Author's response to reviews

Title: Screening for hypoglycemia at the bedside in the neonatal intensive care unit (NICU) with the Abbott PCx glucose meter

Authors:

Cynthia M Balion (balion@hhsc.ca)
Susan Blatz (blatz@hhsc.ca)
Seidlitz Wendy (seidlitz@hhsc.ca)
Afisi Ismaila (ismailas@mcmaster.ca)
Grey Vijaylaxmi (grey@hhsc.ca)

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Author's response to reviews: see over
Reviewer 1

They should analyze the data in the lower range of glucose i.e. less than 4 or 5mM since that is where the problems with the diagnosis of hypoglycemia arise and the weighted effect of concordance at high values will become less significant.

We agree completely with this reviewer, as it is at low concentrations where decisions on treatment will be made. Often method evaluations are done on a wide concentration range and this can minimize concentration specific differences (usually at the lower or upper ranges). We therefore divided the data into two groups (≤ 4 mmol/L and > 4.0 mmol/L) to assess whether the differences between the glucose measurements (RN PCx, LAB PCx and laboratory reference method) was dependent on the glucose concentration. The multivariate regression analysis showed that glucose values ≤ 4.0 mmol/L were significant in explaining why there was a difference between PCx values and laboratory analyzer values (Table 2). Furthermore, it was found that hematocrit had a greater effect on samples with concentrations ≤ 4 mmol/L (Table 3).

To emphasize this difference the data were analyzed at ≤ 4 mmol/L. The following text has been added to the results section (page 8).

“The further analysis of the data at low concentrations (≤4.0 mmol/L, n = 137) showed poorer relationships: LAB PCx = 1.19 PG - .74, r = .78; RN PCx = 1.43 PG - 1.11, r = .73. The comparison between the two PCx glucose measurements was RN PCx = 1.16 LAB PCx - .06, r = .83. The proportion of RN PCx and LAB PCx results outside ±15% were 38.7% and 5.1%, respectively.”

In the discussion this has been emphasized on page 12.

“Only 58% of the all bedside measurements and 39% at low values (≤4 mmol/L) achieved a total error difference of 15% of the laboratory analyzer.”

I also have concern about ROC calculated cut offs since it will convey a wrong message and create a value for standard of care.

The ROC curve illustrates the sensitivity and specificity of the PCx glucose meter to detect hypoglycemia (< 2.6 mmol/L) using the Vitros analyzer as the reference method. In general, this curve shows that increasing the cut point value significantly increases sensitivity, but has minimal effect on specificity. The ROC curve may be different for other glucose meters and reference methods. This point has been clarified in the discussion on page 12.

“The cut off chosen for confirmatory screening will be dependent on the glucose meter and the comparator reference method.”

This will link well with our cautionary statement in the conclusion section of the abstract that a screening cut off must be established when using a glucose meter.
Remove extraneous data from the tables

Table 1 has been shortened by removing the units column (the units now appear next to the characteristic) and the rows containing information about the missing data. A summary of the missing data has been added to the results section on page 8.

“Complete data for all glucose measurements were available on 449 samples. Data missing in other categories ranged from 0.4 to 2.7% except for the time between RN PCx and LAB PCx measurements (5.7%).”

No changes have been made to Tables 2 and 3 as all parameters are referred to in the text. Also, the complete set of results from the analyses allows the reader to make comparisons between the data sets and parameters and assess their relative differences.

Reviewer 2

*I have reviewed this manuscript. It is well written and presents new useful information and should be published. The only modification that I suggest is to include conventional units in the text in addition to SI units. This will make the manuscript much more readable and useful to the American readership and this is an important audience.*

Glucose concentrations in conventional units were added in parentheses next to the glucose concentrations in SI units in the abstract and in Figures 1 and 3. In addition, the conversion factor (mmol/L to mg/dL) was added to the methods section on page 6.

Reviewer 3

*The results would become more accessible to nurses and clinicians (in the U.S.) if the authors also presented glucose values in conventional units (mg/dL). This convenience can be done easily and explicitly in the abstract, in Figure 1 by adding an extra horizontal axis, and in Figure 3 in parentheses next to the mmol/L values, but need not be included everywhere in the text. Also, the glucose conversion factor (mmol/L to mg/dL) should appear in the methods section.*

Glucose concentrations in conventional units were added in parentheses next to the glucose concentrations in SI units in the abstract and in Figures 1 and 3. In addition, the conversion factor (mmol/L to mg/dL) was added to the methods section on page 6.

*Readers will take careful note of the hematocrit effect (vividly illustrated in Figure 2) as a confounding variable in neonates of the gestational age range given in Table 1. For clarity and emphasis, the authors should conclude the abstract with the same statement found on page 14 about the influence of hematocrit and low glucose concentration (esp. the sensitivity issue) as contributors to differences in results obtained with the glucose meter versus laboratory method.*
The following sentence has been revised in the conclusions section of the abstract.

“There was a large difference between glucose results obtained by PCx glucose meter compared to the laboratory analyzer accountable in part by hematocrit and low glucose concentration.”

*Information about calibration and standardization of the glucose meter and laboratory method can be obtained from the manufactures and added to the methods section, as it may explain part or all of the bias observed.*

The following information has been added to the Methods section under ‘Glucose measurements’ on page 6.

“The PCx glucose meter is calibrated against the YSI 2300 analyzer whereas the Vitros 950 uses a calibrator for glucose traceable to the National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 917b.”

Also, a sentence has been added in the Discussion section on page 13.

“Some of the unexplained variance may be due to differences in calibration between the PCx glucose meter and the Vitros analyzer.”

The difference in calibration between these methods may contribute in part to the differences in glucose concentration seen. Surprisingly, in a method comparison with the YSI 2300 an unexpected negative bias was demonstrated with the PCx (Abbott Precision PCx blood glucose monitor with Precision PCx Plus test strips - [http://www.wasp-uk.org/](http://www.wasp-uk.org/)). The effect of hematocrit was also evaluated in this study and gave similar results to ours. Calibration would be unable to adequately correct for hematocrit because of the proportional nature of the relationship. Also, in our study we found the effect of hematocrit was greater for samples with low glucose concentration compared to samples with high glucose concentration. In general, both calibration and methodology differences are needed to explain the differences in glucose results between these two instruments.

*The authors are careful in their use of the word “plasma” and provide explanation of possible mechanisms for the hematocrit effect in terms of plasma filtration. They also point out the vulnerability of young erythrocytes. Thus, they should add whether the glucose meter manufacture claimed accuracy specifically for prematures and neonates, inclusive within the concept of the licensed hematocrit range of 0.20 to 0.70 cited on page 13.*

The accuracy for neonatal blood samples was assessed and the PCx glucose meter has been approved by the FDA. The samples analyzed had hematocris ranging from 27% to 68%. However, in the section “limitations of the procedure” it states that “no significant effect was found for hematocris between 20% and 70%”.

This information has been clarified in the Discussion on pages 13 – 14.
“The manufacturer claims there is no significant effect with hematocrits between .2 and .7. However, it is not clear from the product information material if this range is also applicable for neonatal samples. All samples in this study had hematocrits essentially within this range (.19 – .69). The hematocrit effect using filter-based test strips is well known (including the PCx glucose meter), although not all glucose meters have this problem (10).”

The authors studied a handheld glucose meter system that is used at the bedside, but appear not to have mentioned a competing “portable” instrument (manufactured by HemoCue) known for accuracy and used for near-patient testing in the pediatric setting. Discussion of clinical investigations in peer-reviewed literature for this instrument would be informative for the reader and particularly relevant to future planning because the company is in the process of introducing a handheld model that will be licensed for the diagnosis (yes, diagnosis!) of diabetes in the U.S.

It would be wonderful to have a glucose meter with better accuracy, particularly for application to neonatal hypoglycemia. We commented briefly on the accuracy of other glucose meters in the Discussion on page 12 and suggested a point of care blood gas analyzer (with a glucose module) could be an alternate solution (for accuracy), although it still requires a higher blood volume.

There have been several publications evaluating the HemoCue glucose meter for neonatal samples. This glucose meter also exhibits a hematocrit effect (Arch Dis Child 1996; 75; F202, Pediatr Pathol Lab Med 1996;18:41) to about the same degree as seen in our study (5% for every 10% change in hematocrit)( Pediatr Pathol Lab Med 1996;18:41). More importantly, there were no studies that specifically looked at the concordance of hypoglycemic cases (<2.6 mmol/L), where it is most clinically needed, between the HemoCue and any laboratory method. There was one study however that showed a falsely low values in the low range (≤2.0 mmol/L) compared to a glucose dehydrogenase laboratory method (Scand J Clin Lab Invest 1997; 57: 719). Based on these studies it appears the HemoCue also has limitations in the neonatal setting not unlike other glucose meters.

Reviewer 4

This paper investigates the accuracy of bedside meter testing versus lab results in a NICU setting. The authors do a good job explaining the question of the paper and why an understanding of the data is important. Despite referencing and testing to defined ADA standards, it might be important to state whether the authors believe the ADA standards are applicable in the NICU setting (in the discussion section).

This is a good point. In an NICU setting it is important to have a narrow window of error tolerance because minimal changes in concentration can change treatment. However, the lack of clarity in diagnosis of neonatal hypoglycemia makes it difficult to set a good glucose threshold value and thus define an allowable error.
Theoretically, a reasonable estimate of allowable error can be made using estimates of analytical (method variation) and biological variation (variation around a homeostatic set point) (Biological Variation: from principles to practice by Callum G. Fraser and online at http://www.westgard.com/biodatabase1.htm). The quality specification for analytical variation (CVₐ) is one-half of the biological variation for an individual (CVᵢ). The CVᵢ for glucose ranges from 5.7% (http://www.westgard.com/biodatabase1.htm) to 8.3% (Clin Chem 2004; 51: 450) which would make the desirable CVₐ somewhere between 2.9% and 4.2%. Laboratory methods for glucose are closer to this specification than are glucose meters. In our study the Vitros had a CVₐ of 2.7% at 5.3 mmol/L whereas the PCx had a CVₐ of 6.0% at 2.9 mmol/L. Furthermore, the 95% probability of how close the result will be to the true value is 1.65CVₐ or 4.8 to 6.9%.

The allowable total error (TEa) concept considers both analytical and biological variation. It is an estimate of the desirable difference between the found value and the true value. The desirable TEa quality specification is given by the equation

\[ \text{TEa} < 0.25 \left( CVₐ^2 + CV₇^2 \right)^{1/2} + 1.65 \left( 0.5 \text{CVᵢ} \right) \]

Where:
CVₐ = analytical variation
CVᵢ = individual variation
CV₇ = between individual variation

For glucose the TEa value is 6.9% in Westgard’s database and 7.9% in Fraser’s book. These estimates can be used to get a handle on how accurate a result can really be. Therefore, if a TEa of 6.9% is used for a hypoglycemic threshold value of 2.6 mmol/L a reasonable estimate of error around this value is anywhere between 2.4 and 2.8 mmol/L. This difference is significant because treatment would be initiated at a value of 2.4 mmol/L but not at a value of 2.8 mmol/L.

For assessing neonatal hypoglycemia the error tolerance must be as low as possible and the lowest that can be reasonably achieved is about 7%. The ADA recommendation of 15% is very generous and not appropriate for neonatal hypoglycemia. The definition of neonatal hypoglycemia must take into consideration the broad error limits of glucose measurements.

The Background section on pages 4 and 5 have been revised as follows,

“Glucose meters were originally targeted to glucose self-monitoring of patients with diabetes and concern has been raised about their accuracy in the neonatal setting [5]. In the neonatal intensive care unit (NICU) an acceptable agreement between the laboratory value and the bedside reading of ±0.1 mmol/L or ±5% at the hypoglycemic level and should preclude the need for confirmatory or repeat testing [2]. Although this agreement of 5% is desirable current POC instruments are unable to achieve this. Recommendations for analytical quality for glucose meters are targeted for diabetic patients. The American
Diabetes Association (ADA) recommends that glucose meters should have a total error (bias and imprecision) no more than 10% for all concentrations [6]. More recently, the International Organization for Standardization (ISO) suggested that 95% of measurements with glucose concentrations ≤4.2 mmol/L should be within ±0.83 mmol/L and within ±20% for concentrations >4.2 mmol/L [7]. Few studies reporting the performance of glucose meters in the NICU have been able to achieve any of the above criteria or other reasonable accuracy criteria [8,9,10].”

Also, the Discussion section on page 12 has been revised.

“A 15% error limit is quite a liberal quality specification that should be achievable and has been suggested previously by the ADA and other groups [10]. A 15% error on a value of 2.6 mmol/L gives values between 2.2 to 3.0 mmol/L, which significantly affects clinical management. If the desired 5% error is applied the limits are reduced (2.5 to 2.7 mmol/L) and approach the ISO recommendation of ±0.83 mmol/L. A rational error estimate however depends on what can be achieved analytically (method variation) and biologically (variation around a homeostatic set point). The concept of allowable total error (TEa) combines analytical and biological variation. The TEa for glucose frequently quoted is 6.9% [12]. Therefore, for a hypoglycaemic threshold value of 2.6 mmol/L the practical error around this value is closer to 2.4 to 2.8 mmol/L. The definition of neonatal hypoglycemia must take into consideration the broad error limits of glucose measurements, particularly when less accurate glucose meters are used.”

_Because much of the paper evaluates the effect of various parameters on the data, I would suggest a statistician review the methods and results, since several conclusions about the affect of these parameters on the differences in readings are drawn._

The statistical analyses were performed by one of the authors (AI) who is a statistician.

_The referenced ADA guideline for accuracy of Self-monitoring of Blood Glucose meters recommends that meters be within 10% of glucose values. Since your interest is in the low glucose range however, I suggest an additional analysis of the data using the ISO standard ISO15197, which states that 95% of the meter readings should be within 15 mg/dl of the reference at glucose concentrations below 75 mg/dl, and they should be within 20% at glucose concentrations greater than or equal to 75 mg/dl. The results will change, as will your ROC curve and suggested threshold level for re-testing. If you believe the ISO guideline is too broad at the low end, consider using a different mg/dl threshold for error, but explain your rationale for a tighter accuracy criteria. The ADA guideline was written in 1994 when analyzing data across the glucose range. At low glucose levels, meters would have to be within a few mg/dl of the lab to meet the 10% accuracy criteria, and I’m not sure this was the intent or if its necessary or applicable. For example, 10% error at 40 mg/dl is only 4 mg/dl. Is this level of accuracy required? In summary, I think you should discuss the clinical significance of the levels of inaccuracy you observed in your study._

A discussion of error limits has been presented in the previous comment. The ROC curve will change if a different threshold value is used for the reference test. The choice of the
hypoglycemic threshold value may need to be reconsidered based on the achievable error limits, particularly for glucose meters.