant differences between

TABLE 1 Effect of the four dialysis modalities on the serum levels and clearance ratios of hepcidin, β2-MG, and iPTH

Variables	HD Mean (SD)	HD + HP Mean (SD)	HDF Mean (SD)	HDF + HP Mean (SD)	*p*-value
spKt/V	1.31 (0.13)	1.33 (0.10)	1.29 (0.15)	1.32 (0.13)	0.7122
Pre-dialysis hepcidin (ng/ml)	275.63 (155.92)	218.53 (155.41)	236.22 (152.20)	230.51 (38.90)	0.4597
Post-dialysis hepcidin (ng/ml)	254.73 (129.25)	196.97 (148.48)	209.73 (130.47)	187.78 (32.52)	0.1912
Pre-dialysis PTH (pg/ml)	287.93 (136.46)	297.42 (140.08)	298.67 (226.82)	299.49 (169.00)	0.9945
Post-dialysis PTH (pg/ml)	163.88 (95.33)	142.32 (89.51)	159.96 (201.10)	113.75 (53.49)	0.4452
Pre-dialysis β2-MG (mg/L)	43.21 (7.35)	41.49 (8.83)	41.07 (4.74)	42.76 (4.79)	0.6138
Post-dialysis β2-MG (mg/L)	38.19 (7.94)	25.35 (10.07)	27.26 (7.85)	15.39 (2.62)	<0.0001
Hepcidin clearance (%)	44 (13)	51 (20)	49 (25)	57 (14)	0.1062
β2-MG clearance (%)	4 (13)	16 (15)	10 (13)	18 (5)	0.0003
iPTH clearance (%)	12 (6)	37 (25)	34 (18)	64 (5)	<0.0001

Abbreviations: HD, hemodialysis; HP, hemoperfusion; HDF, hemodiafiltration; β2-MG, β2-microglobulin; iPTH, intact parathyroid hormone.

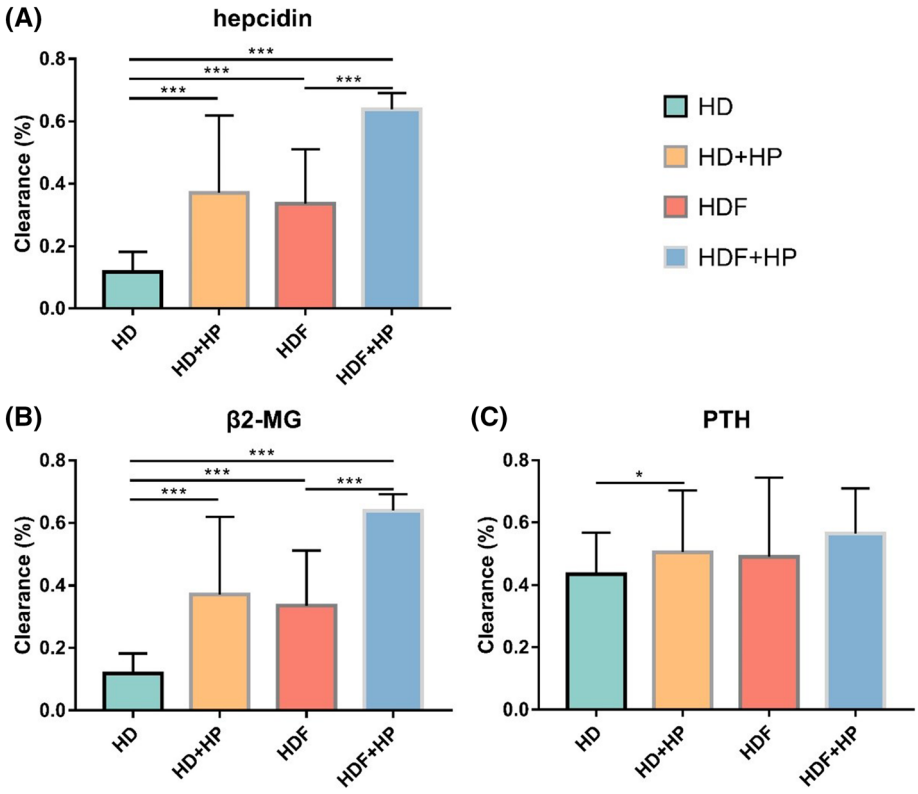

FIGURE 2 Comparison of the clearance of hepcidin (A), β2-MG (B), and iPTH (C) during one dialysis session. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

HDF + HP group and HDF group ($p = 0.0036$), HD + HP group and HD group ($p < 0.0001$), as well as HDF + HP group and HD group ($p < 0.0001$) (Figure 2A).

In addition, the serum levels of β2-microglobulin (β2-MG) also declined greatest in the HDF + HP group, then HDF and HD + HP, and least in the HD group. The HP apparatus composited with HD/HDF dialyzer performed significantly superior to HD/HDF alone in removing β2-MG during a dialysis session (both $p < 0.0001$) (Figure 2B). In the clearance of intact parathyroid hormone (iPTH), HP + HDF performed better than HD, whereas there were no significant differences among other groups (Figure 2C).

3.2 | Effect of regular dialysis plus HP on anemia status

After the 6-month treatment with regular dialysis plus HP once a week, the hemoglobin and hematocrit (HCT) significantly increased in these MHD patients ($p = 0.0004$ and $p = 0.0041$). Meanwhile, the ERI decreased significantly ($p = 0.0431$), which indicated that the ESAs responsiveness was also improved. Moreover, the serum albumin slightly increased ($p = 0.0226$), and serum phosphorus decreased ($p = 0.0012$) (Table 2).

However, there was no statistically significant change in the indexes of iron metabolism, including serum iron, ferritin, unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), and transferrin saturation (TSAT) before and after 6 months of combined HP treatment. Besides, the serum levels of hepcidin, β2-MG and iPTH were not significantly changed during this study period (Table 2).

4 | DISCUSSION

The uremic toxins include small molecular, moderate molecular, macro molecular, and protein-bound substances. The accumulation of these toxins could induce various complications in ESRD patients, therefore the removal of uremic toxins is the main purpose of blood purification in MHD patients. Conventional HD could remove excess water and small molecular toxins (MW < 500 Da) effectively, whereas it has poor efficiency in removing macro-molecular and protein-bound substances. Hemoperfusion (HP) is an absorption-based treatment that purifies blood through direct contact with solid-state sorbent to remove medium-macromolecular and protein-bound toxins. HP could not remove small water-soluble and non-protein-bound substances, such as water, creatinine, and electrolytes, thus, it is always combined with HD/HDF in one treatment session in MHD patients.[10] According to the above theories, the HD/HDF plus HP may be superior to HD/HDF alone in the toxin removal, and improve clinical outcomes of MHD patients.

Compared with the general population, the serum hepcidin remarkably increased in ESRD patients, mainly because of the decreased renal clearance and chronic micro-inflammatory state.[4] As we all know, hepcidin inhibits the intestinal iron uptake and iron

TABLE 2 Baseline and follow-up laboratory characteristics of the MHD patients

	Before	After	*p*-value
Hemoglobin (g/L)[a]	102.35 (12.04)	115.00 (12.22)	0.0008
Hematocrit (%)	31.68 (3.74)	34.62 (3.27)	0.0104
ERI (U/kg/week/g/L)	14.08 (10.43,16.15)	9.53 (5.26,14.44)	0.0431
Hepcidin (ng/ml)	204.62 (147.28,327.49)	197.7 (103.81,261.32)	0.3601
Ferritin (ng/ml)	12.85 (11.4,16.3)	12.8 (10.6,13.9)	0.4153
TSAT (%)	31.73 (20.56,37)	28.54 (19,34)	0.2802
UIBC (μmol/L)	36.15 (26.4,43.8)	36 (31,47.5)	0.3947
TIBC (μmol/L)	51.5 (40.4,55.2)	51.8 (42.9,57.3)	0.5458
Albumin (g/L)	40.67 (3.62)	42.97 (3.40)	0.0226
hs-CRP (mg/L)	4.46 (2.62,6.97)	3.17 (2.13,5.52)	0.1938
Triglyceride (mmol/L)	1.62 (1.21,2.01)	1.32 (1.05,1.95)	0.4584
TCH (mmol/L)	3.73 (2.81,4.02)	3.35 (2.81,4.2)	0.8908
HDL-C (mmol/L)	0.86 (0.78,0.91)	0.87 (0.71,0.97)	0.8474
LDL-C (mmol/L)	2.17 (1.56,2.45)	2.24 (1.46,2.6)	0.3796
Pre-dialysis creatinine (μmol/L)	1161 (852,1367.2)	1123.5 (807,1,307)	0.7143
Uric acid (μmol/L)	479 (421,534)	459 (385,492)	0.1845
Phosphorus (mmol/L)	2.42 (0.50)	1.78 (0.79)	0.0011
Calcium (mmol/L)	2.13 (2.07,2.21)	2.22 (2.16,2.33)	0.0605
Magnesium (mmol/L)	1.17 (1.07,1.26)	1.08 (1.02,1.16)	0.0534
TCO_2 (mmol/L)	19.31 (16.9,20.2)	19.45 (17.6,23.55)	0.1197
Vitamin B12 (ng/ml)	1054.5 (545,2000)	1495 (560,2000)	0.6923
Folic acid (ng/ml)	5.79 (3.4,9.4)	5.09 (4.4,19.22)	0.9927
iPTH (pg/ml)	289.5 (208.2,373.52)	273.95 (97,380.31)	0.4867
β2-MG (mg/L)	40.41 (33.78,44.2)	36.84 (31.88,40.9)	0.1482

Abbreviations: HD, hemodialysis; HDF, hemodiafiltration; HP, hemoperfusion; ERI, erythropoiesis-stimulating agents (ESA) resistance index; TSAT, transferrin saturation; UIBC, unsaturated iron-binding capacity; TIBC, total iron-binding capacity; hs-CRP, high sensitivity C-reactive protein; TCH, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; iPTH, intact parathyroid hormone; β2-MG, β2-microglobulin.
[a]Continuous values expressed as means (SD) if normally distributed or median (interquartile range) if skewed.

release from hepatic and splenic macrophages, and finally exacerbates anemia. Our previous study found that serum hepcidin might be an independent risk factor for all-cause mortality in MHD patients.[8] The reduction of serum hepcidin might help to improve anemia and survival outcomes in MHD patients.

Few studies have been performed to compare the effect of different dialysis modalities on the clearance of hepcidin. In this study, four hemodialysis modalities, HD, HDF, HD + HP, and HDF + HP were performed on the MHD patients to compare their impact on the clearance of hepcidin. Our finding highly indicated that its removal efficiency of combined dialysis modalities was superior to alone HD/HDF in one single treatment session. However, the serum level of hepcidin was not reduced after 6 months of HD/HDF + HP treatment in our patients. Besides its dialysis clearance, other factors might also influence the serum level of hepcidin, such as the iron and erythropoiesis status, as well as inflammation.[4] In this study, the iron metabolism status (ferritin and TSAT), and an inflammation marker (hs-CRP) remained unchanged after the 6-month treatment, which could partly explain the unchanged serum hepcidin. Moreover, our treatment period was relatively short, extending the follow-up time might achieve a statistical difference.

Although the serum levels of hepcidin, ferritin, and TSAT had no significant differences, the hemoglobin still increased in these patients, accompanied by ERI reduction after the 6-month treatment. These results revealed that the erythropoiesis status was improved markedly, probably due to increasing protein-bound uremic toxins removal, such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS), by the combined HP treatment,[11] which might ameliorate the hematopoietic microenvironment in MHD patients.[12,13] The increasing hepcidin clearance during each HD/HDF + HP session may also contribute to iron utilization and hematopoiesis.

Protein-energy wasting (PEW) is a common complication in MHD patients, serum albumin is a classical biomarker in assessing the nutritional status. In patients with MHD, serum albumin was demonstrated

to be a predictor of hospitalization and mortality, with lower levels associated with higher risk.[14] Our study found that after 6 months of regular HD/HDF plus HP, serum albumin increased in these MHD patients, indicating that the combined dialysis modalities might ameliorate the nutritional status and benefit survival outcomes.

Previous studies demonstrated that both serum iPTH and β2-MG were significantly reduced in the HD + HP group than in the HD group after 12, 24, and 36 months treatment.[15,16] Our results also showed that the HD/HDF + HP were superior to HD/HDF in removing β2-MG, and the HDF + HP was superior to HD in removing iPTH by one treatment session, whereas either serum β2-MG or iPTH decreased after 6 months of the combined treatment in these MHD patients, probably because of the relatively short follow-up duration.

5 | LIMITATIONS AND STRENGTHS

This study has strengths. This is the first attempt at hepcidin clearance research by four dialysis modalities, HD, HDF, HD + HP, and HDF + HP until now. HD + HP had been proved to perform better than HD in improving the overall survival rates, cardiac function, cardiovascular events, and quality of life in MHD patients,[17] the cost-effectiveness analysis suggested the HD/HDF + HP treatment should be cost-effective for ESRD patients in China.[18] Our findings might not only help to further explain why the combined therapies are better than the HD/HDF alone but also supply novel therapy advice to improve anemia management in MHD patients.

This study had limitations. This was a single-center study, therefore, the selection of patients could have introduced bias. The serum hepcidin could be regulated by multiple factors, such as inflammation, therefore, unstable MHD patients were excluded, and the conclusions here were not applicable for these patients. It is best to measure and calculate the total solute removal (TSR) of hepcidin during one dialysis session, using the concentration of hepcidin in the dialysate waste fluid (ng/ml), dialysate flow rate (ml/min), average ultrafiltration rate (ml), and dialysis time (min). However, the concentration of hepcidin in the dialysate waste fluid was too low to be measured by ELISA, more sensitive and accurate methods for hepcidin detection need to be further developed and applied.

6 | CONCLUSION

The combined dialysis modalities of regular HD/HDF plus HP could achieve better clearance ratios of hepcidin than HD/HDF alone during one treatment session, thereby, the combined dialysis modalities might improve iron utilization, and benefit anemia management in MHD patients. Further studies with larger cohorts of MHD patients and longer follow-up duration should be performed to confirm these findings.

CONFLICT OF INTERESTS

The authors have no conflict of interests to declare.

ETHICS STATEMENT

The study involved Human Participants and it was performed at the Xuzhou Central Hospital. The study adhered to the International Conference on Harmonization guidelines for Good Clinical Practice and was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethical committee of the Xuzhou Central Hospital (Approval No. XZXY-LJ-20210110-004). All participants provided a written informed consent.

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