Reviewer's report

Title: Simple Citrate anticoagulation protocol for Low Flux haemodialysis

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Reviewer: Richard Singer

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This is a small pilot study reporting on the introduction of a regional citrate anticoagulation protocol to a single dialysis unit and comparing efficacy to saline flush dialysis. There have been much larger studies published looking at regional citrate anticoagulation for dialysis but the novel aspect of this paper is the comparison to saline flush dialysis. Line numbering is difficult to follow since on the PDF I have been given there appear to be two numbering systems. I have used the numbers given in the far left margin in my comments below.

I have some questions and concerns regarding the paper

1. In page 1 of the manuscript, line 28, it is stated that RCA was introduced in 1961. This probably ought to have a citation

2. Page 2, line 25 of the methods section it is mentioned that "either arm could be administered first". How was it decided which arm to administer first. If this was not done randomly then it is a source of bias comparing complications of one treatment with the other.

3. In Table 1: what is the glucose concentration of the dialysate and was it the same in both arms

4. Page 3 lines 27 to 37. I find this section confusing and needed to re-read several times to understand it. I suggest re-wording for greater clarity.

5. Page 4, line 58 it is stated, "aiming at a target of 0.25 - 0.35mM". I cannot see anywhere in the paper that the calcium infusion or citrate infusion is adjusted based on post filter iCa concentrations - how then did the authors target this concentration.
6. Page 5, line 4. The authors should specify that they adjusted the calcium infusion rate according to Table 3 to achieve a systemic iCa of 0.65 to 1.2mM, if that is what they did. The current wording is ambiguous as to the method of adjustment.

7. Page 5, line 4. Targeting a systemic ionized calcium as low as 0.65mM seems rather dangerous as it might be expected to induce seizure and/or tetany in some patients. I suspect such a low target limits the external applicability of the outcome data. On what basis did the authors select such a low target?

8. Page 5, Line 9. It would be easier for readers to determine exactly which point of care analyser was used if the abbreviated name was spelled out in full and the company city/country address was provided.

9. Page 5, line 28. Looking at the results I would guess that an unpaired t-test was used, but given the cross over design a paired t-test is probably more appropriate. Can the authors comment on this please.

10. Page 5, line 30. Were any categorical variables tested? I don't see any in the results section that have had a hypothesis test performed.

11. Table 4. This is confusing. The authors need to clarify that the n of 25 is the number of dialysis sessions, in which case saying there were 19 males is misleading and the median age becomes a bit dubious since not all patients crossed over. Since this has been called a cross over study in the methods it would be better presented with n being given as the number of different subjects and then indicate the number of sessions in a separate cell or column.

12. Page 6, line 38. Data for only 4-5 electrolytes is presented so the statement that there was no change in "electrolytes" is too broad.

13. Table 5 needs to clarify that the data only applies to the citrate anticoag sessions. It ought to provide a (paired) t test comparison to baseline electrolytes in the saline flush sessions. The p value should be stated, rather than just "NS". To my eye a total calcium of 2.54 looks quite a lot higher than one of 2.12. To understand whether the lack of statistical significance is purely due to inadequate sample size I think a confidence interval for the results (or for the difference) would be better than just the standard deviation.
14. Table 5. A range for the iCa would be very informative in determining how many patients developed significant hypo or hyper calcemia.

15. Page 7, line 40. If hypernatramia is going to be mentioned in the discussion then it should also be presented in the results section (eg Table 5).

16. Page 7, line 47. An elevated TCa:iCa ratio was not listed as an exclusion criteria in the methods so what is the justification for excluding him/her. At what time point was this ratio measured? Was this thought to be due to liver failure? Can the authors please expand on their reasons for excluding this patient.

17. Page 7, line 49. I do not have ready access to the full text of citation 8. Can the authors please expand on why they believe metabolic alkalosis indicates citrate toxicity at the completion of a dialysis. Since all patients were dialysed with unphysiologically high bicarbonate, it seems an unreliable measure to me in this situation.

18. Page 7, Line 51. "Cal" is not a standard abbreviation for calcium. It is repeated in several locations in the manuscript.

19. Citation 3 looks to be erroneous. The journal, volume and page correspond to a paper with Aspner as first author, according to PubMed. That paper does not compare citrate dialysance between low and high flux dialyzers and, given that citrate is a small molecule, I wouldn't have thought the dialyzer flux makes any difference to its dialysance.

20. Page 8, Line 14. A lower haematocrit would surely lead to lower plasma citrate levels since citrate is excluded from erythrocytes and citrate dosing is based on whole blood flow in the methods (not on plasma flow).

21. Page 8, line 42. The calcium infused and how it was factored in should be mentioned in the results and methods section first.

22. Page 8, Line 49-53. These two sentences and the sentences on page 9 line 3, don't seem to add to the paper or to relate to technical problems.

23. Figure 2. What do the numbers within the graph (rather than on the axes) refer to?
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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