Reviewer’s report

Title: Transcapillary fluid flux and inflammatory response during neonatal therapeutic hypothermia: an open, longitudinal, observational study

Version: 0 Date: 18 Apr 2016

Reviewer: Noah Cook

Reviewer’s report:

Overall, this study presents a novel approach to evaluating a facet of the symptomatology following perinatal asphyxia which is not commonly explored and which may be of profound clinical significance. A better understanding of the fluid shifts that occur in the context of perinatal asphyxia and its treatment with therapeutic hypothermia could greatly influence the management of this high-risk population for whom treatment options remain limited.

I found the study to be well designed and the manuscript well written, but I have one major concern which is the absence of a power-sample size evaluation. This, together with the large attrition in usable wicks due to blood contamination calls into question the appropriateness of publishing the COP findings and drawing the stated conclusions related to these findings. It specifically raises the question as to whether or not the lack of statistically significant detectable changes in COP were observed because there truly were no changes, or because of insufficient statistical power to detect them. It also raises concerns about the lack of any stated hypotheses. With so many measures being obtained, the likelihood of finding some statistically significant finding(s) were all but assured, so it would have been important to say up-front what was expected.

Some other points:

1) It is not clear to me what is meant by the term 'fluid surplus' (lines 45, 285, 379). The measure should be explained in the methods section. Along these lines, I don't follow the statement: "The changes were significant for excess fluid accumulating during the first 7 hours, with a significant reduction (P < 0.001) compared with the remaining treatment period." Reduction of what? 'Excess fluid' accumulation would not appear to represent a 'reduction'.

2) The evaluation of changes in COP would seem to be rather limited in the absence of documented measures or changes in body weight, urine output or content of IV fluids administered (electrolytes, dextrose, protein content, if not the actual osmolar value), and for this same reason I question some of the stated conclusions, such as attributing findings to early fluid resuscitation. The use of clinical evaluation of subjects' skin was an interesting work-around for the lack of an actual weight measure, but I didn't see presented any grading of this measure which could be applied to the analysis.
3) Further elaboration on the reasoning behind the attrition in study population/usable samples and the nature of the residual analyzable data would seem to be warranted. Specifically:

- for what reason(s) was implementation deemed not feasible for the 12 subjects who were not asked to participate (line 186)?

- Did the attrition in study population due to mortality (line 187) lead to further limitations in samples collected?

- With the loss of one third of usable wicks due to blood contamination, how many were left for each time point?

- How many samples altogether were left for each time-point analyzed?

- Were there sufficient study samples left to detect statistically significant changes?

**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?**
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.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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