BMC Nephrology

STUDY PROTOCOL Open Access

The impact of Hemodiafiltration with endogenous reinfusion (HFR) on micronutrient status in patients undergoing maintenance hemodialysis: study protocol of a randomized controlled trial

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Abstract

Background End-stage renal disease (ESRD) is associated with significant morbidity and mortality, with patients often experiencing micronutrient deficiencies due to dialysis treatments. Hemodiafiltration with Endogenous Reinfusion (HFR) is a novel dialysis modality that combines diffusion, convection, and adsorption mechanisms to remove uremic toxins while potentially preserving essential nutrients. This study aims to assess the impact of HFR on micronutrient levels and removal rates in patients undergoing maintenance hemodialysis (HD).

Methods This is a single-center, open-label, randomized controlled trial. Adult patients on maintenance HD will be randomized to two treatment arms: Arm A (Hemodiafiltration (HDF) followed by HFR) and Arm B (HFR followed by HDF), with a two-week washout period between treatments. Blood samples will be collected pre- and post-treatment to measure trace elements, water-soluble vitamins, and fat-soluble vitamins. Statistical analyses will include paired t-tests and Wilcoxon signed-rank tests for within-group comparisons, and repeated measures ANOVA for between-group differences, adjusting for potential confounders.

Discussion This study will evaluate whether HFR offers superior retention of micronutrients compared to traditional HDF therapies, which may contribute to improved clinical outcomes for ESRD patients. Findings could provide valuable insights into the role of HFR in optimizing nutritional status and reducing dialysis-related complications. The cross-over design minimizes patient variability, enhancing the reliability of comparisons between treatment modalities.

Trial registration This trial is registered with the Chinese Clinical Trial Registry (ChiCTR2500096698).

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Keywords Hemodiafiltration with endogenous reinfusion, Hemodiafiltration, Micronutrient, Randomized controlled trial

Background

End-stage renal disease (ESRD) poses a significant global health burden, characterized by the irreversible loss of kidney function, leading to a cascade of complications and significantly impacting patients' quality of life [1]. The prevalence of ESRD continues to rise, driven by factors such as aging populations, increasing rates of diabetes, and hypertension. This escalating prevalence necessitates effective and optimized renal replacement therapies (RRT) to manage the disease and improve patient outcomes.

Hemodialysis (HD) remains a cornerstone of RRT, providing essential support for patients with ESRD [2]. Over the past decades, advancements in dialytic techniques, including improvements in dialyzers, membranes, and dialysis fluids, have dramatically enhanced the quality of life for individuals undergoing HD [3]. These advancements have contributed to better control of uremia, improved fluid and electrolyte balance, and enhanced cardiovascular stability. However, traditional HD and even hemodiafiltration (HDF), while effective in removing uremic toxins and excess fluid, can inadvertently lead to the depletion of essential micronutrients [4–6]. Emerging evidence suggests a strong association between the status of specific micronutrients, such as vitamins, trace elements, and antioxidants, and the overall prognosis in HD patients [7, 8]. Deficiencies in these vital nutrients can contribute to a range of complications, including inflammation, oxidative stress, cardiovascular disease, and impaired immune function, ultimately impacting patient morbidity and mortality [9].

Hemodiafiltration with online regeneration of ultrafiltrate (HFR) represents a relatively novel dialytic approach that combines the principles of diffusion, convection, and adsorption, which was developed in the recent two decades [10]. This technique distinguishes itself through the incorporation of an adsorbent cartridge containing a combination of resin and charcoal. This unique cartridge plays a crucial role in regenerating the ultrafiltrate, effectively converting it into an endogenous substitution fluid. By utilizing the patient's own filtered plasma, HFR aims to minimize the loss of essential substances while still effectively removing uremic toxins [11].

Previous studies have demonstrated that HFR exhibits superior efficacy in lowering the levels of certain uremic toxins compared to traditional HD and/or HDF [12–15]. This enhanced removal is attributed to the combined effects of the different clearance mechanisms employed by HFR, particularly the adsorption capacity of the specialized cartridge. The broader clearance profile of HFR suggests its potential advantages in managing the complex biochemical derangements associated with ESRD.

Based on the mechanistic principles of HFR, it is hypothesized that this technique may offer improved retention of macronutrients compared to traditional HD and/or HDF. This potential for better nutrient preservation is a key area of interest, especially considering the clinical importance of maintaining adequate nutritional status in HD patients.

Therefore, this study aims to investigate the impact of HFR on micronutrient status in patients undergoing MHD. By comparing micronutrient levels in patients treated with HFR to those receiving conventional HDF, this research will provide valuable insights into the potential benefits of HFR in preserving essential nutrients and improving the overall well-being of ESRD patients.

Methods and analyses

Trial design

This study is a single-centered, open-label randomized controlled trial. (Figures 1 and 2) The study proposal was approved by the institutional review committee of the Naval Medical Center of PLA (registration number: 2024123104). The study will be conducted in accordance with the local legislation and institutional requirements. The research has been registered in chictr.org.cn (ChiCTR2500096698).

Study population

Sample size

Sample size calculation was performed using G*Power 3.1 software. The assumed effect size of 0.45 was derived from a previous randomized controlled trial [16]. To achieve 80% statistical power (1-β) and an effect size of 0.45, with a significance level (α) of 0.05, the sample size calculation suggested a minimum of 26 participants. We opted to recruit 30 participants, ensuring at least 15 individuals per group.

Inclusion and exclusion criteria

Inclusion criteria 1): patients who are 18 years or older. 2): patients on maintenance HD for three times/week in naval medical center of PLA. 3): patients who have signed an informed consent form. Exclusion criteria: 1): patients combined therapy with peritoneal dialysis and HD. 2): patients who underwent general anesthesia surgery within the past week. 3): patients on any unstable clinical conditions. 4): patients with known malignancy or severe liver disease. 5): patients who are unable to eat orally.

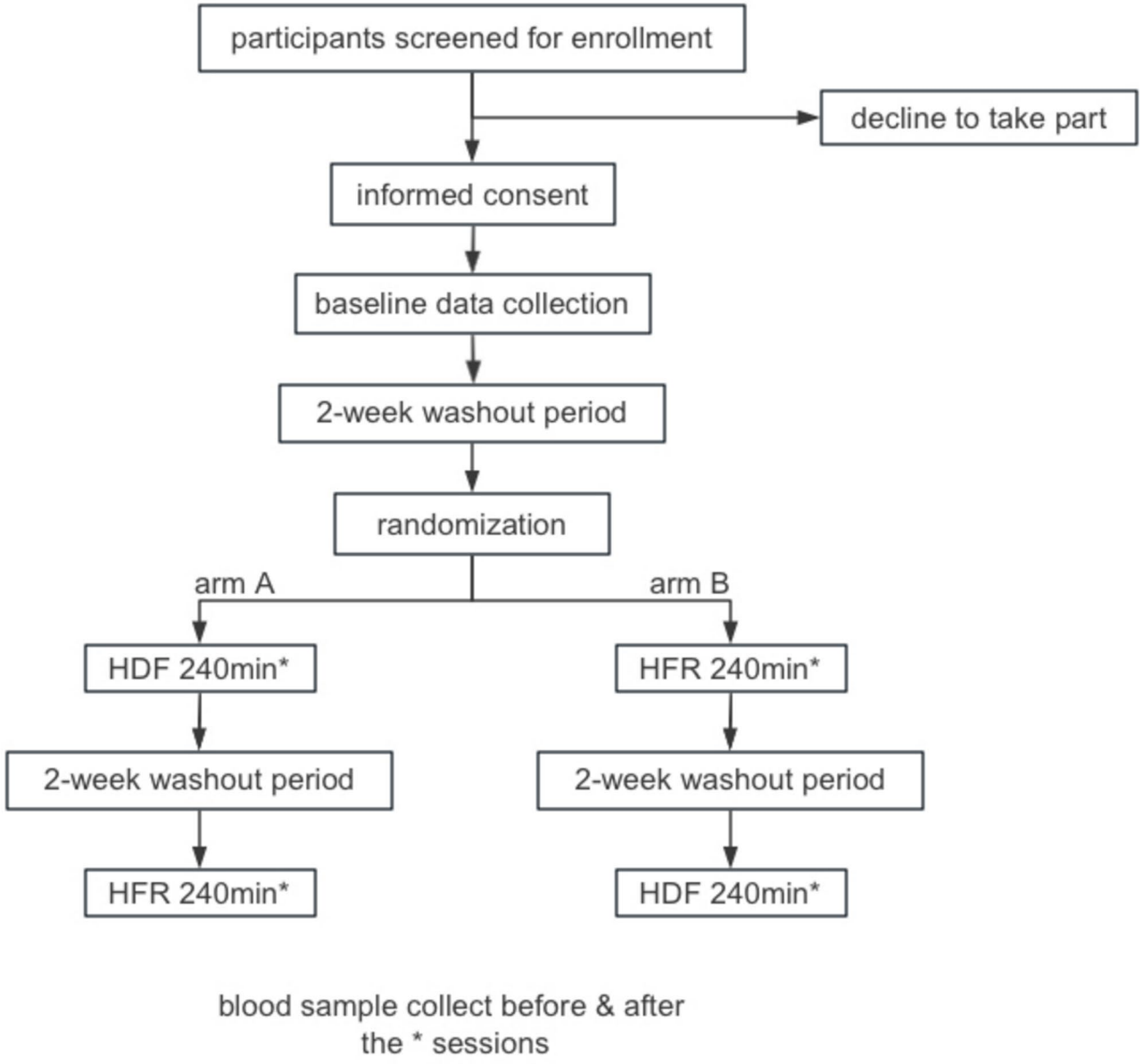

Fig. 1 Study flowchart

Baseline data collection

Before washout, baseline data will be collected from all enrolled patients. Baseline data will include demographic characteristics and clinical background. Demographic characteristics will encompass sex, age, height, and weight, among other relevant factors. Clinical background include: primary renal failure cause, dialysis duration, complications, comorbidities such as cardiovascular disease, diabetes, and stroke. Laboratory tests at baseline are also considered: iron metabolism markers, brain natriuretic peptide (BNP), pro-BNP, albumin, C-reactive protein, blood urea nitrogen, prealbumin, total cholesterol, hemoglobin, corrected calcium, phosphorus, and parathyroid hormone.

Blinding and randomization

After the two-week HD washout period. The randomization procedure will be performed by Dan Ye using a random number generator computer program (Microsoft Excel for MacOS, Version 16.94). The randomization sequence will be concealed using opaque envelopes from both the study participants and the researchers responsible for enrolment and assignment until the moment of treatment allocation. This process ensures that no information about group allocation is available before assignment, preventing any bias in the allocation process. The included patients will be assigned to arm A and arm B in 1:1 ratio. Maintaining blinding of the researchers responsible for implementing the interventions is not feasible.

2. schedule of enrolment, interventions, and assessments.

			STUDY PERIOD								
	Enrolment	washout	Allocation	Post-allocation							Close-out
TIMEPOINT**	2w prior to t_0	2w prior to t_0	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
Allocation			X								
INTERVENTIONS:											
[first intervention duration (HDF or HFR)]					X						
[washout]							X				
[Second intervention duration (HDF or HFR)]									X		
ASSESSMENTS:											
[Baseline variables]	X										
[Primary outcomes]				X		X		X		X	X
[Secondary outcoms]				X		X		X		X	X

**List specific timepoints in this row.

t1: timepoint immediately before the first treatment session
t2: the first treatment session
t3: timepoint immediately after the first treatment session
t4: 2-week washout
t5: timepoint immediately before the second treatment session
t6: the second treatment session
t7: timepoint immediately after the second treatment session

Fig. 2 Schedule of enrolment, interventions, and assessments

However, to ensure the integrity of the data, the researchers tasked with data analysis will remain blinded until the completion of all data analysis procedures. After randomization, patients in arm A will first receive HDF treatment for 240 min, followed by a 2-week washout period with conventional HD, after which they will undergo HFR treatment for 240 min. Conversely, patients in arm B will first receive HFR treatment for 240 min, followed by a 2-week washout period with conventional HD, and then undergo HDF treatment for 240 min. This design aims to minimize potential bias due to the sequence of treatments. The date of HDF or HFR treatment will be defined as Day D or Day R, respectively, with the requirement that the previous HD session occurs on Day D-2 or Day R-2.

Interventions

Low molecular weight heparin is the anticoagulant of choice, with dosing adjusted per routine clinical practice to maintain circuit patency. The blood flow rate is maintained at a minimum of 200 mL/min throughout the treatment. While this is the minimum acceptable rate for the study, clinicians will be encouraged to target higher blood flow rates (e.g., 250–350 mL/min) as tolerated by

the patient's vascular access to optimize clearance, consistent with standard practice. The dialysate flow rate is consistently set at 500 mL/min. Each treatment session is standardized to a fixed duration of 240 min. Dialysis adequacy (e.g., spKt/V) will be monitored quarterly as per standard unit protocol but is not a primary outcome measure for comparing HFR and HDF in this study focused on micronutrients. The ultrafiltration volume is individualized based on the patient's condition, though it is recommended that it not exceed 5% of the patient's dry weight unless clinically indicated and carefully monitored.

Safety monitoring and halting criteria

Patients will be monitored throughout the dialysis sessions according to standard clinical practice, including vital signs and circuit pressures. The HDF or HFR treatment will be halted prematurely under the following circumstances: severe hypotensive episode unresponsive to standard intervention, acute allergic reaction, persistent access issues preventing target blood flow, irremediable circuit clotting, or any other acute event deemed clinically significant by the attending nephrologist and data from the incomplete session may be excluded from the primary analysis depending on timing and reason for stoppage.

HDF protocol

For the HDF treatment, the Fresenius 5008 S HD machine and the FX80 dialyzer will be utilized. Post-dilution online HDF will be performed with a target substitution fluid volume appropriate for the treatment time and blood flow rate.

HFR protocol

The HFR treatment will be administered using the Formula Dialysis Therapy machine (Bellco, Italy). Central to the HFR technology are two essential components: the dual-chamber filter, Supra17 (Bellco, Italy), and the resin adsorption column, Suprasorb (Bellco, Italy).

Outcome measures

Blood sampling

Blood samples will be collected from each patient both before and after HDF and HFR treatments. Blood sampling will be performed immediately prior to starting the treatment, followed by initiation of the dialysis procedure. The method for post-treatment blood sampling will follow the protocol recommended by the KDOQI guidelines [17, 18]: at the end of the treatment, the dialysate flow rate will be reduced to zero, and the blood flow rate will be decreased to 100 mL/min for 15 s, after which the blood pump will be stopped and the sample collected. All the analyses will be conducted in Kingmed diagnostics, Inc. Guangzhou, China.

Primary outcomes

Trace elements level: Iodine (inductively coupled plasma mass spectrometry).

Secondary outcomes

Trace elements level: Cu, Mg, Zn, Se, Fe, Ca, Pb, Cd (inductively coupled plasma mass spectrometry).

Water-soluble vitamins level: riboflavin, niacin, pantothenic acid, pyridoxine, folate, cobalamin (high-performance liquid chromatography-tandem mass spectrometry) and biotin (high-performance liquid chromatography).

Fat-soluble vitamins level: vitamins E (ultra-high performance liquid chromatography), K, ergocalciferol, and cholecalciferol (high-performance liquid chromatography-tandem mass spectrometry).

Statistical analyses

Descriptive statistics will be used to summarize baseline characteristics and outcome measures. Continuous data will be presented as mean ± standard deviation (SD) for normally distributed variables and as median (interquartile range, IQR) for non-normally distributed variables, and frequency (percentage) for categorical variables. Normality will be assessed using the Shapiro-Wilk test.

Baseline demographic and clinical characteristics between the two treatment groups (Arm A and Arm B) will be compared. For continuous variables, an independent t-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data) will be used. For categorical variables, the Fisher's exact test will be applied.

The primary analysis will focus on the primary endpoint: the change in serum Iodine level from pre-treatment to post-treatment. Repeated measures ANOVA will be used, with treatment (HDF vs. HFR) and treatment period (first vs. second) as within-subject factors. The model will account for subject variability as a random effect. Covariates such as age, sex, ultrafiltration volume, dialysis vintage, and baseline I levels will be included to adjust for potential confounders.

Analyses of all other micronutrients (trace elements: Cu, Mg, Zn, Se, Fe, Ca, Pb, Cd; water-soluble vitamins: Vitamin C, B1, B2, B6, B12, Folic acid; fat-soluble vitamins: Vitamin A, D, E, K) are considered secondary and exploratory. The same repeated measures ANOVA model structure will be applied to these secondary outcomes. Given the number of secondary endpoints relative to the sample size, these results will be interpreted with caution due to the increased risk of Type I error from multiple comparisons. For a limited number of pre-specified

key secondary outcomes (e.g., Selenium, Folate), we may apply adjustments for multiple comparisons (such as Bonferroni or False Discovery Rate methods) and will report both adjusted and unadjusted p-values, noting the exploratory nature of these analyses. Sensitivity analyses may explore alternative approaches like ANCOVA on the change scores if model assumptions for repeated measures ANOVA are significantly violated. Statistical significance will be defined as $p < 0.05$, and all analyses will be conducted using SPSS Statistics for MacOS, version 30.0.0.0 (SPSS Inc., Chicago, IL, USA). Data access will be restricted to the principal investigators, designated study coordinators, and the blinded statistical analysis team. Data will be stored securely according to institutional guidelines.

Discussion

This study aims to investigate the impact of HFR on micronutrient status in patients undergoing MHD. As ESRD continues to rise, maintaining optimal nutritional status is crucial for improving patient outcomes [19]. While dialysis therapies such as HD and HDF effectively remove uremic toxins, they can also deplete essential micronutrients, contributing to complications like immune dysfunction and cardiovascular disease [20, 21]. This trial explores whether HFR, which utilizes the patient's own filtered plasma, can better preserve micronutrients compared to traditional HDF.

The RCT design with a cross-over methodology minimizes inter-patient variability and enables within-subject comparisons between treatments [22]. The use of robust statistical methods, such as paired tests and repeated measures ANOVA, will control for confounders like ultrafiltration volume. The study will provide comprehensive data on micronutrients, including water- and fat-soluble vitamins and trace elements, offering a broad understanding of HFR's potential benefits. The single-center design may limit the generalizability of the results, and the open-label nature of the study may introduce performance bias. However, blinding of outcome assessors (laboratory personnel) and data analysts will help minimize this. Additionally, inter-patient variability in nutrient absorption and underlying conditions may affect outcomes, though this will be addressed by controlling for baseline levels and comorbidities in the statistical analysis. Regular monitoring according to clinical standards and defined halting criteria will ensure patient safety during the procedures.

If HFR is shown to preserve micronutrient levels more effectively than traditional HDF, it could become a valuable option for MHD patients at risk of deficiencies. This would not only improve nutritional status but also potentially reduce complications associated with micronutrient depletion.

Future studies should evaluate the long-term effects of HFR on survival, quality of life, and hospitalization rates. Further research on biomarkers for micronutrient status and protein-energy wasting in dialysis patients would enhance clinical decision-making.

In conclusion, this trial will provide important insights into the potential benefits of HFR in preserving micronutrient status in ESRD patients, with the potential to improve treatment outcomes and patient quality of life.

Abbreviations

BUN	Blood Urea Nitrogen
BNP	Brain Natriuretic Peptide
HDF	Hemodiafiltration
HFR	Hemodiafiltration with Regeneration of Ultrafiltrate
HD	Hemodialysis
IQR	Interquartile Range
MHD	Maintenance Hemodialysis
Pro	BNP–Pro Brain Natriuretic Peptide
RCT	Randomized Controlled Trial
RRT	Renal Replacement Therapy
SPSS	Statistical Package for the Social Sciences

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04148-6.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

None.

Author contributions

HW, and BY designed the study together. CZ led the application for ethics approval and consent. LD, NL, and FZ are the study clinicians involved in patient care and data collection. All authors participated in critically appraising and revising the intellectual content of the manuscript. All authors read and approved the final manuscript.

Funding

This study is funded by Naval Medical Center of PLA (21TPQN3201) and Naval Medical University (XJS2024B01).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study proposal was approved by the institutional review committee of the Naval Medical Center of PLA (registration number: 2024123104). The study will be conducted in accordance with the local legislation and institutional requirements. All participants will provide written consent. The consent form will be collected by Dan Ye.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 27 February 2025 / Accepted: 22 April 2025
Published online: 02 May 2025

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