Clinical Efficacy of High-flux Hemodialysis for Treating Uremia and its Effect on Microinflammation and Nutritional Status

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Keywords. High-flux hemodialysis; Uremia; Clinical efficacy; Microinflammation; Nutritional status

Introduction. The objective of this study **was** to evaluate the clinical efficacy of high-flux hemodialysis for treating uremia and its effect on microinflammation and nutritional status.

Methods. This was a case-control study. One hundred and twenty patients under chronic hemodialysis in Qinhuangdao Haigang Hospital from June 2021 to June 2023 were randomly divided into experiment group and control groups, with 60 patients in each group. Patients in the experiment group received high-flux hemodialysis (HFHD), while those in the control group underwent conventional hemodialysis. The differences between the two groups regarding clinical efficacy, inflammatory factors including IL-6, CRP and TNF-a, and macromolecular toxins including β_2-microglobulin, parathyroid hormone, and cysteine protease inhibitor were compared. The levels of nutritional indices including serum transferrin, albumin, and hemoglobin were compared between the two groups after 6 months of therapy. All patients were followed-up for 1.5 to 2 years, and the incidence of their cardiovascular and cerebrovascular events after treatment was analyzed.

Results. The response rate (markedly effective + effective)/total number of cases × 100%.) was 93% in the experiment vs. 80% in the control group (P = .03). After treatment, IL-6, CRP, TNF-a, β_2-microglobulin, parathyroid hormone, and cysteine protease inhibitor significantly reduced and serum transferrin, albumin and hemoglobin significantly improved in the experiment vs. control group (P = .00). At the end of the follow-up period the incidence of cardiovascular and cerebrovascular diseases was 7% in the experiment group, which was markedly lower than that of 22% in the control group (P = .02).

Conclusion. High-flux hemodialysis is a safe and effective treatment for uremia with remarkable clinical efficacy, offering various benefits such as significant reduction of inflammatory biomarkers and macromolecular toxins, improvement of patients' nutritional status, and reduction of the incidence of cardiovascular and cerebrovascular diseases.

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INTRODUCTION

Uremia, representing the end-stage state of various chronic kidney diseases, is a disease that seriously jeopardizes the life of patients.[1] A global increase in the incidence of end-stage kidney disease has been witnessed in recent years. Those

suffering from uremia are typically characterized by water and electrolyte disorders, accompanied by worsening uremic symptoms such as poor appetite, nausea, and anemia; Meanwhile, their hematologic and respiratory systems are also affected, resulting in multisystem disorders.[2] Uremia is a major cause of death in patients with chronic kidney disease. In this regard, dialysis is most commonly used as renal replacement therapy for patients with uremia. Conventional hemodialysis (HD) is mainly performed by solute diffusion and limited ultrafiltration through a dialyzer made of embedded hollow fiber semipermeable membranes. It serves to effectively remove small molecules, correct electrolyte disturbances, and eliminate excess extracellular fluid from the body while retaining important molecules such as albumin for therapeutic purposes.[3] However, conventional HD is less than optimal in adequate removal of medium-molecular weight (500–45,000 kDa) compounds such as interleukins and tumor necrosis factor and macromolecular toxins such as β_2-microglobulin, parathyroid hormone, and cysteine protease inhibitor, which in turn lead to a variety of adverse effects such as nausea, vomiting, fatigue, muscle spasms, and altered mental status.[4] As these uremic toxins accumulate, they lead to exacerbated inflammation, oxidative stress disorders, endothelial dysfunction, and vascular calcification, resulting in an increased risk of cardiovascular disease and death. High-flux hemodialysis (HFHD) was developed to address these limitations. This modality clears uremic toxins, especially medium- and macro-molecular toxins with molecular weights of 500 and above through high-flux membranes. Studies have demonstrated an enhanced clearance of multiple uremic toxins by HFHD compared to conventional HD, which reduces complications arising from the inadequate clearance of medium- and macro-molecular toxins by HD.[5] We designed this study to investigate the clinical efficacy of HFHD for uremia and its effect on microinflammation and nutritional status, together with long term cardiovascular and cerebrovascular effects.

MATERIALS AND METHODS

This was a case-control study. One hundred and twenty patients admitted to Qinhuangdao Haigang Hospital from June 2021 to June 2023; who received hemodialysis for uremia were randomly divided into two groups: the experiment group and the control group, with 60 cases in each group.

The study was approved by the ethics committee of our hospital (No.:20211119; date:November 19, 2021), and written informed consent was obtained from all participants.

Inclusion criteria

- Adults aged 50-70 years old meeting the diagnostic criteria for uremia;[6]
- Maintenance dialysis for at least 6 months;[7]
- Good compliance and ability to complete the study.
- Signing the written consent with awareness

Exclusion criteria

- Previous kidney transplantation;
- Severe infection or hormone therapy within the past 3 months;
- Concomitant hematologic and immune system diseases;
- Concomitant severe cardiac, pulmonary or hepatic disease, malignancies or other vital organ dysfunction;
- Mental disorders or combined psychiatric disorders that could not cooperate and/or consent
- Incomplete clinical data.

Both groups were dialyzed with a dialysis machine (710207t Haemodialysis Machine, B. Braun, Germany). Those in the experiment group underwent high-flux hemodialysis with a dialysis membrane surface area of 1.8 m^2 and an ultrafiltration coefficient of 50 ml/(h-mmHg) (1 mmHg = 0.133 kPa); and those in the control group underwent low-flux hemodialysis with a dialysis membrane surface area of 1.6 m^2 and an ultrafiltration coefficient of 20 ml/h-mmHg). Hemodialysis solution (Guangzhou Koncen BioScience Co., Ltd., NMPA Registration Approval No.20153102392, specification: 10 L/canister) was used, with dialysate flow rate of 500 ml/min and blood flow rate of 200–250 ml/min; dialysis was performed 2–3 times/week for 4 h/session. Low-molecular weight heparin calcium injection was chosen for anticoagulation, which was given as an intravenous bolus at the beginning of hemodialysis with low molecular heparin 60–80 IU/kg.

Observation indices

1. Determination of clinical efficacy: the duration of treatment and the time of improvement of renal function respectively after treatment. Markedly effective: significant improvement in BUN and Cr after treatment (levels reduced by more than 30%), and basic disappearance of clinical symptoms; effective: certain improvement in BUN and Cr after treatment (levels reduced by more than 20%), and some relief of clinical symptoms; ineffective: no significant improvement in clinical symptoms and no significant change in BUN and SCr. The response rate = (markedly effective + effective)/total number of cases × 100%.[8]
2. Indices of changes in microinflammatory response: blood was drawn before dialysis and after 1 week of dialysis in the fasting state and early morning to detect IL-6, CRP, TNF-a to evaluate changes in microinflammatory response.
3. The levels of macromolecular toxins such as β_2-microglobulin, parathyroid hormone, and cysteine protease inhibitor were comparatively analyzed in the two groups after 1 week of treatment.
4. The differences in the levels of serum transferrin (TRF), albumin (ALB), hemoglobin (HB) and other nutritional indicators between the two groups after 6 months of treatment were comparatively analyzed.
5. All patients were followed up for 1.5 to 2 years and their post-treatment cardiovascular event rates were subsequently analyzed in comparison.

Statistical analysis

Data were statistically analyzed using SPSS 25.0 software, and measurement data were expressed as ($\bar{X}$ ± S). The power of the test/confidence interval was 95%, and an independent sample t-test was employed to analyze the data between the experiment and the control groups, and a Chi-square test was used for the comparison of categorical data. $P < .05$ was considered to indicate a statistically significant difference.

RESULTS

In the experiment group (HFHD), there were 37 males and 23 females, aged 54-70 years, with an average of 62.36 ± 8.25 years; and in the control group, there were 36 males and 24 females, aged 56-70 years, with an average of 62.75 ± 8.83 years. No significant difference was found in the baseline data between the two groups, which was comparable between the groups (Table 1).

Comparative analysis of clinical efficacy

The comparison of clinical efficacy between the two groups after treatment showed that the response rate was 93% in the experiment group, which was significantly higher than 80% in the control group ($P = .03$) (Table 2).

Table 1. Comparative analysis of general data between the two groups ($\bar{X}$ ± S) n = 60

Indices	Experiment group	Control group	t/χ^2	*P*
Age (years)	62.36 ± 8.25	62.75 ± 8.83	0.25	.80
Male (No., %)	37 (62%)	36 (60%)	0.04	.85
Duration of uremia	12.53 ± 2.37	13.05 ± 2.82	1.09	.28
Body mass index (kg/m^2)	23.04 ± 2.10	22.89 ± 1.87	0.41	.68
Primary disease				
Glomerulonephritis	25 (42%)	27 (45%)	0.14	.71
Diabetic nephropathy	16 (26%)	18 (30%)	0.16	.69
Hypertensive renal damage	13 (22%)	7 (12%)	2.16	.14
Others	6 (10%)	8 (13%)	0.32	.57

*$P > 0.05$

Table 2. Comparison of treatment efficiency between the two groups ($\bar{X}$ ± S) n = 60

Group	Markedly effective	Effective	Ineffective	Response rate*
Experiment group	37	19	4	56 (93%)
Control group	30	18	12	48 (80%)
χ^2				4.62
P				0.03

*$P < 0.05$

Comparative analysis of the levels of inflammatory factors

The changes in serum tumor markers of the two groups before and after treatment are shown in Table 3. No statistically significant difference was found between the experiment group and the control group in terms of indices such as IL-6, CRP and TNF- before treatment ($P > .05$), whereas the above indices were significantly lower in the experiment group than in the control group after treatment ($P = .00$) (Table 4).

Indices of changes in macromolecular toxins

No statistically significant difference was found between the experimental group and the control group in terms of macromolecular toxins such as β_2-microglobulin, parathyroid hormone, and cysteine protease inhibitor ($P > .05$). After treatment, the above indices decreased significantly in the experiment group compared to the control group ($P = .00$) (Table 4).

Analysis of changes in nutritional indices

No statistically significant difference was found between the experiment group and the control group in terms of indices such as TRF, ALB and HB before treatment ($P > .05$). After treatment, the above indices improved significantly in the experiment group compared to the control group, ($P = .00$) (Table 5).

Comparative analysis of the incidence of cardiovascular and cerebrovascular diseases between the two groups

Both groups completed follow-up without missing patients, with follow-up lasting 1.5-2 years. The incidence of cardiovascular and cerebrovascular diseases was 7% in the experiment group, which was significantly lower than that of 22% in the control group ($P = .02$) (Table 6).

DISCUSSION

Uremia, a clinical syndrome commonly observed

Table 3. Comparison of the indices of inflammatory factors between the two groups before and after treatment ($\bar{X} \pm S$) n = 60

Indices	Observation points	Experiment group	Control group	t	*P*
IL-6 (ng/L)	Before treatment	15.72 ± 5.03	15.45 ± 5.16	0.29	.77
	After treatment*	8.59 ± 1.27	10.33 ± 2.80	4.38	.00
CRP (mg/L)	Before treatment	4.18 ± 0.73	4.24 ± 0.67	4.50	.64
	After treatment*	2.25 ± 0.13	2.78 ± 0.34	11.28	.00
TNF-a (ng/L)	Before treatment	42.24 ± 12.73	42.68 ± 11.75	0.20	.84
	After treatment*	21.36 ± 7.42	26.06 ± 8.34	3.26	.00

*$P < 0.05$

Table 4. Comparison of macromolecular toxin indices between the two groups before and after treatment ($\bar{X} \pm S$) n = 60

Indices	Observation points	Experiment group	Control group	t	*P*
β2-microglobulin (mg/L)	Before treatment	20.13 ± 5.07	19.86 ± 5.33	0.28	.77
	After treatment*	9.12 ± 3.48	11.33 ± 4.06	3.64	.00
Parathyroid hormone (pg/ml)	Before treatment	657.72 ± 52.63	661.07 ± 51.42	0.43	.67
	After treatment*	413.37 ± 43.06	438.59 ± 44.80	3.15	.00
Cysteine protease inhibitor (mmol/L)	Before treatment	5.63 ± 1.32	5.57 ± 1.13	0.28	.79
	After treatment*	2.04 ± 0.28	2.45 ± 0.46	6.33	.00

**P* < 0.05

Table 5. Comparison of nutritional indices between the two groups after treatment ($\bar{X} \pm S$) n = 60

Indices	Observation points	Experiment group	Control group	t	*P*
TRF (mg/L)	Before treatment	1.58 ± 0.36	1.56 ± 0.23	0.36	.72
	After treatment*	3.22 ± 0.71	2.13 ± 0.64	8.83	.00
ALB (g/L)	Before treatment	30.57 ± 4.37	29.79 ± 4.40	0.97	.33
	After treatment*	42.87 ± 5.42	38.72 ± 4.36	4.61	.00
HB (g/L)	Before treatment	87.65 ± 12.41	89.06 ± 12.38	0.62	.53
	After treatment*	106.50 ± 15.72	98.08 ± 12.21	3.26	.00

**P* < 0.05

Table 6. Comparison of the incidence of cardiovascular and cerebrovascular diseases between the two groups ($\bar{X} \pm S$) n = 60

Group	Myocardial infarction	Arrhythmia	Heart failure	Cerebral infarction	Cerebral hemorrhage	Incidence
Experiment group	1	2	0	1	0	4 (7%)
Control group	3	4	2	3	1	13 (22%)
χ^2						5.55
P						0.02

*$P < 0.05$

in various advanced kidney diseases, arises from the loss of renal function, which ultimately results from irreversible kidney damage triggered by multiple factors.[9] The continuous accumulation of toxins results in a large number of metabolites and toxic substances in the body, leading to a variety of deleterious effects on the organism, including malnutrition, skin atrophy, metabolic acidosis, coagulation dysfunction and cardiovascular disease. Currently, kidney transplantation and dialysis are the available methods for treatment of uremia. Kidney transplantation, despite its obvious superiority, is costly and limited by the scarcity of kidney resources. For this reason, hemodialysis is still used as a main type of therapy relying on clearance of waste metabolic substances by applying the principles of diffusion and convection. High concentration of waste products and excess electrolytes diffuse from blood to the dialysate through the semi-permeable membranes of the dialyzer, to clear the waste products and regulate the balance of water and electrolytes. Despite the advances in dialysis techniques witnessed in recent years, the mortality rate of uremic patients treated with dialysis is still approximately 22.8% per year.[10]

High-flux dialysis is hemodialysis performed with high-flux membranes, which have the capacity of a high fluid removal rate, together with better clearance of medium and large molecular solutes. Hestekin showed that HFHD using biocompatible membranes protects patients' residual renal function, reduces inflammatory reactions, and significantly increases therapeutic efficacy compared to conventional dialysis.[11] This was confirmed in our study with a better efficacy presented as a response rate of 93% in the experiment group, which was significantly higher than 80% in the control group ($P = .03$), which is in general agreement with the findings of Švára. Our study also showed that after treatment, medium-molecular weight inflammatory factors such as IL-6, CRP, TNF- and macromolecular toxins such as β_2-microglobulin, parathyroid hormone, and cysteine protease inhibitor were reduced in the experiment group compared with the control group, with statistically significant differences ($P = .00$), which suggests that high-flux hemodialysis can alleviate inflammatory response in uremic patients. The microinflammatory response is a result of increased monocyte macrophage activity. During hemodialysis, monocytes are activated by substances such as contaminated endotoxin, which increases the level of inflammatory factor expression. This in turn leads to a mild inflammatory response in the body.[12] In general, the molecular weight of medium-sized inflammatory factors causes a microinflammatory state. Therefore, conventional hemodialysis is unable to remove them. High-flux hemodialysis introduces a high clearance rate of medium and large molecules, which can partially remove inflammatory factors, effectively reduce the level of inflammatory factors in the patient's body, and reduce the microinflammatory state of the patient. Meanwhile, the favorable biocompatibility of high-flux membranes is capable of reducing the level of monocyte macrophage activity, thus alleviating the microinflammatory state.[13] The inflammatory response causes changes in the intra- and extracellular environment, thereby increasing the production of oxygen free radicals and other reactive oxidizing substances, which in turn cause or aggravate oxidative stress; the two are mutually reinforcing, creating a vicious cycle of increased production of oxidizing substances. These substances activate the inflammatory response, causing infiltration of inflammatory cells and release of inflammatory mediators.[14]

Chronic kidney disease (CKD) is often associated with anemia. High-flux membranes can increase the removal of uremic toxins that lead to anemia in end-stage kidney disease patients and improve the nutritional status of the patient. Insufficient

data describe the advantages of high-flux dialysis in promoting erythropoietin response in CKD patients.[15] However, in this study, we showed that nutritional indicators, including serum transferrin, albumin and hemoglobin, improved significantly in HFHD compared to conventional HD (P = .00). Serum transferrin is the major iron-containing compound in plasma and is mainly responsible for the transportation of iron ions for the production of mature red blood cells. ALB is the most abundant circulating protein in the body and is essential for maintaining plasma osmolality and as a carrier of substances (e.g., hormones, vitamins, and drugs). Dialysis patients often exhibit a microinflammatory state, which impairs hepatic albumin synthesis, increases albumin catabolism and vascular leakage, and ultimately leads to hypoalbuminemia.[16] Reduced hemoglobin level is mostly related to the decreased secretion of erythropoietin due to chronic kidney damage and conventional HD is ineffective in removing toxins such as PTH that suppress erythropoietin production in these patients.

Cardiovascular disease, as the main cause of death in patients with CKD is closely related to hyperphosphatemia.[17] Considering the impaired phosphorus excretion in CKD patients, many of them have a high rate of cardiovascular disease when they start dialysis treatment. Hence, cardiovascular events have become an important challenge for dialysis patients.[18] Dialysis patients have about 15 times higher rate of cardiovascular disease mortality compared to the general population.[19] Based on this study, we found that the incidence of cardiovascular disease was significantly lower in the experiment group compared to the control group (P = .02). This finding confirms that high-flux hemodialysis has benefits in terms of the cardiovascular and cerebrovascular systems in uremic patients. The cause may involve damage to the vascular endothelium by inflammation and oxidative stress. In addition, medium and high-molecular-weight toxic substances damage the myocardium and brain cells. High-flux dialysis can well remove these toxic substances, and is thus more favorable to the cardiovascular and cerebrovascular systems. However, some authors believe that its long-term effect on patients' cardiovascular and cerebrovascular systems, compared to conventional hemodialysis, needs to be further confirmed.[20]

THE STUDY LIMITATIONS

There are still some shortcomings in this study, mainly a small sample size and short follow-up time. Studies with larger sample size and an extended follow-up period are needed.

CONCLUSION

In summary, high-flux hemodialysis (HFHD) is a safe and effective treatment for uremia, offers various benefits such as significant reduction of inflammatory factors and macromolecular toxins, improvement of patients' nutritional status, and reduction of the incidence of cardiovascular and cerebrovascular diseases.

AUTHORS CONTRIBUTION

Fei Guo carried out the studies, participated in collecting data, and drafted the manuscript, and are responsible and accountable for the accuracy or integrity of the work; Jiakang Sun performed the statistical analysis and participated in its design; Deheng Wan and Yan Wang performed the statistical analysis and participated in its design; All authors read and approved the final manuscript.

DATA AVAILABILITY

The datasets used and analyzed during the current study are available from the corresponding author upon request.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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