Reviewer's report

Title: Pilot study of a model-based approach to blood glucose control in very-low-birthweight neonates

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Reviewer: Garry Steil

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This study compares glucose control achieved using a computer model to determine insulin infusion rates in 22 VLBW infants (25.4 weeks gestational age; median weight 760 grams, 3168 hours of control, target 4-7 mmol/L [72-126 mg/dL]) versus results obtained in 21 VLBW infants (26.6 weeks median gestation, median weight 845 grams) managed with sliding-scales/clinician-intuition (historical data, 2005-2006). Results are also reported on a pilot study of 8 VLBW infants managed with the computer algorithm but monitored more closely and for a shorter period of time (24 hours; results used to assess safety/efficacy of the computer based algorithm).

The authors report that: i) there were no hypoglycemic episodes during the 24-hour trial; ii) a lower median blood glucose concentration was achieved with the computer algorithm (6.6 [IQR: 5.5 – 8.2] mmol/L, 1,003 measurements, versus 8.0 mmol/L; p < 0.01); iii) the percentage of blood glucose within the target range was increased by 83% (p < 0.01); and iv) there was no difference in the incidence of hypoglycemia observed in the trial period compared to historical control (p = 0.51).

They conclude that a computer model that accurately captures the dynamics of neonatal metabolism can provide safe and effective blood glucose control without increasing hypoglycemia.

Major Compulsory Revisions

1. The sliding scale used to effect insulin therapy needs to be described together with a discussion of how “clinician intuition” may or may not have affected its use. Specifically, the target range used for the sliding scale needs to be reported as it makes little sense to compare glucose levels achieved with two algorithms targeting different ranges. As well, some sliding scale algorithms implicitly define a desired rate at which the target is to be achieved; for example, the Portland Protocol only recommends an increase in insulin if the glucose is above target and not falling at a desired rate. Finally, comparing to a sliding scale that is routinely overridden based on clinician intuition make little sense. The authors should provide a complete description of the sliding scale used for comparison in this reports, perhaps as an appendix, and discuss whether the protocol was followed.
2. Throughout the manuscript, results from statistical tests are reported without data. Examples taken just from the abstract include No significant difference in incidence of hypoglycemia during long-term trials was observed (p = 0.51), and Percentage of blood glucose within the target range was increased by 83% compared to the retrospective cohort (p < 0.01).

Here, the actual hypoglycemic incidence rates and percentage of blood glucose values within target range need to be reported.

3. Care needs to be taken to provide complete descriptions of what was done. For example, the manuscript reports that 3168 hours of computer control and 1003 blood-glucose measurements were obtained using computer control but does not report how many hours of retrospective control was evaluated, or how many blood samples were used to assess hypoglycemic rates. These data are essential.

4. Similar care needs to taken to define outcome measures and make statistically valid comparisons. Is the “incidence of hypoglycemia” defined “per day”, “per patient”, or “per blood sample” and is the number or frequency of blood samples the same in the “long-term computer control” and “sliding-scale” groups. The manuscript reports that: All blood glucose results are resampled hourly to aid comparisons across studies that had different BG measurement frequencies. [Note, scientific results should be reported as past tense – the verb here should be “were”]. It is not clear which – if any – results were obtained hourly. More importantly, the authors should consider whether any bias was introduced in the comparison of hypoglycemia in the two groups by any difference that might have been present in the number or frequency of blood samples obtained.

5. Once the actual incidence rate is established – which the reviewer expects to be very low if normalized to the number of blood samples – the authors should provide a statistical power analysis. Generally, per patient rates as low as 3-4% have been reported using other computer-based algorithms suggesting that the present study may be severely underpowered to detect changes in the overall rate.

6. The manuscript reports that Infants received most nutrition via parenteral solutions containing 10-12.5% dextrose. This is rather vague. The data on which patients received nutrition via gastric tube (or regular feeding) versus IV should be available. Moreover, the algorithm is described as using nutrition data to determine insulin infusion rate. The reviewer’s concern is that many infants – particular infants that are sick – are given food which they do not manage to keep down (i.e. they throw-up). This creates problems whenever insulin is administered after the food is taken but before the carbohydrates are absorbed into the blood stream. The manuscript should make clear whether the present algorithm can be used in an infant who is receiving nutrition via the gastro-intestinal tract and if so whether insulin is delivered in advance of that nutrition being absorbed into the blood stream (in advance of the rise in glucose). If so, how does the algorithm deal with instances in which insulin is delivered and the food purged.
7. A more complete description of the algorithm should be provided together with some discussion about the relative merits of combining the insulin infusion with glucose infusions to prevent or correct hypoglycemia. Recognizing that the manuscript is already above 3000 words this added material could be accompanied by a reduction in the length of the Discussion, which includes topics strictly related to the study’s objective or results (e.g., the discussion as to what the appropriate target is).

8. The authors should discuss the use of blood glucose values obtained from different sources (arterial line if present; capillary otherwise). Did the authors conduct preliminary tests to ensure there was no statistical difference in these measures or quantify the variance.

Minor Essential Revisions

1. There are numerous typing and grammatical errors. The aforementioned use of present tense where past tense is called for (see item 4 above).

2. The sentence This study presents the first trials of model… trials should read trial.

3. “Moribund” and “not expected to survive” man the same thing. The sentence Infants who were moribund or not expected to survive were excluded is redundant.

4. The sentence including …and BG within the wider 4.0 – 8.0 mmol/L band was 42% higher (p < Chi-squared test) should report a p-value.

5. The sentence including …with the 4.0-7.0 mmol/L and 4.0-8.0 mmol/L bands was consistently higher for model-based control (p < 0.01 for both banes, Mann-Whitney test), what are “banes”?

6. A careful proofreading is required.

Discretionary Revisions

1. The authors should consider reporting that a pilot study on 8 subjects was performed in advance of implemented the algorithm to assess safety of 24 hours but not report the actual results. These 8 subjects are not treated sufficiently like the subsequent 22 to combined with that group, and do not constitute a sufficiently large enough group to draw independent conclusions on. Excluding the data would allow more room to describe both the sliding scale algorithm and the computer algorithm, and explore the results obtained once the computer algorithm was actually implemented.

2. The author’s should also consider presenting the results in Figure 2 as a daily average with 95% CI. This could be obtained by first averaging all the blood values obtained for a given subject on a given day into one number, and then averaging across subjects (N=22 or 21 with N decreasing as time goes on). This would allow differences between protocols to be more easily identified, clarify
how long each algorithm takes to achieve target etc.

3. The present study does not provide any outcome data on the underlying causes of hyperglycemia, its relationship to co-morbidities, whether tight glycemic control should be done and if so what the target should be etc. Thus, space devoted in both the Introduction and Discussion to these items might better be devoted to introductory comments highlighting the underlying objective of the present study and a discussion of the results showed.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

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

**Declaration of competing interests:**

I declare that I have no competing interests