A randomized, open-label, multi-centre trial comparing hemodialysis plus hemoperfusion versus hemodialysis alone in adult patients with end-stage renal disease (HD/HPvsHD): study protocol

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SPECIFIC AIMS AND HYPOTHESIS

The prevalence of end-stage renal disease (ESRD) is increasing with an enormous financial burden.[1,2] About 50 years ago, ESRD was invariably lethal. Although maintenance dialysis have now successfully prolonged the life of ESRD patients, mortality remains high.[3]

Approximately 9-13% of patients on hemodialysis in India die within 1 year.[4] The adjusted rates of all-cause mortality are 6.3-8.2 times greater for dialysis patients than the general population.[5] The adequacy of dialysis and factors such as pre-dialysis care, late referral to nephrology specialists and non-compliance greatly affect patient's survival.

The gold standard of hemodialysis therapy is yet to be identified. New approaches are required to improve overall mortality rates and to achieve an acceptable level of survival and rehabilitation in hemodialysis patients.[6] As the toxic components of uremic toxins and their corresponding biological effects become increasingly clear, blood purification treatment that aims to remove these toxins has developed from a stage of life-sustaining to improving the quality of life and enabling the patients to return to society. Clinical applications of various models of extracorporeal blood purifi cation technology show the clearance rates of middle and large molecule uremic toxins for these models take place in the following order: HD + hemoperfusion (HP) > HP > bio-artificial kidney > hemodiafiltration (HDF) > hemofiltration (HF) > HD. [7, 8]

In this application, we outline an innovative research proposal to **test the hypothesis that combination of hemoperfusion and hemodialysis treatment would be superior to regular hemodialysis treatment alone in maintenance hemodialysis (MHD) patients.** We hope the result of this study will be an international reference to the optimized use of dialysis therapy in MHD patients.

Specific aim 1: The primary outcome of this study is to test if hemodialysis plus hemoperfusion treatment is superior to regular hemodialysis treatment alone in reducing all-cause mortality in MHD patients. The study will be conducted as a multi-center, open-label, randomized controlled trial in 1364 MHD patients, who will be randomly divided into 2 treatment groups: combination of hemoperfusion and hemodialysis treatment group and regular hemodialysis treatment group. The rate of all-cause mortality between 2 groups will be compared. *We hypothesize that patients receiving hemodialysis plus hemoperfusion treatment have lower rate of all-cause mortality than those receiving hemodialysis alone.*

Specific aim 2: The secondary outcome is to test if hemoperfusion combined with hemodialysis treatment is superior to regular hemodialysis treatment in terms of reducing cardiovascular-related mortality and major cardiovascular events (MACEs) as well as improving the quality of life. In the same proposed study outlined in **Specific aim 1**, the rate of cardiovascular-related mortality and MACEs as well as the quality of life will be compared between the 2 treatment groups. *We hypothesize that patients treated by combination of hemoperfusion and hemodialysis therapy will have lower rate of cardiovascular-related mortality and MACEs and have better quality of life than those receiving hemodialysis alone..*

RESEARCH DESIGN AND METODOLOGY

Study design: We propose to conduct a multi-center, open-label, randomized controlled trial in 1364 biopsy-proven MHD patients, who will be divided into 2 treatment groups (combination of hemoperfusion and hemodialysis treatment vs. regular hemodialysis treatment).

Ethics approval: The study protocol will be submitted to the ethics committees of all participating hospitals for final approval, and the study is in adherence with the Declaration of Helsinki.

Study duration: The duration of this study is composed of a 24-month observation period. The patient recruitment period should take 6-month. MHD patients who are eligible and have signed the informed consent will firstly enter a 1-month screening period. Patients who are eligible after the screening period will be randomized to 1 of the 2 intervention groups.

Inclusion criteria: Patients with the following criteria will be included in the study:

1） Age at 18-75 years old
2）Regular blood purification treatment at least 3 months before enrolled in this study
3） Standard Kt/V ≥ 1.2

Exclusion criteria: Patients with any of the following criteria will not be included in the study:

1）White blood cell count < 4×10^9/L and / or platelet count < 100×10^9/L
2）Cerebral hemorrhage in the past 12 weeks
3）MACEs in the past 8 weeks
4）Severe heart failure (New York Heart Association [NYHA] class III or IV) [9]
5）Active gastrointestinal bleeding, or coagulation dysfunction
6）Malignant tumor
7）Active infection
8）Pregnancy or lactation
9）Participating in clinical trials in the past 3 months
10) Mental disabilities

Treatment details:

Screening phase: All eligible patients will receive regular hemodialysis treatment for a screening period of 1 month.

Regular hemodialysis group: Patients randomized to this group will receive low-flux hemodialysis treatment at a frequency of 2 times a week and online-hemodiafiltration treatment at a frequency of once a week, with each treatment session lasting 4 hours.

Combination of hemoperfusion and hemodialysis treatment group: In this group, in addition to the treatments in regular hemodialysis group, hemoperfusion will be conducted once every two weeks using a HA130 resin hemoperfusion apparatus containing 130ml resin. During the treatment session, patients receiving hemodialysis and hemoperfusion for the first 2hrs using a HA130 resin hemoperfusion apparatus containing 130ml resin (Zhuhai Jafron Biomedical Co., Ltd, China) and the blood flow rate maintains between 150-200ml/min. After 2hrs when the hemoperfusion apparatus was depleted, the hemoperfusion cartridge will be removed and the blood went through the low-flux hemodialysis dialyzer alone for the rest 2hrs with the blood flow rate between 200-250ml/min.

Primary endpoints: All-cause mortality.

Secondary endpoints: Secondary endpoints include: 1) Cardiovascular-related mortality; 2) major cardiovascular events (MACEs); 2) Evaluation of quality of life.

Interim analysis: An interim analysis at month 12 will be performed by an independent data monitoring board to assess the risks and benefits of this study at time points prior to 24-month.

Statistical approach and power calculations:

Sample size calculation is based on the following assumptions: 1) α (2-sided) at 0.05; 1) 1-β at 80%; 3) 18% 24-month all-cause mortality in the control arm (subjects receiving hemodialysis and hemodiafiltration only) [10, 11]; 4) a reduction of 24-month all-cause mortality by 30% (to 12.6%). Expecting a 15% attrition rate, a total of 682 patients per arm is needed, thus a total of 1364 patients will be needed in this trial.

For data analysis, categorical variables will be analyzed using the $\chi 2$ or Fisher's exact test. Continuous variables will be analyzed using Student's *t*-test upon normal distribution, or the Mann-Whitney *U*-test otherwise. Primary outcomes will be analyzed using the Kaplan-Meier method followed by the log-rank test. Multivariate Cox regression will be used to analyzed factors that could influence all-cause mortality and CVD mortality after the adjustment for multiple relevant traditional and uremia-related risk factors for mortality. Data were analyzed on an intention-to-treat basis. All statistical analyses will be conducted using STATA (Version 14.0; Stata Corporation, College Station, Texas, US).

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