Reviewer’s report

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

**Version:** 0  **Date:** 08 May 2016

**Reviewer:** Deirdre Murray

**Reviewer’s report:**

Review for BMC Pediatrics:

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

I have significant concerns regarding the methods, analysis and presentation of data in this manuscript which would need to be addressed before it would be suitable for publication.

My biggest concern is that the authors claim to give inside into the effects of therapeutic hypothermia, but they have no data on non-cooled infants. The effects they see may take place in non-cooled infants with HIE

Secondly they compare to data reported for healthy children, which is not scientific. They, themselves state that COPi and COPp are lower in neonates, so they must compare to healthy neonates. Is this data available? Even if available I would suspect that there is a significant inter-user variability in these measures and they could not directly compare to previously reported historical data.

They report on 29 infants over 5 years. These seems like a very small number. It is not clear what percentage of their total HIE population this represents. We are not told the number of deliveries in the hospital. What are the grades of HIE in the studied infants. I would suspect it to be severe based on the very low Apgar scores even at 10 minutes. The findings may change depending on the grade of HIE and may not be applicable across all grades. Why were 12 asked not to participate? How did they differ? Were they not severe and so more active?

The next issue is the statistical analysis. Despite only 17 subjects they have used parametric analysis to compare between groups. Only mean(SD) values are reported, except for albumin. (the reason for this is not explained). Alterations may be present if non-parametric tests where used as we cannot be sure of the spread of the data with such small numbers.

Abstract: the conclusions are not supported by the data. No therapeutically valuable information is presented.

Line 69: hibernation: this is not a scientific term. We do not really know why TH works.
Results: line 219 paragraph regarding findings: non-significant findings should not be reported as findings. This should read: no differences were seen.

Table 3: Multiple measures are compared. The authors should correct their significance cut off, using a correction to avoid false discoveries, such as a Bonferroni correction.

Many of the changes described are known to occur in infants with HIE, whether or not they are cooled. Not sure what added information this gives and they cannot be attributed to Cooling.

Table 4: the authors do not mention what the normal ratio of serum to IF for cytokines should be. Does this depend on the size of the IL. These are large molecules, do they readily diffuse into the IF? Again multiple comparisons so the p values should be corrected.

Discussion: the data does not support the summary given at the beginning of the discussion.

The authors claim that the decrease in MAP with cooling is related to COP alterations. It is much more likely to be related to sedation. Have them examined this? The fluid surplus reported is more likely to be due to SIADH and supported by reduced sodium despite fluid restriction.

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.

No

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 am able to assess the statistics

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