PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Lu, Wei; Jiang, Geng-Ru; the HD/HPvsHD, trial Group

VERSION 1 – REVIEW

REVIEWER	Leonid Feldman Assaf Harofeh Medical Center, Nephrology Department, Sackler Faculty of Medicine, Tel Aviv University, Israel
REVIEW RETURNED	04-Mar-2018

GENERAL COMMENTS	1. Hemoperfusion for 2 hours once in every 2 weeks in study group will, probably, produce too little change in clinical outcomes. Better evidence of yes or not impact would be shown in addition of hemoperfusion to every HD session. 2. Hemodialysis protocol seems strange and unusual: low-flux HD twice weekly + HDF once weekly. It would better to do conventional high-flux HD 3 times per week. 3. Examination of kidney function is mentioned in methods. It seems that the authors mean "residual renal function". This point must be clarified and described.

REVIEWER	Dean Markić University Hospital Rijeka, Croatia
REVIEW RETURNED	24-Mar-2018

GENERAL COMMENTS	Minor revisions: 1. In the abstract, abbreviations are not properly explained, e.g. hemodialysis (HD)... 2. Excluding criteria will be a life-expectancy <1 year. How authors will done this? By questionnaire?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Leonid Feldman
Institution and Country: Assaf Harofeh Medical Center, Nephrology Department, Sackler Faculty of Medicine, Tel Aviv University, Israel
Question 1. Hemoperfusion for 2 hours once in every 2 weeks in study group will, probably, produce too little change in clinical outcomes. Better evidence of yes or not impact would be shown in addition of hemoperfusion to every HD session.

Response to the reviewer: After careful consideration of the reviewer question, I decided to use the proposed protocol (hemoperfusion for 2 hours once in every 2 weeks) mainly for 2 reasons. First, hemoperfusion added to every HD session might be associated with more hemoperfusion-related complications, including leukocytopenia, thrombocytopenia as well as a decrease in fibrinogen (added reference 23: Ghannoum M, et al. Semin Dial 2014, 27: 350-61). From the results of our preliminary study which started from 2009, we observed that the incidence of leukocytopenia and thrombocytopenia in patients receiving hemoperfusion once every two weeks were significantly reduced than those receiving hemoperfusion every week. Second, we found that the levels of uremic toxins such as hsCRP and □□-macroglobulin in patients receiving hemoperfusion once every two weeks were significantly lower than those only receiving hemodialysis. The efficacy of hemoperfusion at the frequency of once every two weeks were also associated with better blood pressure control and less symptoms such as pruritus. The Discussion section of the manuscript has been expanded to address this issue.

2. Hemodialysis protocol seems strange and unusual: low-flux HD twice weekly + HDF once weekly. It would better to do conventional high-flux HD 3 times per week.
Response to the reviewer: Due to the higher cost (both HD-related equipment and accessories) associated with high-flux HD, low-flux HD twice weekly + HDF once weekly is a widely-used protocol in China. I understand the reviewer concern, and expanded the Discussion Section of the manuscript to alert the readers: the results of the proposed trial must be interpreted with caution when extrapolating to US and Europe, where conventional protocol is high-flux HD 3 times per week. Regardless, the results of the proposed trial will provide useful information that could potentially change the medical practice in the US and Europe if additional trials are conducted in subjects receiving high-flux HD 3 times per week.

3. Examination of kidney function is mentioned in methods. It seems that the authors mean "residual renal function". This point must be clarified and described.
Response to the reviewer: I apologize for the confusion, and have replaced “kidney function” with “residual renal function” under the subheading of “Data collection and management”.

Reviewer: 2
Reviewer Name: Dean Markić
Institution and Country: University Hospital Rijeka, Croatia
Minor revisions:
1. In the abstract, abbreviations are not properly explained, e.g. hemodialysis (HD)...
Response to the reviewer: I appreciate the reviewer comment, and revised the entire manuscript carefully. In the revised manuscript, all abbreviations are defined with full terms upon first appearances. I also made sure that no full terms are used upon repeated appearances.

2. Excluding criteria will be a life-expectancy <1 year. How authors will done this? By questionnaire?
Response to the reviewer: I appreciate the comment, and remove this item as the main clinical assessments of life expectancy such as severe heart failure and intractable malignancy have been already included in the exclusion criteria. The trial registration has been revised accordingly.

VERSION 2 – REVIEW

REVIEWER	Leonid Feldman Assaf Harofeh Medical Center, Sackler faculty of medicine, Tel Aviv University, Israel
REVIEW RETURNED	25-Apr-2018

GENERAL COMMENTS	The authors adequately adressed all the nessesary points and

	completed the Discussion section appropriately. The manuscipt quality is improved sufficiently for publication.

REVIEWER	Dean Markić Department of Urology, University Hospital Rijeka, Croatia
REVIEW RETURNED	26-Apr-2018

GENERAL COMMENTS	According to me this paper is adequate for publication.