Reviewer’s report

Title: Short and long term outcome of neonatal hyperglycemia in very preterm infants: a retrospective follow-up study

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Reviewer: kathryn Beardsall

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This study is a retrospective follow up study of a cohort of 33 infants who were <32 weeks gestation and who were defined as hyperglycaemic based on blood glucose >10mmol/l and ‘requirement’ for insulin treatment for >12 hours and were compared with 63 ‘matched’ controls.

The issue of the clinical importance of hyperglycaemia in the setting of intensive care is topical and there is limited data on the long term impacts and there is a need for further information in this area. However there are a number of concerns I have with the paper as presented which do need to be addressed.

1. The rationale for the definition of hyperglycaemia used in this study is unclear as this is not one commonly used in the literature or known to have any clinical significance.

2. There is limited data on the frequency of blood glucose monitoring in either the ‘at risk’ or matched population to be sure that episodes of either hyperglycaemia or hypoglycaemia have not been missed. The clinical significance in a population being treated with insulin in terms of outcomes is important. This needs to be presented.

3. Why were data only collected for the first 5 days of the hyperglycaemic episode – was there any significant hyperglycaemia outside this period?

4. Clinical criteria were for treating infants with insulin are not well presented statements such as ‘necessity of insulin treatment’ need clarifying – and this would be helpful for those wishing to know of the relevance to their own practice – similarly what were the criteria for stopping insulin?

5. It is not clear whether the controls were infants who did not have hyperglycaemia and the necessity for insulin treatment for >12 hours, but could have had unspecified periods of hyperglycaemia but not started on insulin or had insulin but for < 12hours. – description of these infants would be helpful.

6. Exclusion criteria – there is no explanation for why infants with parenchymal haemorrhage or infarction were excluded from the study – this needs to be discussed.

7. The ‘behavioural outcome’ is not clearly described or referenced it is difficult to know what ‘inadequate’ behavioural outcome defines. This needs clarification.

8. The data presented is not always consistent Table 1 n=33 however in Table 3
characteristics of glucose control are given for n=66.

9. Infants with missing baseline characteristics were excluded from regression analyses – It would be helpful to know how many were excluded?

10. The multivariate regression analyses does not provide any information regarding the variables included in the model. In regression analyses it is usual to see if the outcome is related to other potentially confounding variables not to simply include only the variables that are statistically significantly different in the two study arms. For example IVH grade 3/ 4 may not statistically significantly different between the groups but it is likely to impact on outcomes and such relationships with outcomes should be explored -especially as there appear to be a higher incidence of IVH in those with hyperglycaemia. Similarly, regarding potential effect of hypoglycaemia.

Additional points

In the Abstract
i. The statement ‘Morbidity was more common in infants >1000g’ – is this really true?

ii. Statements that behavioural and development were more frequently abnormal among those with hyperglycaemia should be supported statistically

iii. The conclusion gives the impression that the use of insulin treatment as opposed to the presence of hyperglycaemia is linked to mortality – this can not be concluded from this study.

Results

The details of the cohort would be better presented in a table 1 as an extra column

Table 4 : This is reported to be multivariable regression analysis for mortality but it does not provide any information regarding what are the multiple variables included in the regression analyses? Were gestation and birth weight included as variables? The tables do not include all the necessary units

Discussion

Given the definition of hyperglycaemia including the use of insulin for >12 hours one can not assume that the association is due to poorly controlled hyperglycaemia in this design it may be the effect of insulin. This needs to be discussed. In addition the discussion would benefit by limiting to the data presented rather than hypothesis about animal data.

Conclusions

Can not make any concluding comments about changes in brain structure, as this study does not report any data regarding brain structure and the conclusion would benefit from being more focused
**Level of interest:** An article whose findings are important to those with closely related research interests

**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'