Reviewer’s report

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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Reviewer: Justin Belcher

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Wen et al. have performed a retrospective study evaluating the effectiveness, efficiency, safety and cost of regional anticoagulation using a 30% citrate solution versus systemic heparin versus a combination of the two in sustained low efficiency dialysis (SLED). The identified 75 patients in the citrate group, 76 in the heparin group and 128 who used a combination of the two. They found that the in-hospital mortality did not differ between the groups but that the citrate group suffered fewer serious bleeding events than the heparin alone group. In addition, the authors found a significant decrease in the incidence of circuit clotting in the citrate group as compared to heparin alone.

This study in interesting and addresses some unresolved questions. Over the last 5 years citrate has become the preferred anticoagulant for CRRT but there has been little data in SLED. In addition, there is significant variance in the formulations of citrate in use and it is not clear which should be the standard of care. I do however have several questions/concerns.

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.

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 I think this would significantly add to the manuscript.
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.

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.

In the discussion it notes 72% of included patients were at a "high risk of bleeding". Please indicate how this was defined.

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"?

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

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
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