IJKD KIDNEY DISEASES

Clinical Efficacy and Long-term Prognosis of High Flux Hemodialysis Combined with Different Frequency Hemodiafiltration in the Treatment of Middle-Aged and Elderly Patients with Uremia

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Keywords. uremia, high flux hemodialysis, hemodiafiltration, clinical efficacy, long-term prognosis

Introduction. To analyze the clinical efficacy and long-term prognosis of high flux hemodialysis (HFHD) combined with different frequency hemodiafiltration (HDF) in uremic patients.
Methods. 86 middle-aged and elderly patients with uremia were divided into the HF group (HFHD combined with high-frequency HDF) and the LF group (HFHD combined with low-frequency HDF). The changes between the two groups in various indicators after 12 months of dialysis and the survival rate at 5 years of follow-up were compared. We used SPSS 25.0 software for data analysis.
Results. The differences of the levels of serum albumin, hemoglobin and transferrin in HF Group was significantly higher than LF Group before and after treatment ($P < .05$). The differences of the levels and clearance rate of calcium, phosphorus, parathyroid hormone, β_2-microglobulin and cysteine protease inhibitor C in the patients' blood after dialysis were significantly higher in HF Group than in LF Group ($P < .05$). The all-cause mortality rate, new cardiovascular event rate, new cerebrovascular event rate, and new infection event rate of HF Group were significantly lower than those of LFHD group, respectively ($P < .05$). The LF Group had a significantly higher risk of all-cause mortality events, new cardiovascular cerebrovascular and infectious events than the HF Group ($P < .05$).
Conclusion. 1 week/time HDF combined with HFHD can more effectively eliminate the vascular related toxins in middle-aged and elderly patients with uremia, improve their nutritional status, treatment effect, and long-term prognosis.

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INTRODUCTION

Chronic kidney disease (CKD) is a universal public health problem, and the global incidence rate has reached above 11%.[1] CKD may develop into end-stage kidney disease (ESKD) if the disease continues to progress.[2] Hemodialysis (HD) has become a safe and effective method for renal replacement therapy in ESRD patients.[3]

Hemodialysis with the use of high-flux dialyzers (HFHD) removes solutes through diffusion and convection, and has the biocompatibility of high permeability membranes.[4] The clearance of macromolecule and medium-size molecules and toxins could be increased by increasing the pore size of dialysis membranes.[5] Hemodiafiltration (HDF) is a blood purification technique that mimics the filtration function of the renal glomerulus and functions through a combination of diffusion

and convection.[6] It has a good clearance rate for small-size molecule, medium-size molecule, and macromolecular toxins.[7] Research shows that the combination of HFHD and HDF in uremic patients has better effect on the elimination of toxin.[8] However, there is currently limited research on how frequently HDF is used in the application process to achieve the best results.

Therefore, this study compared the clinical efficacy and long-term prognosis of the combination of HFHD and HDF with different frequencies in middle-aged and elderly patients with uremia. In this way, better blood purification methods can be screened to enable patients to achieve dialysis differentiation, prolong their survival time, and improve their quality of life.

PATIENTS AND METHODS

Clinical Data

Eighty-six middle-aged and elderly uremic patients treated by maintenance hemodialysis from January 2015 to December 2017 were selected from blood purification room of Yantai Yuhuangding Hospital (Shandong, China). Patients were followed for 60 months. The study was approved by the hospital Ethics Committee (No.: 2015012410, Approval Date: 24 January 2015). Written informed consent was obtained from the study participants.

Inclusion Criteria

The inclusion criteria were: patients 1) aged 45 to 80 years old, 2) suffering from ESKD, undergoing maintenance hemodialysis, 3) using autologous arteriovenous fistulas or artificial blood vessels as vascular access, 4) undergoing dialysis three times a week for approximately 4 hours each time, lasting for more than 12 weeks, and 5) having stable blood pressure and blood sugar, with no infection, heart failure, active immune disease, and no history of blood transfusion.

Exclusion Criteria

Patients: 1) who used temporary central venous catheters, 2) with malignant tumors that have not been cured or require chemotherapy and radiation therapy, 3) with an expected lifespan of less than 12 months, 4) who were estimated to be unable to complete at least 24 weeks of follow-up, such as planned kidney transplantation, and 5) with incomplete clinical data.

Experimental Grouping Basis

With the informed consent of the patients, eligible patients were paired according to sex, age, and course of disease (pairing method): 1) the same sex, 2) age difference not more than 5 years, 3) course of disease, grouping according to " < 6 months", "6 months-", "3 years-", and " > 10 years"), and randomly allocated to the low-frequency group (LF group) and the high-frequency group (HF group), with 43 people in each group.

Dialysis Methods

HFHD. Fresenius company 4008 B dialysis machine and polysulfone membrane hemodialyzer FX60 (Fresenius company, membrane area 1.4 m^2, ultrafiltration coefficient 46 mL/h · mmHg). Each dialysis lasted for 240 minutes, with a dialysis blood flow rate of 260 mL/min.

HDF. Fresenius company 5008 S dialysis machine and polysulfone membrane hemodialyzer HF80S (Fresenius company, membrane area 1.8 m^2, ultrafiltration coefficient 55 mL/h · mmHg). Each dialysis lasted for 240 minutes, with a dialysis blood flow rate of 260 mL/min.

Dialysis methods HF Group. HFHD was performed three times a week, and on this basis, HFHD was replaced with HDF for the last treatment every week. That is to say, HFHD was used for the first two times a week and HDF for the third time. The patient maintained this circulation throughout the treatment process.

Dialysis methods in LF Group. HFHD was perform three times a week, and on this basis, HFHD was replaced with HDF for the last treatment every four weeks. That is to say, HFHD was used for the first 11 times a week and HDF was used for the 12th time. The patient maintained this circulation throughout the treatment process.

Observation Index

Clinical Effect. Blood samples for the assessment of clinical efficacy indicators were collected 30 minutes before the initiation of the first dialysis, 30 minutes after the end of the first dialysis treatment, and after 12 months of continuous treatment, 30 minutes before the start of the last dialysis and 30 minutes after the end of the last dialysis treatment. The blood samples were collected from the patient's median elbow vein, with a sampling volume of 4mL, 2mL, etc., and then were sent to

the laboratory of Yantai Yuhuangding hospital for testing within 2 hours.

Blood Indicators. *Blood indicators were;* parathyroid hormone (PTH), urea, creatinine, uric acid, potassium, phosphorus, β_2-microglobulin (β_2-MG), cysteine protease inhibitor C (Cystatin C), serum albumin (ALB), hemoglobin (HGB), and transferrin (TRF). We calculated the urea removal index (Kt/V),[9] standard protein catabolism rate (nPCR),[10] and time-average concentration of urea (TA Curea)[11] to evaluate the adequacy of the two dialysis methods for dialysis.

Long-term Prognosis Observation. After one year of treatment, patients were followed up for five years to observe the endpoint events during the follow-up period, including: all-cause mortality events, new cardiovascular events, such as congestive heart failure, angina pectoris, arrhythmia, myocardial infarction and death due to cardiovascular disease, new cerebrovascular events, such as cerebral infarction, cerebral hemorrhage, death due to cerebrovascular disease, new infectious events and deaths due to infectious diseases. The survival time was defined as the time from the beginning of follow-up to death, and the deletion value was defined as the patients who were still alive or missing at the end of a 5-year follow-up period. The follow-up time was recorded in terms of months.

Statistical Analysis

SPSS 25.0 software was used for the statistical analysis of the data. The measurement data were expressed as mean ± standard deviation (x ± s), repeated measurement analysis of variance was used to compare the indexes, T test was used to compare the two groups, the counted data were expressed in percentages, χ^2 test was used to compare the two groups, the hazard ratio (HR) was determined via a Cox regression model and survival curves were plotted from Kaplan-Meier estimations. $P < .05$ was considered to indicate a statistically significant difference.

RESULTS

Basic Information

There was no significant difference in sex, age, dialysis time, height, weight, body mass index (BMI), body skin area (BSA) and types of primary diseases between the two groups ($P > .05$) (Table 1).

Blood Nutritional Status

The differences of the levels of ALB, HGB and TRF were significantly higher in HF Group than in LF Group (t = 5.364, $P = .011$; t = 7.093, $P = .000$; t = 4.254, $P = .000$) (Table 2).

Table 1. Characteristics of the Study Participants

	HF Group (n = 43)	LF Group (n = 43)	χ^2 (t)	*P*
Male (n (%))	24 (50%)	24 (50%)	0.000	1.000
Age (mean, SD)	68.57 ± 7.81	67.95 ± 7.51	0.094	.893
Dialysis Time, mo	34.31 ± 6.59	35.54 ± 5.78	1.234	.653
Height, m	1.69 ± 0.06	1.70 ± 0.05	0.821	.807
Weight, kg	62.93 ± 12.89	60.54 ± 13.94	2.550	.412
BMI, kg/m^2	20.23 ± 4.91	21.77 ± 4.09	0.839	.726
BSA, m^2	1.68 ± 0.21	1.66 ± 0.23	0.125	.911
Types of Primary Diseases (n (%))				
Chronic Glomerulonephritis	17 (39.53%)	21 (48.84%)	2.576	.241
Benign Arteriole Nephrosclerosis	8 (18.60%)	11 (25.58%)		
Chronic Pyelonephritis	5 (11.63%)	2 (4.65%)		
Diabetic Nephropathy	13 (30.23%)	9 (20.93%)		

Table 2. Comparison of Blood Nutritional Status Differences Between Two Groups Before and After Treatment

	The differences of the levels of ALB (g/L)	The differences of the levels of HGB (g/L)	The differences of the levels of TRF (mg/dL)
HF Group (n = 43)	7.03 ± 0.64	13.01 ± 1.29	30.55 ± 3.25
LF Group (n = 43)	5.76 ± 0.61	9.84 ± 0.84	26.41 ± 2.43
t	5.364	7.093	4.254
P	.011	.000	.018

Comparison of Clearance of Small Molecule Toxins

There was no statistically significant difference between the two groups in the levels of urea, creatinine, uric acid, and potassium following dialysis ($P > .05$). The differences in the levels of calcium and phosphorus in HF group was significantly higher than that in LF group after dialysis (t = 5.166, $P = .083$; t = 5.142, $P = .000$). The clearance rates of urea, creatinine, uric acid, and potassium in both groups after dialysis were not statistically significant ($P > .05$). The clearance rates of calcium and phosphorus in HF Group were significantly higher than that in LF Group after dialysis (t = 7.032, $P = .000$; t = 6.377, $P = .000$) (Table 3).

Comparison of Clearance of Medium Molecule Toxins

The differences of the levels and the clearance rate of PTH in the HF group were significantly higher than the LF group after dialysis (t = 8.206, $P = .000$; t = 7.075, $P = .000$) (Table 4).

Comparison of Clearance of Macromolecular Toxins

The differences of the levels of β_2-MG and Cystatin C in the HF group were significantly higher than the LF group after dialysis (t = 3.457, $P = .011$; t = 6.124, $P = .000$). The clearance rate of β_2-MG and Cystatin C in the HF group were significantly higher than the LF group after dialysis (t = 6.124, $P = .000$; t = 21.33, $P = .000$) (Table 5).

Comparative of Urea Dialysis Adequacy

There was no significant difference between the two groups in the urea dialysis adequacy indicators Kt/V, TACruea, and nPCR (t = 0.257, $P = .839$; t = 1.256, $P = .092$; t = 1.833, $P = .067$) (Table 6).

Long-term Prognosis Analysis

All-cause mortality events. The total number of all-cause mortalities during the 5-year follow-up period for all patients was 21 (24.42%), with six cases in the HF group (13.95%) and 15 cases in the LF group (34.88%). The survival curve (Figure 1) showed that there was a statistically significant difference in the all-cause mortality survival rate between HF group and LF group ($c^2 = 4.897$, $P = .027$). The results of calculation, using Cox

Table 3. Comparison of Clearance of Small Molecule Toxins

	Urea		Creatinine		Uric acid		Potassium		Phosphorus		Calcium	
	The differences of the levels (mmol/L)	Clearance rate (%)	The differences of the levels (μmol/L)	Clearance rate (%)	The differences of the levels (mmol/L)	Clearance rate (%)	The differences of the levels (mmol/L)	Clearance rate (%)	The differences of the levels (mmol/L)	Clearance rate (%)	The differences of the levels (mmol/L)	Clearance rate (%)
HF Group (n=43)	13.02 ± 1.59	54.17 ± 4.35	511.37 ± 49.63	57.54 ± 5.12	289.07 ± 27.66	41.94 ± 3.51	2.18 ± 0.21	36.21 ± 3.07	0.46 ± 0.03	20.91 ± 0.19	0.16 ± 0.01	7.44 ± 0.56
LF Group (n=43)	12.63 ± 1.71	52.08 ± 4.67	503.15 ± 44.36	56.64 ± 5.43	283.51 ± 30.15	41.07 ± 3.97	2.16 ± 0.23	35.88 ± 3.81	0.35 ± 0.03	17.13 ± 1.13	0.12 ± 0.02	5.53 ± 0.53
t	0.851	1.295	0.543	1.479	1.870	0.533	0.428	1.504	5.166	7.032	5.142	6.377
P	.537	.108	.632	.151	.105	.501	.651	.083	.000	.000	.000	.000

Table 4. Comparison of Clearance of Medium Molecule Toxins: PTH

	The differences of the levels (pg/mL)	Clearance rate (%)
HF Group (n = 43)	209.12 ± 18.10	30.38 ± 3.85
LF Group (n = 43)	173.15 ± 16.07	25.15 ± 2.97
t	8.206	7.075
P	.000	.000

regression model, were "*P* = .036, HR = 0.363, and 95% Cl: 0.141 to 0.936", indicating that the LF group is more likely to cause all-cause mortality than the HF group.

New Cardiovascular Events. The total number of new cardiovascular events during the 5-year follow-up period for all patients was 39 (45.35%), with 10 cases in the HF group (45.35%) and 29 cases in the LF group (67.44%). The survival curve (Figure 2) showed that there was a statistically significant difference between HF group and LF group in the all-cause mortality survival rate ($c^2 = 17.080$, *P* = .000). The results of calculation by using Cox

Table 5. Comparison of Clearance of Macromolecule Toxins

	β_2-MG		Cystatin C	
	The Differences of the levels (mg/L)	Clearance rate (%)	The differences of the levels (mg/L)	Clearance rate (%)
HF Group (n = 43)	10.96 ± 1.09	58.08 ± 5.34	2.78 ± 0.02	51.10 ± 5.06
LF Group (n = 43)	9.11 ± 0.09	47.91 ± 4.15	1.33 ± 0.02	24.29 ± 2.15
t	3.457	6.124	15.158	21.33
P	.011	.000	.000	.000

Table 6. Comparison of Urea Dialysis Adequacy

	Kt/V	TACurea (mmol/L)	nPCR (g/Kg·d)
HF Group (n = 43)	1.23 ± 0.11	16.44 ± 1.52	3.19 ± 0.30
LF Group (n = 43)	1.22 ± 0.12	16.03 ± 1.61	3.11 ± 0.27
t	0.257	1.256	1.833
P	.839	.092	.067

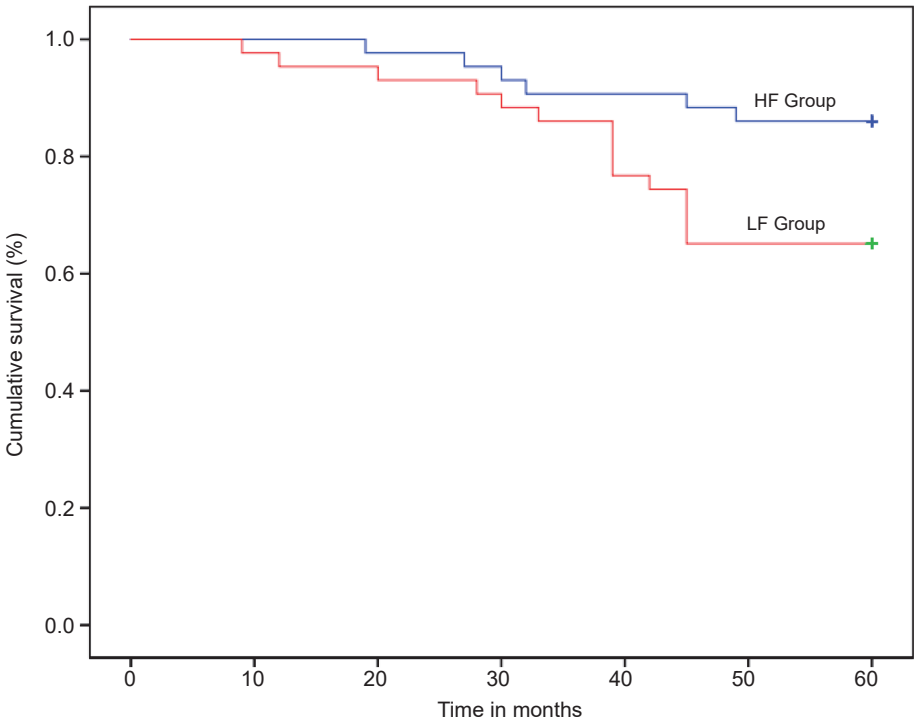

Figure 1. Survival Analysis of All-cause Mortality

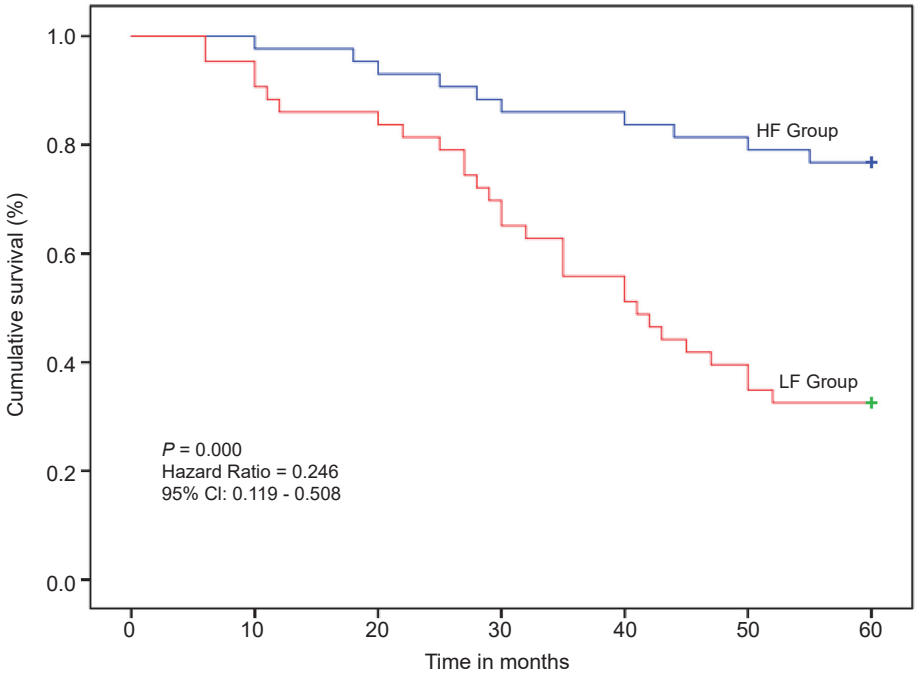

Figure 2. Survival Analysis of New Cardiovascular Events

regression model were "*P* = .000, HR = 0.246, 95% CI: 0.119 to 0.508", indicating that the LF group is more likely to cause new cardiovascular events than the HF group.

New cerebrovascular events: The total number of new cerebrovascular events during the 5-year follow-up period for all patients was 35 (40.70%), with nine cases in the HF group (20.93%) and 26 cases in the LF group (60.47%). The survival curve (Figure 3) showed that there was a statistically significant difference between HF group and LF group in the all-cause mortality survival rate

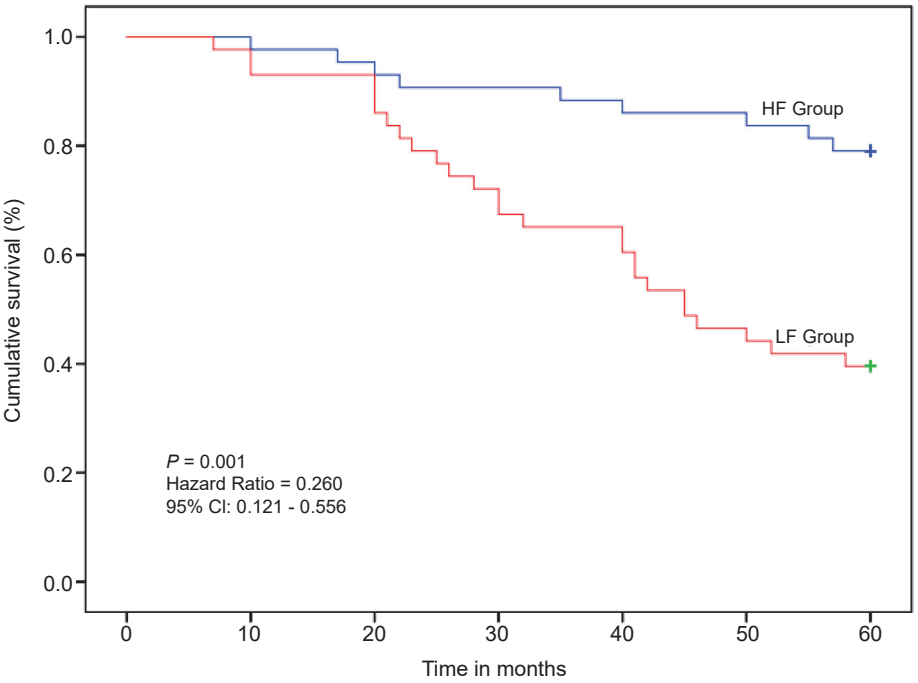

Figure 3. Survival Analysis of New Cerebrovascular Events

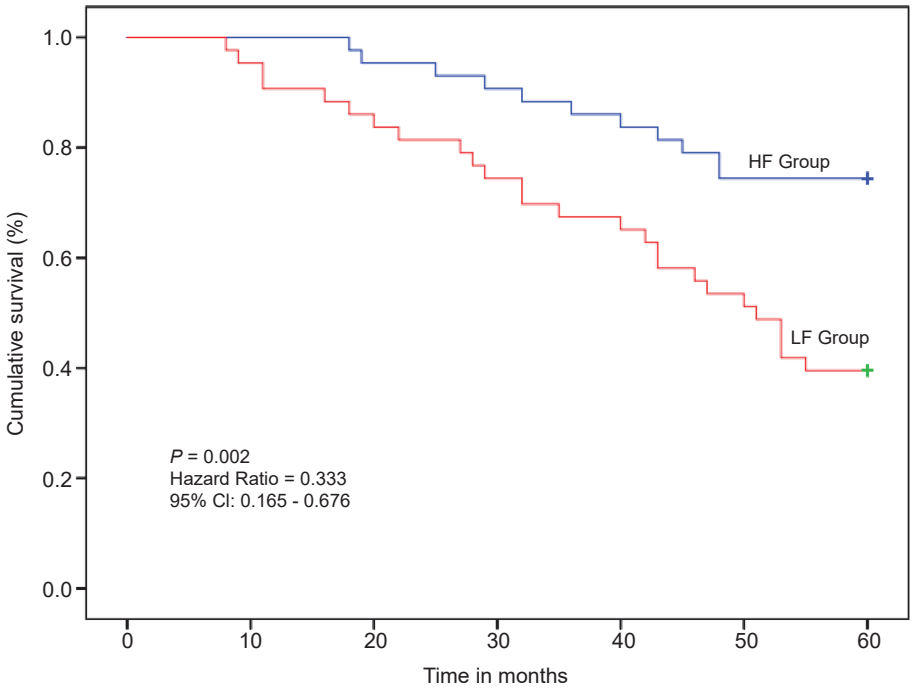

Figure 4. Survival Analysis of New Infectious Events

(c^2 = 14.093, *P* = .000). The results of calculation by using Cox regression model were "*P* = .001, HR = 0.260, 95% CI: 0.121 to 0.556", indicating that the LF group is more likely to cause new cerebrovascular events than the HF group.

New Infectious Events. The total number of new infectious events and deaths from infectious diseases during the 5-year follow-up period for all patients was 37 (43.02%), with 11 cases in the HF group (25.58%) and 26 cases in the LF group (60.47%). The survival curve (Figure 4) showed that there was a statistically significant difference between HF Group and LF Group in the all-cause mortality survival rate (c^2 = 10.373, *P* = .001). The calculated results by using Cox regression model were "*P* = .002, HR = 0.333, 95% CI: 0.165 to 0.676", indicating that the LF group is more likely to cause new infectious events than the HF group.

DISCUSSION

Chronic malnutrition is a common problem in ESKD patients undergoing hemodialysis.[12] The incidence of anemia in maintenance hemodialysis patients is as high as 98.2%.[13] This study shows that HF group can improve anemia compared to LF group. Fuhrman *et al.* showed that the ALB levels of dialysis patients are generally lower than normal.[14] This may be because the ultrafiltration coefficient of membrane materials is generally higher than normal needs, resulting in significant loss of nutrients in the blood. Meanwhile, HDF can reduce the occurrence of infection, resulting in a decrease in the consumption of ALB.[15] So HDF has a significant effect on improving anemia and hypoalbuminemia. This study analyzed the efficacy of HDF treatment every 1 week and every four weeks and showed that both groups were able to improve the HGB and ALB levels of dialysis patients. This may be because the high-frequency use of HDF can effectively improve patients' blood nutritional indicators and increase the effectiveness of dialysis.

Transferrin (TRF) is the main iron-containing protein in plasma, responsible for carrying the iron that is absorbed by the digestive tract and the iron that is released by erythrocyte degradation.[16] TRF can enter the bone marrow in the form of TRF-Fe^{3+} complex for the generation of mature red blood cells.[17] This study shows that high-frequency application of HDF can increase the differences in the levels of TRF. Maduell *et al.* also showed that HDF can control redox status, effective utilization of iron, and erythropoiesis.[18]

With the continuous progress and deterioration of the condition of CKD patients, there are some symptoms such as retention of metabolic wastes and toxins.[19] The levels of uremic toxins in patients during the uremic phase will rapidly increase.[20] The clinical manifestations will evolve into acute heart failure, severe hyperphosphatemia, severe hyperkalemia, or gastrointestinal bleeding, that could be even life-threatening.[21] This study shows that the clearance rates of calcium, phosphorus, PTH, β_2-MG, Cystatin C in HF Group were higher than those of LF Group ($P < 0.05$). This may be because the high-frequency use of HDF can enhance the clearance rate of various toxins in the patient's body.

Kt/V, nPCR, and TACruea are indicators for evaluating dialysis efficacy, and these three indicators are correlated. Kt/V reflects the urea clearance rate and is the actual dialysis volume of the patient, NPCR reflects the indicator of urea increase, and TACruea is an indicator for evaluating the effectiveness of hemodialysis.[22] When Kt/V remains constant, TACurea increases with the increase of nPCR. When nPCR is fixed, TACruea decreases with an increase in Kt/V.[23] This study found that there was no significant difference between HF group and LF group regarding Kt/V, nPCR, and TACruea ($P > .05$), indicating that the difference between the two methods in dialysis efficacy is not significant. This may be because both dialysis methods can achieve the goal of sufficient urea dialysis.

The study participants were followed up for 60 months to observe the impact of HFHD combined with different frequencies of HDF on the long-term prognosis of middle-aged and elderly uremic patients. The results showed that there was a statistically significant difference between the two groups in all-cause mortality. High-frequency application of HDF can reduce all-cause mortality, the incidence of new cardiovascular, cerebrovascular, and infection events, improving the prognosis of patients. This may be because, high-frequency HDF compared to using HDF at low frequencies can better improve the biocompatibility of dialysis membranes, have higher permeability to water and solutes, and can remove more medium and macromolecular toxins. Studies have confirmed that HDF can reduce the risk of heart disease and death in patients with uremia, and effectively eliminate non-traditional risk factors such as β_2-MG, FGF-23, thereby reducing chronic complications and improving the patient's long-term prognosis.[24]

The Study Limitations

Firstly, we did not include several frequencies of HDF usage, such as not using HDF or using it once every 2 weeks. Secondly, this study is a single center study and the number of included cases is relatively small, which may increase the errors. These two directions should further be explored and improved in future research, to improve the treatment effects of patients with uremia.

CONCLUSION

In conclusion, one week/time HDF combined with HFHD can more effectively eliminate the vascular related toxins in middle-aged and elderly patients with uremia, improve their nutritional status, treatment effect, and long-term prognosis. So, this study has some research prospects, this method is worth promoting and applying in clinical practice.

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Yantai Yuhuangding hospital. Patients who participated in the study had complete clinical data. Signed written informed consents were obtained from the patients and/or guardians.

PATIENT CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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