**Author’s response to reviews**

**Title:** A novel citrate-based protocol versus heparin anticoagulation for sustained low-efficiency dialysis in the ICU: safety, efficacy, and cost

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**Author’s response to reviews:**

Dear Dr. Luciano, Dr. Belcher, Dr. Turner, and Editors,

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “A novel citrate-based protocol versus heparin anticoagulation for sustained low-efficiency dialysis in the ICU: safety, efficacy, and cost” (BNEP-D-17-00101).
We read through all the comments carefully and found them most helpful. Not only are these comments informative for revising our paper, they are also valuable for guiding our future researches.

To address each issue raised in the comments, our responses to the two reviewers are listed point-by-point below.

We have revised our manuscript accordingly and hope that this revised version is suitable for publication.

We look forward to your further feedback.

Yours sincerely,

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Reviewer 1 (Randy Luciano):

1. Comment 1: There is no mention of whether the PTT goals were achieved in the patients who were using heparin as a therapeutic agent. This will have a significant impact on whether clotting occurred (if the patient was below the therapeutic range) or whether bleeding occurred (if the patient was above therapeutic range).

Response:

We fully agree that achieving PTT goals is critical for controlling clotting and bleeding in heparin group. As nephrologist, we recommend a PTT goal of 50-70 sec. However, physicians in ICUs do not always follow the recommendation.

In our study, PTT was controlled in 460 out of 976 SLED sessions with systemic heparin (47%). In detail, the PTT goals were achieved in 181 sessions (39.4%). In the other controlled sessions, PTT was either below the range (144 sessions, 31.3%) or above the range (135, 29.3%).

We added these information to the result section of our manuscript.

(Results section, line 19-24, page 11)
2. Comment 2: In Table 3: the number of patients with circuit clotting in the citrate group is 38. However in the breakdown there are 3 patients with access and 36 patients with dialysis catheter related clotting - this totals 39 patients, not 38 - please correct or explain the difference.

Response: We are sorry for our negligence. The number in Table 3 refers to dialysis session, but not patient. We modified the header of table 3. There was in fact 35 sessions with dialysis catheter related clotting. This number has been corrected.

3. Comment 3: In table 3 please describe/breakdown the metabolic complications - may be important when considering citrate based therapy.

Response: In the result section, we describe the metabolic complications. (Results section, line 1-4, page 11)

Also, we added the following footnotes to table 3 for references.

“4 dialysis sessions performed with citrate were interrupted due to metabolic complication: 2 increased metabolic acidosis, 1 derangement of sodium, 1 uncontrollable hyperpotassemia. 1 SLED session with heparin anticoagulation was broken due to uncontrollable hyperpotassemia.”

4. Comment 4: Please describe in detail how the both group received anticoagulation - were PPT goals similar? Was duration continuous for both therapies? What was the breakdown of heparin use vs citrate use and if treatment was changed from heparin to citrate (or vice versa) what prompted the switch? This needs to be addressed as these patients have more dialysis sessions and longer hospital stays.

Response:

A. The standard anticoagulation for SLED performed in our hospital is systemic heparin anticoagulation, if patients do not show any risk of bleeding, such as operation, active bleeding, puncture, or invasive intervention. The PTT goal (50-70 sec.) was the same for all heparin dialysis. All SLEDs were conducted for an 8-12 h dialysis.

B. In our study, a total of 207 patients received SLED with heparin: 79 patients only received SLED with heparin (group Heparin), 128 received both heparin anticoagulation and citrate anticoagulation for SLED (group Both). 3 patients in group heparin passed away due to bleeding: one patient with cerebral bleeding, one with intra-abdominal bleeding, one with pulmonary bleeding.

C. In group Both, 34 patients first with heparin sessions changed to citrate sessions due to bleeding, while 6 patients changed due to suspicion of HIT. The other patients received firstly citrate anticoagulation while they had risks of bleeding such as operation,
intervention, or active bleeding. The anticoagulation was afterwards changed to heparin. The realistic incidence of bleeding should be 18% (37/207).

D. We are not able to assess the bleeding incidence in SLED with citrate. Some of the patients were already undergoing active bleeding before SLED. Thus, it is difficult to define if the bleeding was caused by anticoagulation.

We have re-written parts of our manuscript according to the Reviewer’s suggestion.

Methods section, line 10-15, page 7
Methods section, line 9, page 6
Results section, line 13-17, page 9
Results section, line 16-23, page 10
Table 2
Discussion section, line 11-12, page 14

Reviewer 2 (Justin Belcher):

1. Comment 1: How frequently was SLED performed without any anticoagulation? Patients in this setting were excluded. If there were only a handful it would be impossible to look at them with any statistical power but if there were a reasonable number I would like to see data on them, specifically the incidence of filter clotting and bleeding. In retrospective studies such as this the major concern is always confounding by indication and seeing data on patients who were either deemed not to need anti-coagulation or who were though too high of a risk for any anti-coagulation (due to coagulopathy, thrombocytopenia or, for citrate, perhaps liver dysfunction) would be illuminating.

Response:

We absolutely agree with you that SLED performed without any anticoagulation is a very important concern. It was also one of the secondary endpoint of this study. But we could not collect enough data on them in this study.

During the observation period, only 37 SLED sessions performed without any anti-coagulation in 15 patients were documented. Six out of these 15 patients suffered from acute liver failure, while 9 patients with thrombocytopenia / coagulopathy with bleeding which were difficult to be controlled.

In total, four sessions were interrupted: two sessions were interrupted due to irreversible clotting of the extracorporeal circuit, one due to seizure during dialysis, and one due to death of patient.
To assess the safety and efficacy of SLED performed without any anti-coagulation vs. citrate/heparin, we therefore conduct a retrospective, prospective study since 2016. The estimated study completion date is December 2017. The points mentioned by reviewer are all final goals of the study, in particular the incidence of clotting and the indications for anticoagulation. We hope that we could answer this question with a meaningful statistical evaluation at the future phase of this study.

2. Comment 2: The definition of a "severe bleeding event" as one that resulted in the interruption of SLED AND death is a very unusual and extremely conservative definition. Bleeding can be quite severe and extremely clinically relevant to the safety of an anti-coagulation regimen without resulting in death. As the authors note, "severe bleeding" has been reported in 10-50% of previous studies looking at heparin for anti-coagulation in CRRT. Using extremely strict definition the incidence was only 2% in this study. If anything, this definition will bias the findings against citrate (assuming it does in fact lead to less bleeding) as numerous clinically significant bleeds, requiring transfusions and perhaps switching from heparin to citrate, were not counted against heparin. It is difficult to come up with a universally accepted definition of what a "severe bleed" is but if the authors have data on bleeds that required a transfusion and/or number of units required by patients while on SLED

Response:

Thank you very much for this comment. We realized, according to your comments and the comments from the other reviewer that we should make a better definition of the bleeding incidence so as to make a more meaningful analyze.

In our study, a total of 207 patients received SLED with heparin: 79 patients only received SLED with heparin (group Heparin), 128 received both heparin anticoagulation and citrate anticoagulation for SLED (group Both). 3 patients in group Heparin passed away due to bleeding: one patient with cerebral bleeding, one with intraabdominal bleeding, and one with pulmonary bleeding. These 3 bleeding events also caused interruption of SLED as show in table 3.

The anticoagulation in 34 patients in group Both has been changed from heparin to citrate due to bleeding, in 6 patients on suspicion of HIT. The other patients received firstly citrate anticoagulation while they had a risk of bleeding such as operation, intervention, or active bleeding. The anticoagulation was afterwards changed to heparin. The realistic incidence of bleeding should be 18% (37/207).

We are not able to assess the bleeding incidence in SLED with citrate. Some of the patients were already undergoing active bleeding before SLED. So, it is difficult to define if the bleeding was caused by anticoagulation. Also, the number of transfusion was not well documented.

We have re-written this part according to the reviewers’ suggestion.
3. Comment 3: Please define, if possible, what was meant by a "temporary bleeding risk" in the group that started on heparin and then went to citrate. In addition, did all patient go this way? Were some in the Both groups ones who started on heparin and then switched to citrate due to bleeding or concern for HIT? It is critical to include this data if available.

Response:

We mean here a risk of bleeding such as operation, intervention, active bleeding. Patients with known HIT in the medical history were excluded.

We add further description in the manuscript.

(Result section, line 11 and 13-17, page 9; line 14, page 13)

4. Comment 4: In the Results section on Efficacy, data is presented on filter clotting while on heparin vs citrate. Does this include patients from all 3 groups, i.e. does it include patient from the Both group and break down clotting episodes by which modality they were on at the time? Or does it only include Heparin and Citrate group patients? Please clarify in the manuscript.

Response:

Data about SLED efficacy shown in Results section were collected from all 3 groups. The dialysis modality in group Both was: The anticoagulation in 34 patients has been change from heparin to citrate due to bleeding, in 6 patients on suspicion of HIT. The other patients received firstly citrate anticoagulation while they had a risk of bleeding such as operation, intervention, active bleeding. The anticoagulation was afterwards changed to heparin.

We add further description in the manuscript.

(Result section, line 13-17, page 9)

5. Comment 5: In the discussion it notes 72% of included patients were at a "high risk of bleeding". Please indicate how this was defined.
We have further illustrate this definition in our manuscript. Patients were considered to be at high risk of bleeding for heparin anticoagulation if they were undergoing active bleeding, within the initial 24 h after invasive intervention (puncture, biopsy), or acute decrease in hemoglobin (> 2 mg/dl within 24h).

We add further description in the manuscript.

(Methods section, line 9-15, page 7)

6. Comment 6: In the limitations section, the authors note that this was not a randomized controlled trial. They then state, "However, randomized trials without patient selection in critically ill patients are not possible". I am not really sure what this is supposed to mean. Randomized trial can be difficult in the ICU but are performed quite frequently. What is meant by "without patient selection"?

Response:

We mean here "without patient selection biases". Patients with bleeding risk such as post-operation, active bleeding, post puncture could not be included in randomized trials of regional citrate versus heparin anticoagulation. The treatment could risk those patients if they were randomized to the heparin arm. Those patients were all excluded in the previous randomized trials.

Related parts has been modified.

(Discussion section, line 9-12, page 16)

7. Comment 7: In Table 4, the entry under 4hr and in row Blood flow rate should be formatted to fit on one line

Response:

Thank you for pointing out. Table 4 has been modified.