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Effects of combined haemodialysis-haemoadsorption therapy in maintenance haemodialysis patients: study protocol for a multicentre, open-label, randomised, parallel controlled trial

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ABSTRACT

Introduction Haemodialysis (HD) is an essential treatment for end-stage renal disease patients to improve their quality of life. However, conventional HD may not effectively remove medium and large molecules and protein-bound toxins, leading to the occurrence of various complications. Haemoadsorption (HA), on the other hand, can address this limitation. Therefore, a multicentre, open-label, randomised, parallel controlled study will be conducted to compare HA combined with HD (HAHD) with HD alone in maintenance haemodialysis (MHD) patients. The primary endpoint is the change in serum β2-MG, PTH and CRP values.

Methods and analysis We plan to enrol 410 MHD patients from 10 participating medical centres in Shanghai. Patients will experience a 4-week washout period and a 52-week observation period. After the washout period, the eligible patients will be randomised in a 1:1 ratio to the two groups: the control group, 3 times/week conventional HD treatment; and the experiment group, 3 times/week conventional HD treatment+1 time/week HA treatment. The baseline and follow-up data at 0, 4, 12, 24, 36 and 52 weeks were collected from both groups, including the following: medical history, routine physical examination, dialysis regimen, laboratory tests, dialysis adequacy as defined by standard Kt/V, chest X-ray, ECG, cardiac ultrasound and three scales. Comorbidities, combined medications and adverse events will also be captured. The primary outcomes will include change in serum β2-MG, PTH and CRP values. Secondary outcomes will include change values for serum protein-bound toxins, improvement in patient quality of life, sleep disturbance and pruritus.

Ethics and dissemination The protocol has been approved by the Ethics Committees of 10 participating medical centres. Shanghai Changhai Hospital Ethics Committee will oversee the study. The results will be presented at national and international academic meetings, and publications will be submitted to peer-reviewed journals.

Trial registration number NCT05639010.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ To our knowledge, this is the first multicentre clinical trial using the KHA80 haemoadsorption (HA) device, validating its clinical effects.
- ⇒ The efficacy of HA combined with haemodialysis in removing protein-bound uremic toxins can be verified, as these substances have not been widely tested in previous studies.
- ⇒ The inability to test more medium and large molecular toxins because of the conditions is a major limitation of this study.
- ⇒ All participating medical centres are in Shanghai, which may restrict the generalisability of the findings.

INTRODUCTION

The incidence of chronic kidney disease (CKD) is increasing annually and has become a significant threat to human health, and CKD can eventually lead to end-stage renal disease (ESRD).[1] Many studies have shown that in ESRD patients, the inability to effectively remove uremic toxins causes a range of disease states, impacting survival and quality of life. Uremic toxins are generally divided into three categories: (1) small molecule water-soluble substances with a molecular weight <500 Da, such as urea nitrogen and creatinine; (2) medium molecule substances with a molecular weight ≥500 Da, such as parathyroid hormone (PTH), β2-microglobulin (β2-MG) and C-reactive protein (CRP); and (3) protein-bound toxins, such as advanced glycation end products and indoxyl sulphate (IS).[2–4] Among them, elevated levels of PTH can cause dialysis complications such as pruritus and ectopic calcification[5]; elevated levels of β2-MG can cause dialysis-related amyloidosis and other complications[6–8]; and protein-bound toxins, in particular p-cresyl sulphate (pCS) and indoxyl sulphate, are potential contributors to the pathogenesis and progression of cardiorenal syndromes, and both have been shown to be associated with nephropathic progression and increased cardiovascular mortality.[9 10] Meanwhile, due to the burden of high uremic toxins, malnutrition and decreased immune function, patients are in a state of chronic microinflammation and fatigue (SONG-HD Fatigue[11]), which are the risk factors for cardiovascular events.[12 13]

Blood purification is the most important method for the treatment of ESRD. Traditional blood purification modes such as haemodialysis (HD) and peritoneal dialysis have been maturely carried out and are commonly used in clinical practice. With the continuous development of blood purification technology, the survival rate and quality of life of maintenance haemodialysis (MHD) patients have been improving. Currently, HD is commonly used to eliminate metabolic waste and harmful substances from the blood of uremic patients, to regulate electrolyte balance and reduce the damage of toxins. However, HD can only remove small molecular toxins through a semi-permeable membrane, while it is difficult to remove medium and large molecule toxins, which can be achieved by haemoadsorption (HA).[14 15] On the other hand, HA has a poor clearance effect on water-soluble substances and cannot correct water and electrolyte acid-base disturbances. Haemoadsorption combined with haemodialysis (HAHD) in series can complement each other's advantages, comprehensively remove toxic substances of different molecular weights and effectively prevent and treat various complications of long-term dialysis. Several studies have been conducted on HAHD in the treatment of uremia and have confirmed good clinical efficacy.[14–23] It has been shown that HD combined with HA130 (Jafron haemoadsorption device) treatment for 1–2 years resulted in a significant reduction of hsCRP, CRP and TNF-α; meanwhile, once-a-week HA130 treatment had the effect of significantly reducing β2-MG and PTH levels as well as improving pruritus symptoms in dialysis patients.

The Jafron KHA80 apparatus is a dedicated HA device for MHD patients to remove large molecule toxins in uremia. According to the in vitro experimental data, the KHA series has shown a clearance rate of 64.6% for CRP, 86.9% for PTH and 83.2% for β2-MG, indicating a positive therapeutic effect. Moreover, with the scientific design of the column structure and a smaller loading volume, the HA device can save the clinical operation time, provide a better operating experience, guarantee the safety and effectiveness of clinical use and make clinical operations more compliant with standard operating procedure (SOP) requirements. Therefore, we will conduct a multicentre, open-label, randomised, parallel controlled study to observe the impact of HAHD on the clearance of serum β2-MG, PTH and CRP in MHD patients and simultaneously assess whether there is any improvement on serum protein-bound toxins, quality of life, pruritus level and sleep disorders of the patients, aiming at evaluating the efficacy and safety of the Jafron KHA80 apparatus and providing a basis for the establishment of future clinical use and guidelines.

METHODS AND ANALYSIS

Patient and public involvement

Neither patients nor the public were involved in the design and conduct of this study.

Objectives

The primary outcome of HAHD compared with HD is to evaluate the effectiveness of KHA80 devices on the clearance of medium and large molecules such as serum β2-MG, PTH and CRP in MHD patients. The secondary outcome is to evaluate the effectiveness of HA devices on the clearance of serum protein-bound toxins (eg, p-cresyl sulphate and indoxyl sulphate) and the improvement of quality of life (Kidney Disease Quality of Life Short Form), sleep disturbance (Pittsburgh Sleep Quality Index) and pruritus (Duo's pruritus score) in MHD patients. We will also assess the safety of KHA80 therapy use by analysing the nature, frequency, severity and association of adverse events that occur during treatment.

Study design

The study is a multicentre, open-label, randomised controlled trial. Ten medical centres in Shanghai have expressed interest in participating. The study will consist of a 1-month washout period and a 12-month period of intervention and follow-up. Participant enrolment commenced in January 2023, with clinical follow-up scheduled for completion in December 2025. Figure 1 shows a diagram of the study flow.

Eligibility criteria

Inclusion criteria (patients who meet all of the following criteria are suitable for enrolment in this study) are as follows:

1. Age 18–80 years, regardless of gender.
2. Stable maintenance haemodialysis for ≥3 months with relatively fixed dialysis pattern.
3. Haemodialysis treatment three times per week, total treatment duration ≥10 hours per week, vascular access unlimited.
4. Serum β2-MG >30 mg/L and/or 300 pg/mL <intact parathyroid hormone <800 pg/mL and/or CRP ≥16.2 pg/mL.
5. Kt/V ≥1.2 8 weeks prior to enrolment.
6. Signed informed consent form.

Exclusion criteria (patients will not be allowed to enter this study if they meet any of the following conditions) are as follows:

1. Known allergic reaction, contraindication or intolerance to the material of the dialyser or perfusion apparatus.

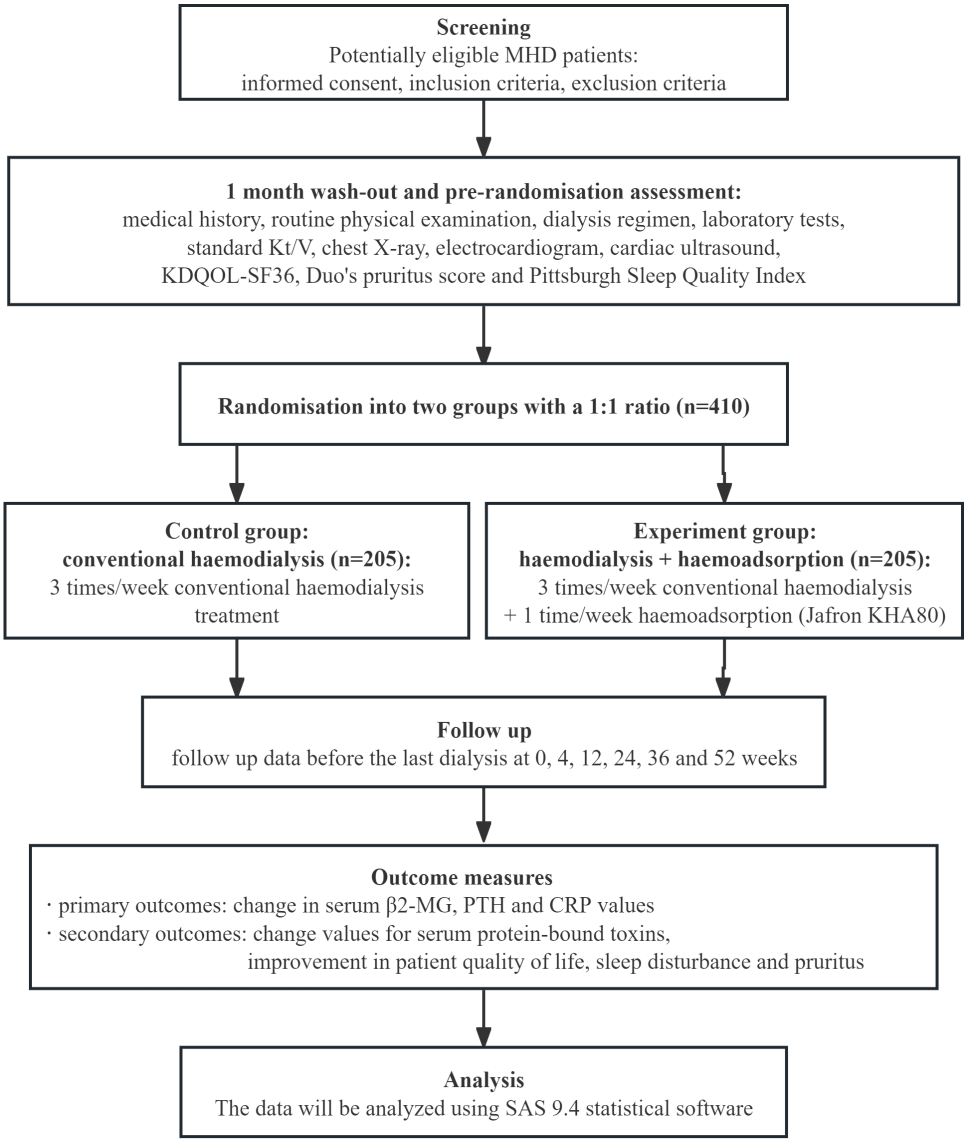

Figure 1 Study flow chart. β2-MG, β2-microglobulin; CRP, C-reactive protein; KDQOL-SF36, Kidney Disease Quality of Life Short Form 36; MHD, maintenance haemodialysis; PTH, parathyroid hormone.

2. Test indicators meeting one or more of the following: white blood cell $<4\times10^9$/L, platelet count $<60\times10^9$/L and serum albumin <30 g/L.
3. Blood flow <200 mL/min.
4. Regular haemoadsorption treatment for more than 3 months and at least once every 2 weeks.
5. Active bleeding or chronic gastrointestinal bleeding, or other severe bleeding tendencies or coagulation disorders.
6. History of unstable angina pectoris, myocardial infarction, severe arrhythmia, pericarditis, myocarditis, cardiac surgery or peripheral vascular surgery in the last 8 weeks.
7. Cerebral haemorrhage in the last 12 weeks.
8. Severe heart failure (New York Heart Association class IV).
9. Acute infection, acute or critical illnesses such as severe cardiac, pulmonary, hepatic or neurological disease and malignancy.
10. Pregnancy or breastfeeding.
11. Participation in a clinical trial or ongoing clinical trial within 3 months.
12. Not considered suitable for participation in this trial by the investigator.

Withdrawal criteria are as follows:

1. Patients voluntarily withdraw from the study.
2. Serious complications and/or adverse events that the investigator judges to be inappropriate for continuation.

Sample size calculation

The differences in β2-MG, PTH and CRP between weeks 52 and 0 are used as the primary study endpoint to calculate the sample size. A bilateral α=0.05 is set with 95% certainty.

According to the results of the multicentre study initiated by Chen Xiangmei,[22] the overall mean difference between the decreasing values of β2-MG in the two groups after treatment in MHD patients is expected to be 6 mg/L, with a SD of 13 mg/L. The sample size N1=123 cases for the control group and N2=123 cases for the experiment group are calculated, totalling 246 cases.

Similarly, the overall mean difference in PTH decline values between the two groups after MHD patients received treatment is expected to be 80 pg/L, with a SD of 200 mg/L. The sample sizes N1=164 cases for the control group and N2=164 cases for the experiment group are calculated, totaling 328 cases.

Based on previous studies and clinical practice, the overall mean difference in CRP decline values between the two groups after treatment is expected to be 8 mg/L, and the SD is 5 mg/L. The sample size of N1=12 cases for the control group and N2=12 cases for the experiment group is calculated, for a total of 24 cases.

Therefore, assuming no correlation between the three study endpoints, $\alpha=0.05$ and considering a 20% drop-out rate, the experiment group has a combined test efficacy of at least 85% for the three combined endpoints with 205 patients in each group and a total of 410 patients. The sample size is calculated using PASS 15.0.5.

Procedures and treatment

In this HAHD versus HD trial, the duration will be 56 weeks that is divided into two phases: a 4-week washout period and a 52-week observation period, requiring a total of 7 visits.

The first visit is considered a screening visit. Patients decide to participate in this clinical trial after full consideration and then sign the informed consent form (see online supplemental material for the patient consent form). We will take the patients' medical history and dialysis regimen and perform relevant physical and laboratory examinations (table 1).

After the first visit, we will determine whether the patients are suitable for this study based on the inclusion and exclusion criteria, and if so, all patients will be first treated with HD only for 4 weeks as a washout period. After the washout period, the eligible patients will be visited for a second time and randomised to the control group or the experiment group. Meanwhile, the baseline data will be collected before the first dialysis at week 0 of treatment (week 0 data), followed by a 52-week visit.

Simple randomisation will be used to assign patients in a 1:1 ratio to the two groups. A random number table

Table 1 Clinical research flowchart

	Washout period	V0	V1	V2	V3	V4	V5
	–4W	0W	4±1W	12±1W	24±1W	36±1W	52±1W
Consent form	X						
Medical history	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Eligibility		X					
Dialysis regimen	X	X	X	X	X	X	X
Blood routine	X	X	X	X	X	X	X
Serum β2-MG		X			X		X
Serum PTH		X			X		X
Serum CRP		X			X		X
Blood chemistry*		X			X		X
Standard Kt/V		X			X		X
ECG		X					X
Chest X-ray		X					X
Echocardiography		X					X
KDQOL-SF36		X			X		X
Duo's pruritus score		X			X		X
Pittsburgh Sleep Quality Index		X			X		X
Comorbidity	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X

*Liver function (ALT, AST, ALP, Alb, TB and DB), renal function (BUN and creatinine before and after dialysis), electrolytes (sodium, potassium, chloride, calcium and phosphorus), iron metabolism (serum iron, total iron binding and ferritin), lipids (TC, TG, LDL and HDL), glucose, cardiac enzyme series (CK, CK-MB and LDH), PRO-BNP, troponin I, myoglobin, protein-bound toxins (p-cresyl sulfate, indoxyl sulfate, etc).
CRP, C-reactive protein; KDQOL-SF36, Kidney Disease Quality of Life Short Form 36; PHT, parathyroid hormon; β2-MG, β2-microglobulin.

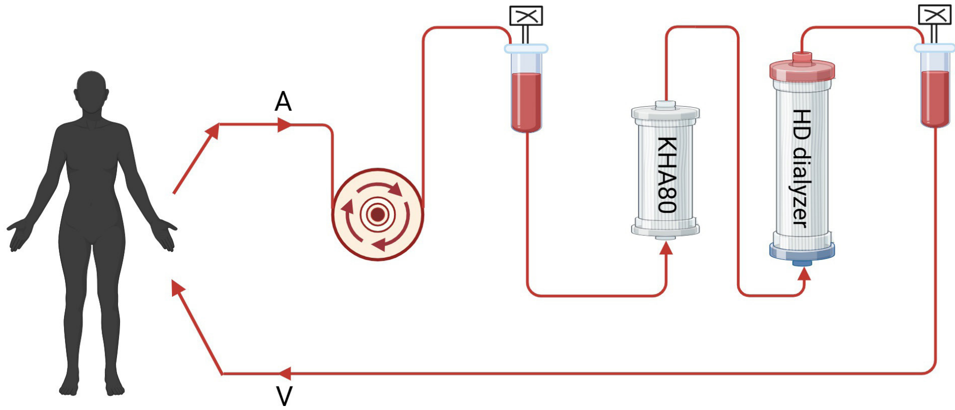

Figure 2 KHA80 haemoadsorption combined with haemodialysis (HAHD) treatment pattern diagram.

will be generated by statistical professionals using SAS 9.4 software and delivered to every participating centre using opaque envelopes for concealment. Patients will be randomised into two groups: the control group (205 patients), 3 times/week conventional haemodialysis treatment; and the experiment group (205 patients), 3 times/week conventional haemodialysis treatment +1 time/week haemoadsorption (Jafron KHA80) treatment. Patients have the same chance of being assigned to either group, all with a one in two chance, as determined by the randomisation results, not by the patients themselves or investigators.

Patients randomised to the control group will receive HD treatment at a frequency of three times a week, with each treatment session lasting 4 hours. In the experiment group, in addition to the treatments in the control arm, HA will be conducted once a week using a KHA80 apparatus containing 80 mL resin (Zhuhai Jafron Biomedical Co., Ltd, China). During the treatment session, patients received HAHD for the first 2 hours using a KHA80 apparatus. After 2 hours when the HA apparatus was depleted, the HA cartridge was removed and the blood went through the HD dialyser alone for the next 2 hours (figure 2).

Data collection

The baseline and follow-up data before the last dialysis at 0, 4, 12, 24, 36 and 52 weeks of treatment were collected from both groups, including the following: medical history, routine physical examination, dialysis regimen, laboratory tests (blood routine, blood biochemistry, β2-MG, PTH, CRP, liver/kidney function, coagulation system tests, etc.), dialysis adequacy as defined by standard Kt/V, chest X-ray, ECG and cardiac ultrasound. Three scales, including the quality of life assessed by the Kidney Disease Quality of Life Short Form 36 (KDQOL-SF36), Duo's pruritus score and Pittsburgh Sleep Quality Index, will be calculated. Comorbidities, combined medications and adverse events will also be captured. All data will be recorded in an electronic case report form (eCRF). An outline of the study visits and examinations to be performed is shown in table 1.

Data management

The Data Monitoring Committee (DMC) is responsible for the data management. The original records (such as original medical records, examination reports, etc.) need to be properly preserved. The data in the CRF comes from the original medical records and is filled out by the researchers. The completed CRF is reviewed by the clinical monitor and then handed over to the data manager for data entry and management.

A clinical research database will be established to record all the information in the CRF. To ensure the accuracy of numerical data, Epidata 3.1 will be used for dual data entry and verification. Manual and system checks will be conducted to examine the consistency and logic of the data in the CRF. After the data is completed and locked, the database will be handed over to the statistical analysts who will perform statistical analysis as required. The DMC is independent from investigators and has no competing interests. To ensure evaluation and supervision by regulatory authorities and sponsors, researchers should agree to keep all research data for 10 years after the completion of the clinical trial.

AE monitoring

During the clinical trial, it is important for researchers to carefully observe any adverse events (AEs) that occur in the participants. When AEs are identified, necessary measures should be taken based on the condition. Regardless of whether the AEs are related to the haemoadsorption scheme, researchers should document them in detail in the CRF for analysis. The record of AEs should include a description of the events and all relevant information, such as the time of occurrence, severity, duration, measures taken and final outcomes.

In the case of serious adverse events (SAEs) occurring during the clinical trial, researchers must take immediate actions to ensure the safety and rights of the participants. Meanwhile, it is vital to report to the sponsor, ethics committee and clinical medical research centre within 24 hours of the occurrence of a SAE. If it is determined that the SAE is related to the haemoadsorption scheme, the research centre is responsible for the costs of rescuing and treating the patient, as well as providing appropriate economic compensation. Researchers must fill out a 'Serious Adverse Event Report Form' and provide detailed documentation of the handling and reporting of the SAE in the original data.

All AEs should be monitored until recovery to normal or baseline levels, or until the researchers can provide a reasonable explanation for the abnormality and determine that follow-up is not necessary, in order to ensure the safety of the participants.

Quality assessment

All researchers will follow SOPs to ensure quality control in the clinical trial. It is important to verify all observed results and findings to ensure the reliability of the data and the validity of the conclusions derived from the original data.

Before the official start of the trial, the research centre director is responsible for training the research personnel on the study protocol. This training aims to ensure a unified understanding and familiarity with the data collection methods and procedures, which will enhance the internal and inter-observer consistency of the clinical research data collectors, ultimately guaranteeing the reliability of the conclusions. Meanwhile, it is also required that researchers strictly adhere to the SOPs throughout the entire process of the clinical trial to ensure the implementation of quality control measures.

Appointment of qualified monitors to conduct regular auditing of research centres to ensure that all elements of the protocol are strictly adhered to. The frequency of auditing visits will be determined by the site enrolment rate. The audit is independent of the study investigators.

Data analysis

The data will be analysed on an intention-to-treat basis using SAS 9.4 statistical software. Continuous variables will be expressed as mean±SD deviation if they conform to normal distribution, and median and interquartile spacing if they do not, and t-test and Wilcoxon rank-sum test will be used to compare differences between two groups, respectively; count data will be expressed as composition ratio or percentage, and differences between groups will be compared by chi-square test or Fisher's exact probability method; rank data will be compared between groups by rank-sum test. The test level is set at 0.05 for both sides.

ETHICS AND DISSEMINATION

The study protocol, informed consent form and any relevant documents directly related to the participants have been submitted to the ethics committee for written approval before the research can officially proceed and will also be reviewed and supervised by the Changhai Hospital Ethics Committee (Approval number: CHEC2022-207) during implementation. Meanwhile, the researchers must inform the ethics committee in writing when the research is suspended and/or completed.

This study will adhere to the Declaration of Helsinki. Each participant is required to agree and sign an informed consent form. Participants will be provided with all updated versions of the informed consent form as well as written information for the duration of their participation.

The guidelines for protecting the privacy of participants are confirmed and supported by researchers. Throughout the entire process of this study, the participants' raw data will only be connected to the clinical research database through a unique identifier. Limited participant characteristics such as gender, age or abbreviated initials of participant names can be used to verify the accuracy of participants' identification numbers, with the approval of applicable laws and regulations. The results of this study may be presented at national and international scientific meetings and be presented as manuscripts submitted for peer-reviewed journal publication, but researchers will maintain the confidentiality of patient information as required by law, and patient personal information will not be disclosed unless required by relevant laws.

DISCUSSION

This study is a multicentre, open-label, randomised, parallel controlled trial to investigate the efficacy of HAHD therapy versus HD alone on the removal of medium and large molecule toxins, as well as to explore the improvement on protein-bound toxins, patients' quality of life, pruritus level and sleep disturbances. There are several strengths of this trial compared with prior trials of HAHD. To our knowledge, this is the first multicentre clinical study using the KHA80 device. Compared with the HA130 device, which was mostly used in previous HAHD trials,[22–24] the KHA80 is specifically designed and manufactured for the removal of large molecule toxins in MHD patients with uremia, which is more targeted; at the same time, it has a smaller loading volume and size, with less blood circulation, and thus offers a higher dialysis safety profile. In addition, we performed assays for protein-bound uremic toxins such as phenols and indole compounds, which have not been implemented on a large scale in previous studies. On the other hand, the HAHD procedure involves a first 2-hour period of simultaneous HA and HD, followed by a further 2 hours of HD alone. The total duration remains unchanged, with a simple operational process, thereby avoiding additional staffing and time costs. The previous studies[25 26] have also demonstrated that, compared with the conventional HD treatment, the long-term application of HA (Jafron resin device) combined with conventional HD can prolong patient survival and offers cost-effectiveness. This study employs the KHA80 device from the same brand, which is more targeted towards large molecular toxins, with the expectation of favourable health economic benefits. Furthermore, the patient perspective is central to this protocol, which incorporates several validated patient-reported outcome measures (PROMs), including the KDQOL-SF36, Duo's pruritus score, and the Pittsburgh Sleep Quality Index. These tools will provide robust quantitative data on how the intervention impacts the aspects of life that matter most to patients, directly addressing the core issues of symptom burden.

The design of this study also has some limitations. Only a few representative medium and large molecular toxins, namely PTH, CRP and β2-MG, were selected for the study. The inability to test more toxins because of the conditions is a major limitation of this study. All of the participating medical facilities located in Shanghai may also restrict the generalisability of the findings. Meanwhile, unlike the USA and Europe, where the conventional protocol is high-flux HD three times weekly, China generally employs low-flux HD, which may pose challenges for future implementation/transferability to international practices. In addition, HA treatment is associated with potential complications and side effects, such as biocompatibility abnormalities, adsorbent particle embolisation, haemorrhagic coagulation disorders and hypotension.[27]

In conclusion, this study will provide an opportunity to evaluate the efficacy of HAHD in improving the efficacy of medium and large molecular toxins in MHD patients. The results of this trial may inform the clinical use of the KHA80 device and help to improve blood purification therapy for MHD patients.

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Contributors ZG from Changhai Hospital conceived and designed the study. WH, LZ, HW and WC from Changhai Hospital participated in the drafting and revision of the article. ZG is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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