Author’s response to reviews

Title: On-line hemodiafiltration did not induce an overproduction of oxidative stress and inflammatory cytokines in intensive care unit-acute kidney injury

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Version: 1 Date: 12 May 2017

Author’s response to reviews:

Ref: BNEP-D-17-00121

Dear Prof. Justin Belcher

Handling Editor, BMC Nephrology

Thank you for the reviewing of our manuscript intitled " On-line hemodiafiltration did not induce an overproduction of oxidative stress and inflammatory cytokines in intensive care unit-acute kidney injury "
The manuscript has been revised according to the reviewers' helpful comments. We appreciated their constructive contributions and remarks. We have followed their recommendations and hope that we have answered their questions thoroughly. Attached are the answers to questions or comments in the order in which each was addressed. We are pleased to submit this revised manuscript.

I hope that this manuscript is now suitable for publication in "BMC Nephrology" and I would like to take this opportunity to thank the independent referees for all their comments and help in improving the quality of this article.

Sincerely yours

Prof. K. Klouche

Ref: AOIC-D-16-00021

Response to Reviewer #1:

Q1. Important information about the dialysis treatments is missing. Total convection volume (Qb was 300 mL/min), treatment time. Sessions were done with Qb=300mL, since all patients did not have previous CKD or HD dependency I assume they all had central venous catheters as HD access. Was recirculation measured? It is questionable whether sufficient sub volumes were achieved during these kind of dialysis conditions.

R1: We added information about OL-IHDF treatments as asked by the reviewer. On-line IHDF duration time ranged from 4 to 6 h (median time: 4h) with a mean ultrafiltration rate of 590 ml/session. HDF parameters used in the study were as follows: blood flow: 300 ml/mn, dialysate flow: 500 ml/mn and predilution infusate flow at 100 ml/mn. It means that convection volumes ranged from 20 to 36 l per session. The addition of dialysate and infusate flows permitted us to reach a fair Kt/v at 1.12 per session.
Vascular access was obtained through double lumen jugular catheter. Venous recirculation was measured according to the formula and was less than 5%.

All these informations were added in this manuscript. Please see Results line 175-180 (in bold)

Q2. The authors conclude that online IHDF can be used safely in septic AKI on the ICU. I do not believe this statement can be made on the basis of their data. This is an observational study without a comparison group and it is not known whether the same patients if placed on continuous RRT would not have experienced less hypotensive episodes.

R2: We agree with the reviewer that this study was only observational. Our aim in this study was to demonstrate that Ol-IHDF did not induce an additional inflammatory risk since it is a RRT modality based on cold sterilization of dialysis fluid to prepare the infusate which is readily administered into the extracorporeal bloodstream. Indeed, we found that there was no increase in circulating inflammatory markers after sessions. Our concern was about the infectious safety of this technique. Clinical tolerance of OL-IHDF was fair in our study but we may not conclude about any comparison with continuous RRT. The rate of hypotensive episodes may be only compared to previous reported results. We amended Discussion section accordingly. Please see line 267-273.

Q3. The discussion needs to be expanded and it should be discussed why there was no decrease in the levels of circulating inflammatory markers (molecular size, clearance mechanism etc).

R3: We discussed these issues as suggested by the reviewer. Indeed, the observed non significant decrease on cytokines may be due to the predilution hemofiltration mode, convection volume less than 30l per session and cytokines short life. This result is however in agreement with previous studies. Please see Discussion section, line 254-260.
Responses to Reviewer #2:

Q1. Abstract: Minor comments: Line 2: I think that there is still some debate as to whether OL-IHDF is the 'gold standard' for chronic HD patients (see letter from Marano M et al. On-Line Hemodiafiltration: All That Glitters Is Not Gold. Blood Purification 2016) rather than simply an accepted modality with potential benefits.

R1: Modalities of long term renal replacement therapy for stage 5 chronic disease patients include conventional hemodialysis with low flux membranes, high-flux membrane hemodialysis and hemo/dia/filtration. None of these modalities have shown any superiority on outcome. However, the use of an optimal convection volume during OL-IHDF has been showed to significantly improve intradialytic hemodynamic tolerance (Morena et al KI 2017; and others referenced 9,10). Consequently, OL-IHDF is routinely used in chronic hemodialysis facilities. We agree with the reviewer, saying that “OL-IHDF is the gold standard treatment for ESRD patients” may be overstated. As suggested by the reviewer, we corrected the abstract accordingly.

Q2. Background: Line 47: References 8-10 do not really address the effectiveness of OL-IDHF.

R2: References 8-10 have been changed to best address the effectiveness of OL-IHDF. Please see References 8-10.

Q3 Line 49: Is there any reference to support the statement that begins: "The intensivists aversion..."?

R3: There is no reference to support the statement that intensivists have an aversion to OL-IHDF technique. However, a few intensivist teams reported their experience with this technique underlying a very restrictive use of OL-IHDF in ICUs. We should not use « aversion » to describe this situation but rather restrictive or limited use of OL-IHDF in ICUs. This has been corrected in Background section as correctly pointed by the reviewer.

Q4. Line 52: The statement beginning with "A regular bacteriological...." needs to be referenced.

R4: This statement refers to reference 11. We referenced this statement.
Q5. Line 57: The wording of the statement "However, a non-inflammatory acute harm..." should be reworded for greater clarity.

R5: We rephrase it as: ‘‘However, this potential acute inflammatory risk induced by OL intermittent HDF (OL-IHDF) which remains possible in ICU-AKI has never been evaluated ’’. Please see line 57-58.

Q6. Methods: Line 66: Need to clarify if other patients were admitted during this time who underwent IHD without OL-IHDF so as to ensure that there wasn’t selection bias (i.e. only certain patients got OL-IHDF).

R6: On-line HDF initiated in our unit in 2004, was developed and proposed to all critically ill. None of our patients could underwent conventional hemodialysis. Methods section was amended to precise so. Please see line 66.

Q7. Line 97: Did intradialytic hypotension encompass initiation of vasopressors also (I assume so but need to be clear about this).

R7: Indeed, intradialytic hypotension includes initiation of vasopressor. This information was precised in the Methods section, line 99.

Q8. Minor comments: Line 70: Regarding the statement " Decisions regarding the initiation. according to the KDIGO recommendations": I suspect this may or may not be true in all cases. Either this is an assumption that all physicians practiced in according to the KDIGO recommendations, or physicians' initiation practices' were specified by the study itself, or they were measured in some way and can be reported in the results.

R8: In our ICU, all physicians followed our initiation RRT protocol according to the KDIGO recommendations.

Q9. Results: Major comments: Line 183: Why were only 76 of 203 sessions evaluated? How were these sessions selected vs those that were not? This is potentially a major limitation of this study if this can't be clearly addressed as it introduces the potential for significantly biased results relative to the what might have been found if all OL-IHDF sessions were included for analysis.
R9: As stated in statistical analyses, 2 or more sessions were investigated per patient. For each patient, we analyzed the worst session regarding to inflammatory markers. This explain the evaluation of 76 sessions out of 203 sessions and the use of a linear mixed model. We precise that in statistical analyses (lines 155-158) and Results section (lines 190-191).

Q10. Line 177: The term 'per-dialytic hypotension' is being used in the results. The methods describe 'intradialytic hypotension'. I suggest using intradialytic hypotension throughout.

R10: We thanks the reviewer for his help as he suggested the use all along the manuscript intradialytic hypotension instead of perdialytic hypotension.

Q11. Discussion/Conclusions: -In general, the authors should temper their conclusion that their findings have implications with respect to the overall safety of OL-IHDF in critically-ill patients. There were no 'hard outcomes' measured. Conclusions can be made with respect to the impact of OL-IHDF on inflammatory markers but not much beyond that especially since any complex therapy (such as OL-IHDF) may have unintended consequences. Overall safety/benefit is difficult to evaluate outside of adequately powered trials which use all-cause mortality as the primary outcome.

R11: We totally agree with the reviewer. Our concern in this study was only to demonstrate that OL-IHDF do not add an inflammatory risk in AKI critically ill patients. We demonstrated herein the safety of this technique and not much beyond. Conclusion was amended to clarify that accordingly.

Q12. Is anything known about the impact of HD with biocompatible membranes (i.e. not OL-IHDF) on the same inflammatory markers that were measured in this study? I don't think this is very likely but without a non-OL-IHDF comparison group in this study, the possiblity exists that inflammatory markers usually decrease after IHD so that OL-IHDF is actually causing more inflammation since levels did not decrease.

R12: On the best of our knowledge, a decrease in inflammatory markers has never been investigated with biocompatible membrane IHD in AKI patients. We agree with the reviewer
that assuming this, a potential decrease with high flux and biocompatible membrane HD may occur. It will be of interest to evaluate so in forward studies.

Q13. Lines 218-221: This section should be reworded for clarity.

R13 : We rephrase it for more clarity. Please see lines 229-231.

To the editor

We hope to have comply with the recommendations of the editor and the reviewers.

We do feel that their contribution improved the quality and the meaning of our work to a significant extent. It is now our hope that this manuscript shall be considered for publication in BMC Nephrology.

Sincerely,

K Klouche.