The Efficacy of Hemoperfusion Combined With Hemodialysis in Improving the Survival of Maintenance Hemodialysis (MHD) Patients: A Multi-center, Open-label, Randomized, Parallel Group Study

SPECIFIC AIMS AND HYPOTHESIS

The prevalence of end-stage renal disease (ESRD) is increasing with an enormous financial burden.\textsuperscript{[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.\textsuperscript{[3]}

Approximately 9-13\% of patients on hemodialysis in India die within 1 year.\textsuperscript{[4]} The adjusted rates of all-cause mortality are 6.3-8.2 times greater for dialysis patients than the general population.\textsuperscript{[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.\textsuperscript{[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 purification 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.\textsuperscript{[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: To test if combination of hemoperfusion and hemodialysis treatment is superior to regular hemodialysis treatment in reducing all-cause and cardiovascular mortality in MHD patients. We will conduct a multi-center, open-label, randomized, parallel group study 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 and cardiovascular mortality between 2 groups will be compared. We hypothesize that patients treated by combination of hemoperfusion and hemodialysis therapy will have lower rate of all-cause and cardiovascular mortality than treated by regular hemodialysis alone.

Specific aim 2: To test if combination of hemoperfusion and hemodialysis treatment is superior to regular hemodialysis treatment in reducing newly onset or recurrent cardiovascular events in MHD patients. In the same proposed study outlined in Specific aim 1, the rate of newly onset or recurrent cardiovascular events 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 newly onset or recurrent cardiovascular events than treated by regular hemodialysis alone.

Specific aim 3: To test if combination of hemoperfusion and hemodialysis treatment is superior to regular hemodialysis treatment in improving the quality of life (QOL) of MHD patients. In the same proposed study outlined in Specific aim 1, 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 better QOL than treated by regular hemodialysis alone.

RESEARCH DESIGN AND METHODOLOGY

Study design: We propose to conduct a multi-center, open-label, randomized, parallel group study 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 18-75 years, male or female
2) Maintenance hemodialysis duration ≥ 3 months
3) Regular blood purification treatment, 3 times a week, 4-5 hours per session
4) Kt/v ≥ 1.2
5) Written informed consent signed

Exclusion criteria: Patients with any of the following criteria will not be included in the study:
1) Life expectancy < 1 year
2) White blood cell count < 4×10^9/L and / or platelet count < 100×10^9/L
3) Cerebral vascular accident occurred in the last 8 weeks
4) Cardiovascular events occurred in the last 8 weeks
5) Chronic congestive heart failure (> grade 3) (According to New York Heart Association classification)
6) Active or chronic gastrointestinal bleeding, or a clear coagulation dysfunction
7) Malignant tumor, active infection
8) Pregnancy or lactation
9) Participating in clinical study in last 3 months or undergoing clinical study
10) Unwilling or unable to comply with the research program
11) Not suitable for this study
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Treatment details:

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

Regular hemodialysis group: Regular blood purification treatment (including HD, HDF and HFHD) 3 times a week, 4-5 hours per session.

Combination of hemoperfusion and hemodialysis treatment group: 1) Regular blood purification treatment; 2) Hemoperfusion combined with hemodialysis treatment will perform once every two weeks. The hemoperfusion apparatus will use type HA130 resin hemoperfusion apparatus (Zhuhai Jafron Biomedical Co., Ltd, China)

Primary endpoints: All-cause mortality and cardiovascular mortality.

Secondary endpoints: Secondary endpoints include: 1) Newly onset or recurrent cardiovascular events; 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 evaluation of the adjusted rates of all-cause mortality of MHD patients. It was estimated that a study that included a sample of 682 patients per group (including a 15% dropout adaptation) would give the study 80% power, at a two-sided significance level of 5%, to detect mortality rates of 18% in the regular hemodialysis group and 12.6% in the combination of hemoperfusion and hemodialysis treatment group after 24 month. Patients will be randomized into one of the two treatment groups after the screening phase by means of a computer-generated randomization code. Results will be evaluated on an intention-to-treat analysis in all randomized patients, irrespective of adherence to the assigned treatment.

For data analysis, dichotomous and polychotomous baseline characteristics will be compared using the Chi-square or Fisher’s exact test. Continuous baseline characteristics will be compared with Student’s t-test or the Mann-Whitney U-test. Outcomes were compared by univariate survival analysis using the Kaplan-Meier method for estimation of survival to each of the primary endpoints and the log-rank test. Data will be analyzed using STATA Version 14.0 MP software.

REFERENCES
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