Reviewer's report

Title: Early Blood Glucose Profile and Neurodevelopmental Outcome at Two Years in Neonatal Hypoxic-Ischaemic Encephalopathy

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Reviewer: Alistair Gunn

Reviewer's report:

This retrospective study confirms the association reported by Basu between asphyxia and low blood sugars, and by Salhab et al 2004 that hypoglycaemia in the first 6 h after birth, but not hyperglycaemia, is associated with adverse short-term outcome in term infants with acute HIE. Critically, it extends these findings to demonstrate that it is also associated with death or abnormal neurodevelopmental outcome at 24 months. This is an important validation study.

The primary limitation, which the authors recognise but only partly discuss, is that this study cannot determine whether we should treat hypoglycaemia or not. The major reasons are of course partly just that this is an association, but more importantly that as shown by Salhab, that hypoglycaemia is more common with more severe encephalopathy. Given that in experimental studies of prolonged umbilical cord occlusion blood sugar falls it may well be that more severe insults cause lower sugars, not the other way around.1

In view of this it is critical that all therapeutic recommendations should be removed (repeated in several places with similar wording in the discussion), and appropriate warnings added to their conclusions, similar to those given by Salhab.

It would greatly strengthen this paper to give the results of the full multivariate model including early hypoglycaemia as well as HIE severity, Apgar scores etc. Although the authors use multivariate logistic regression to show that the association of severity of HIE with primary outcome is not affected by glycaemic status, they do not tell us whether there is any independent effect of glycaemia. I suspect that there is not.

Minor amendments.

The discussion of the limited experimental literature is confusing, because the authors don’t specify species, models and age. This is very important since there is evidence for example that intra-insult hyperglycemia is protective against hypoxia-ischemia in the infant rat 2,3, but not in the piglet 4. I am not aware of similar data in post-insult infusions, but the authors may wish to note that leblanc and colleagues found no effect of glucose infusion after HI in the term piglet, supporting their current study. 5

Table 1. Please add mortality structured by severity of HIE.
How was repeated sampling accounted statistically for within each time period? Particularly in the severe group, babies may well have had multiple measurements.

Trivia
Page 5 repeated “fetal brain ATP”
Ibid. 5000 what?
Ibid. Since all children had HIE, I suspect that the criteria actually required evidence of HIE.

Page 7. Since 4 children were born at home, were these babies really able to have a blood sample within 30 min? If not, please present their time of first sample.

Page 10. first para. ‘hypoglycemia reduced’ please change to specify was associated with etc.

Ibid. Please delete ‘nevertheless, hypoglycaemia should be avoided’ etc. This study does not address this issue.

Page 10, bottom para, line 2. “part of EEG study” missing preposition.

Page 11, top. What does definitive duration mean?
Page 11. please delete “nevertheless, early hypoglycaemia “ etc.

Figure 1. Please spread out data points so that they do not overlap. Many programmes will do this automatically.

How many datapoints can each child have at each time? Ie are their repeated samples here or have samples been averaged?

Figure 2. Please specify in the legend what the bars and whiskers represent.


5. LeBlanc MH, Huang M, Patel D, Smith EE, Devidas M. Glucose given after

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests