Reviewer’s report

Title: A pilot cohort study of cerebral autoregulation and 2-year neurodevelopmental outcomes in neonates with hypoxic-ischemic encephalopathy who received therapeutic hypothermia

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Reviewer: Dennis Shaw

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The authors employ a cerebral vascular autoregulatory assessment measure (hemoglobin volume index- ‘HVx’) they have pioneered to evaluate the adequacy of cerebral perfusion; using this measure to define the optimum arterial blood pressure at which cerebral autoregulation remains intact (mean arterial pressure optimum- ‘MAPopt’). They calculated this measure and compared to the actual ABP in a group of newborns with HIE who underwent hypothermia (measurements were recorded during hypothermia as well as during and immediately after rewarming) and correlated poorer compliance with the HVx derived optimum in the group with impaired versus the group with unimpaired neurodevelopmental outcomes at 2 years.

The author’s finding of less adequate cerebral perfusion by HVx in the group with poorer outcomes during the 6 hours immediately following rewarming is interesting and merits further investigation (i.e. those as a group with poorer outcome spent more time with a MAP under the HVx individual defined MAPopt during the rewarming phase).

Minor essential revisions:
(1) typo line 429 'Intracranial hypertension and hyperemia during rewarming occur(s) in some brain-injured....'
(2) Presume this is a different cohort, but if some of these subjects were part of the earlier study referenced (Howlett et al Pediatr Res 2013), this should mentioned.

Discretionary revisions: authors to address at their choice:
(3) In considering the potential explanatory power of the VHx derived measures on outcome appears some limited as only 3/8 subjects with impaired outcomes spent a greater % time below MAPopt than the 95th percentile of the 9 unimpaired subjects, while only 4/8 had AUC below optimal MAP exceeding the 95th percentile of unimpaired group. Is there any speculation as to what other factors might be contributing to the outcomes?

(4) The HVx derived MAPopt was found to be higher on average in the group with impaired neurodevelopmental outcome, presumably a reflection of greater injury. The conclusion that monitoring MAPopt may be superior to current
measures is appropriately cautious, and similar caution is warranted in proceeding with the suggestion that maintaining a MAP closer to this HVx derived MAPopt might improve neurodevelopmental outcome; the damage may not be responsive to increasing MAP and elevating MAP to the HVx implicated MAPopt would not be without potential risk.