Reviewer's report

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

Version: 1 Date: 20 March 2010

Reviewer: Anne van Kempen

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This is a retrospective cohort study on the short and long-term effects of hyperglycemia in preterm infants who were treated with insulin. The authors conclude that:
- mortality was higher in infants treated with insulin
- morbidity was more common in a subgroup for birth weight of >1,000 gram
- growth was normal at 2 years in survivors
- survivors had a higher incidence of behavioural and neurological problems.

Major Compulsory Revisions

1. The main question is whether hyperglycemia by itself causes mortality, short term morbidity and long term neurodevelopmental problems or that hyperglycemia is an epiphenomenon of other neonatal diseases that increase neonatal morbidity and mortality and thereby influence long term neurodevelopment.

The main difficulty of this study is that the chosen design makes it very complex to establish a reliable conclusion to the study question. A causal relationship between hyperglycemia and unfavorable outcome – as suggested throughout the report – is not proven by this study.

2. This study does not fulfill several criteria for the methodologic validity of prognostic studies:

# Sample of subjects: Only hyperglycemic patients who were treated with insulin were included. Because the study was retrospective, the question is whether the decision to start insulin therapy was comparable in all patients. This could cause a selection bias. Second, it is unclear if the postnatal age was comparable at the time of hyperglycemia.

# Because of the high mortality rate (27/66) and loss to follow up (1 excluded, 5 lost) the study group was quite small (n=33).

# Most important: it is difficult to establish whether the control group is really similar to the insulin-treated group. Several important variables were addressed: the control group was matched according to gestational age and birth weight. Pre- and postnatal clinical conditions were reported like chorioamnionitis (although the used definition is questionable), sepsis, severe IRDS, severe IVH, PVL, NEC, BPD and pre- and postnatal steroids. All except BPD were
comparable in the treatment and control group. However, length of stay and mortality were much higher in the treatment compared with the control group (47 vs. 26 days and 41% vs. 8%). These differences suggest that the infants in the treatment group had a more complicated neonatal course than the control group, which also could be responsible for their less favorable neurodevelopmental outcome. The authors state that this was the case in a subgroup of infants >1000 gram. More detailed information on especially the postnatal condition of the infants in both groups is needed, e.g. ventilation days, oxygen days, parenteral nutrition days, days of antibiotic therapy, CRIB score, etc.

3. Treatment with insulin is not unequivocally associated with better outcome. The first study in adults by van den Berghe showed very promising results. However, it proved to be difficult to repeat the positive results in later studies in adults, and some studies even showed negative effects. Early treatment with insulin in preterm infants (without hyperglycemia) even showed higher mortality at 28 days in the early-insulin group than in the control group (Beardsall NEJM 2008). The less favorable outcome in the insulin-treated group in this study could therefore also be due to the insulin therapy. This aspect must be addressed in the discussion.

Minor Essential Revisions
1. Units are missing in table 3.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.