Author's response to reviews

Title: Online-Haemodiafiltration vs. conventional haemodialysis: a cross-over study.

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Author's response to reviews: see over
Reviewer's report:
This well-designed crossover study compared several clinical and laboratory parameters in hemodiafiltration and high-flux hemodialysis.

Minor essential revisions:
1. Please indicate treatment method as postdilution HDF in the method part of Abstract. Please correct “predilution HDF” written mistakenly in Conclusion (page 9) as “postdilution HDF”.

Response: we agree and make the change.

2. Please check if the reference given for ESA dose in page 4 (line 25).

Response: reference deleted.

3. It would be better to give data regarding blood flow rate, dialysate flow rate and convection volumes for each of three periods, in the Table-1.

Response: we agree and make the changes.

4. The authors reported that lower albumin levels were associated with the presence of diabetes and lower convection volumes in HDF periods. The authors mention much more prominent decrease of serum albumin by HDF in diabetic patients and speculate that albumin loss by HDF is higher in diabetics. We do not know whether decrease of serum albumin after switch to HDF is different in diabetics and non-diabetics (no data on this). It would be interesting to see levels of albumin and also beta-2 microglobulin in three periods in diabetic and nondiabetic patients separately. Would authors like to discuss another possibility that diabetic patients may have lower serum albumin levels in general compared to non-diabetics without regarding HD or HDF treatment (as a result of more prominent overhydration, inflammation, malnutrition) and high convection volume can not be achieved in those patients due to low serum albumin?

Response: we agree and add a paragraph in the result part.

5. Discussion is quite long, is it possible to shorten by removing parts not directly related to results of the current study (for example discussion of survival)?

Response: we agree and remove the survival paragraph.

Discretionary revisions:
1. I would suggest to remove the numbers given for proportion of patients on alfacalcidol, Ca-based PO4-binder, sevelamer, cinacalcet, anti-hypertensives in the results part of the Abstract and to give three numbers (instead of two which may cause confusion in readers) showing proportion of patients on those medications in three periods of the study in the Results section (page 5)

Response: we agree and make the changes.

2. I would suggest to remove Figure 5 and also relevant part in Results section because I believe that lower convection volume might be the result of having low
serum albumin level.

Response: We disagree since we report no relationship between serum albumin and convective volume (added in the result part).

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Reviewer's report
Title: Online-Haemodiafiltration vs. conventional haemodialysis: a cross-over study.
Version: 2
Date: 5 November 2014
Reviewer: Claire H den Hoedt

Major Compulsory Revisions.
1. Abstract: Line 14-16 ‘Patient medications…. Medication’ is unnecessary information for the abstract.

Response: we agree and delete this part.

2. Abstract: The authors perform HDF, is this predilution/postdilution. From the conclusion it seems to be predilution, but in the methods it is postdilution.

Response: it was only postdilution; the mistake is corrected in conclusion.

3. Introduction. Line 14-15. In the introduction quite a lot of advantages of HDF are mentioned, regarding to the authors there are only two disadvantages. The reason why this study was conducted is unclear to me, what is the gap in knowledge you want to clarify? What is new information? The aim is not specific about which clinical and biochemical parameters you are looking and why you are interested in these?

Response: Previously, conventional dialysis was set to 5 hours 3 times weekly. For organizational and cost reasons, it was set to 4 hours and it has been hypothesized that HDF could compensate the missed hour. The aim was simply to assess both known advantages and disadvantages in our haemodialysis population in a short-term study. A sentence is added in the introduction.

4. Methods: Line 2 ‘The study protocol was in accord’ no sound English. Furthermore I would like to know if it was ethical according to national standards and to the declaration of Helsinki.

Response: this precision is added in the methods.

5. Statistical analysis: Line 9- Why were only last 2 months of 6 months periods compared? You should use all the measurements you did, making it less probable that external factors other than the dialysis form are the cause for the concentrations of biochemical parameters.

Response: we observed, in some cases, a progressive decline in both serum albumin and B2 microglobulin level after 3 months that could not be identified with the mean of the 6 months period. So we prefer to analyze only the final part of the 6 months periods.

6. Statistical analysis: ‘The differences between the 3 periods were investigated using ANOVA and a paired-t test.’ What was the input for the ANOVA? Were it the means of the 3 periods? Or were the delta’s period 1 to 2 and delta 2 to 3 the input for the ANOVA? The p values of which test are in the figures? I do not see
the results of paired T-tests in the results section.

Response: We agree and make the changes with ANOVA in Table 1 and t-test in figure 1 and 2.

7. Statistical analysis: Line 34. In my opinion one way correlations do not add information in such complex patients as dialysis patients and no conclusions can follow a correlation without adjustments for confounders. The analysis should be left out.

Response: statistical analysis has been changed.

8. Statistical analysis: ‘ A receiver operator curve (ROC) was generated for the primary continuous data associated with albumin concentration changes.’ ROC curves are mainly used in diagnostic research (therefore sensitivity and 100-specificity) and are as far as I know no tool to show a correlation/association between the mean convective volume and serum albumin decreases, how it was used in this study. This ROC analysis should be left out.

Response: we agree and deleted this analysis.

9. Results line 30-32. Which comparison does the p-value represent? What are the lines depicted in Figure 1 and 2: Confidence intervals? Standard errors or standard deviations? In figure 1 and 2 a large overlap of values is visible, with the mean always projecting over the confidence intervals (?) of the other periods, making a statistically significant difference unrealistic with these numbers.

Response: we agree and make the precision.

10. The distribution plot in Figure 3 does not add much information.

Response: We agree and delete the figure.

11. Results page 6 Line 4-6: ‘ Factors associated with lower serum albumin levels during the HDF periods included diabetes (64 vs. 23%, p= 0.04) and lower convection volumes (20.8 vs. 22.9 L, p= 0.04).’ It is not mentioned, which other factors were tested. Furthermore it is not clear what was tested against diabetes, was it the delta (than which delta), was it de albumin concentration, or was there a cut-off value for ‘lower serum albumin’, or was it a negative delta in both periods? As I wrote at point 7 in my opinion the correlation analysis is not useful without adjustments and actually the numbers are to low. The same holds true for the correlation with convection volume and b2m.

Response: we agree and make logistic regression (Table 2).

12. Figure 5 should be left out.
Response: Figure 5 has been deleted

13. Discussion: The first paragraph with the conclusion might be different if all the measurements of the 6 months periods would be used.

Response: see previous response

14. Discussion: The part of the discussion on correlation of albumin decrease and diabetes and convection is unnecessary if this analysis is not in the results anymore.

Response: we agree and make some changes in the discussion

Minor Essential Revisions.

1. Results line 26 ‘Kt/V ranged from 1.64….’, no standard deviations are mentioned.

Response: SD has been added.

2. Discussion: p6 line 31- page 7 line 3: We showed in a long term RCT that no difference in rate of change of serum albumin was found between HDF and low-flux HD (den Hoedt et al., Kidney International 2014). Furthermore it is interesting to note that changes in albumin occur over time as a result of clinical events (both cardiovascular and infectious), changes in nutritional status etc. Patients with diabetes seem to have a larger decline of albumin over time. (den Hoedt, Clin J Am Soc Nephrol. 2014 Feb). The question is: Is this an effect of time, or an effect of treatment? In our KI study we did not find dan interaction of diabetes on the effect of HDF compared to HD on changes in albumin.

Response: CONTRAST in a RCT comparing OL-HDF with low-flux HD mainly in Netherlands. As compared to our study, patients were younger, with less dialysis vintage, were more frequently diabetics, with higher baseline serum albumin level, and with lower blood flow rate, dialysis session time and convective volume. We think that a direct comparison is not possible since short term biological data is not provided. However, we agree to cite this important paper in the discussion.

3. Discussion: Line 2-3, page 7, ‘independent of’ suggests adjustments, which were not carried out.

Response: we agree and make change


Response: we agree and make change

5. Page 7 Line 17: ‘negative impact of albumin’, Is albumin really causally
related to mortality or a marker of worse prognosis?

Response: we agree and make change

6. Discussion page 7 Line: 15-28: You could shorten this paragraph by concluding the results of the RCT’s, leaving out the observational studies and not getting into detail about the limitations of these studies, since survival is not the subject of your study.

Response: we agree and make change

7. The same holds true for the paragraph of phosphate. (points 6). In this paragraph are also some typo’s.

Response: We disagree since phosphate reduction comparison was part of our aims.

8. Page 8 Line 28-30, can be left out. Does not add information to your findings. Why do some studie find better haemodynamic control and others not?

Response: we think that lack of hemodynamic improvement in HDF is also an important data since most nephrologists argue of this advantage.

9. Page 9 ‘However, the crossover design of the study allowed for highly significant differences between the 3 periods. Besides, we plan to measure albumin loss using an appropriated device for dialysate analysis.’ A cross-over study could give a more sound comparison, but there was also drop-out and the same patients can be in very different state after 6 or 12 months. ‘Allow for differences’ is a strange formulation.

Response: we agree and make the change.

10. Conclusion page 9. ‘The long-term clinical impact of these biochemical observations, and their association with diabetes’ these parameters have been assessed in large RCT’s.

Response: we disagree since few data are available on the impact of albumin loss comparing diabetic and non-diabetic patients using high and low convective volumes.

Discretionary revisions.
1. Introduction Line 9- For your information: Mazairac et al. showed no effect of HDF on Quality of life in a long term randomized controlled trial. CJASN 2013

Response: thank you for this reference; however, we prefer not to increase the reference number.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics