Determining the best method for first-line assessment of neonatal blood glucose levels

CL THOMAS, L CRITCHLEY and MW DAVIES
Level 2 Special Care Baby Unit, Nambour General Hospital, Nambour, Queensland, Australia

Objective: To evaluate and compare the accuracy and performance of two electrochemical glucose meters. To determine the user acceptability of these glucose meters and the ABL 620 Blood Gas Analyser (Radiometer, Copenhagen, Denmark) with an electrochemical glucose oxidase electrode for use in a Level 2 special care baby unit.

Methodology: A total of 108 blood samples were collected from 47 babies at risk for hypoglycaemia. The blood glucose level was measured with two glucose meters, the Advantage Glucose Meter (Roche Diagnostics, Castle Hill, Australia) and the Precision-G Blood Glucose Testing System (Medisense, Melbourne, Australia), and the true blood glucose (TBG) measured with the ABL 620 blood gas analyser. Results from the glucose meters were compared with the TBG (as a percentage of the TBG).

Results: The mean (SD) percentage difference between the Advantage Glucose Meter and TBG was 4.5% (12.5), and Precision-G Glucose Meter and TBG was 15.4% (12.4). The sample haematocrit did not significantly influence the glucose meter/TBG differences. There was an overall preference by the nursing staff for the Advantage Glucose Meter.

Conclusions: The Advantage Glucose Meter was significantly more accurate than the Precision-G with similar precision. It was the preferred method of screening for neonatal hypoglycaemia.

Key words: blood glucose; glucose meter; hypoglycaemia; infant, newborn.
glucose meters traditionally used which are photometers relying on reflectance-based technology. The electrochemical detection technique uses an enzymatic reaction (glucose oxidase for the Precision-G and glucose dehydrogenase for the Advantage) to generate a current which is measured by the meter. The size of the current is proportional to the amount of glucose present in the drop of blood, which gives an accurate reading. The older reflectance meters used a colorimetric reaction. The colour generated is dependent on the amount of glucose present and is interpreted electronically by the reflectance meter giving a qualified blood glucose value. This method is dependent on user technique, adequate cleaning of the photometric window, can be interfered with by skin preparations, and the size of blood sample. These problems are not encountered with the new meters, which allow universal sampling (capillary, arterial and venous blood), and quick analysis. There is no requirement for wiping, blood can be re-applied, and the strips can be handled without interference thus reducing the source of analytical and user error.

The Advantage Glucose Meter was already in use within the SCBU, and the Precision-G glucose meter was considered as a viable alternative. Both glucose meters have been specifically recommended to accurately estimate neonatal blood glucose.

The ABL 620 blood gas analyser (Radiometer, Copenhagen, Denmark), with attached electrochemical glucose oxidase electrode, was used as the reference method in determining the true blood glucose (TBG). It has been shown to be very precise and to provide reliable and accurate results.9 A recent study demonstrated the ABL 620 to have a high correlation with the reference laboratory method.10 The ABL 620 uses a multilayer membrane with glucose oxidase immobilized between the inner and outer membrane. The outer membrane has pores of well-defined density limiting the crossing of red cells into the glucose oxidase layer. The enzymatic reaction generates a current, which the Analyser converts to a plasma glucose concentration.

All three methods use whole blood for analysis of blood glucose. Whole blood glucose concentration is influenced by haematocrit (HCT), with high HCT giving a lower apparent blood glucose concentration. The manufacturers claim that the Advantage Glucose Meter is not affected by a HCT of 0.2–0.65, and the Precision-G a HCT of 0.2–0.7. The ABL 620 showed no interference by HCT for a range of 0.35–0.75 IU/L, and this was due to the outer low-porous membrane. A haematocrit level was measured by the ABL 620 (on the same sample of blood), to test for possible interference with the glucose result.11

**Procedure**

Thirteen selected members of the neonatal nursing staff received in-service training on the study protocol, correct blood collection technique and machine procedure prior to the commencement of the study. Daily quality control checks were carried out on the Advantage and Precision-G blood glucose meters, in accordance with the manufacturer’s guidelines. The ABL 620 was calibrated by the staff of the Pathology Department at the recommended times, in compliance with manufacturer’s guidelines.

An arterial or capillary blood specimen was collected on each occasion. This single specimen was used for each of the three machines: the two glucose meters and for measurement of the TBG.

The volume required for the Advantage and Precision-G glucose meters, was one large drop, or 0.02 mL each. The ABL 620 required 0.09 mL if using a capillary tube or 0.3 mL if a heparinized syringe was used.

Arterial blood was collected from indwelling arterial lines and capillary samples from heel pricks. Arterial blood was collected into a 1-mL preheparinised syringe. Single drops were expelled to completely cover the test windows on the Advantage and Precision-G strips. The remainder (0.3 mL) was transferred immediately to the intensive care unit to be analyzed using the ABL 620 glucose Analyser. The syringe was inverted several times and air bubbles were removed prior to insertion of blood into the required port. Haematocrit was also measured at this time.

Capillary blood was collected from a pre-warmed heel after the first drop was wiped away. The next two drops were used to fully cover the windows on the Advantage and Precision-G strips. A capillary tube collected the next drop and was capped securely. A magnet was used to slide the mixing wire in the capillary tube. The blood was then inserted into the ABL 620 Glucose Analyser. The capillary tube contained no inhibitors of glycolysis and the specimen was tested within 15 min of collection.

Records were kept of the glucose meter blood glucose levels for both meters, the TBG, HCT, and any delay in obtaining a result. The nursing staff were asked to comment on any difficulties encountered with the procedure, including delays and/or machine difficulty. The nursing staff completed a questionnaire, rating the ABL 620, Advantage, and Precision-G glucose meters, on ‘ease of use’. A scale of 1–5 was used with 1 being very easy and 5 being very difficult.

The Research Ethics Committee of The Royal Women’s Hospital and District Health Service, Brisbane, gave ethical approval for the study.

**Statistical methods**

Comparison of means for continuous non-skewed data were analysed using the Student’s t-test. Comparison of medians for continuous skewed data were analyzed using the Kruskal–Wallis and Mann–Whitney tests. Differences between individual glucose meter measurements and the TBG were plotted against the TBG as a percentage of the TBG. The mean percentage difference between individual glucose meter measurements and the TBG (as a percentage of the TBG) was calculated. The closer the mean difference to zero, the greater the accuracy, and the smaller the standard deviation (SD) around the mean the greater the precision, as compared with the TBG. Sensitivity, specificity, likelihood ratios of a positive and negative test, positive predictive value (PPV) and negative predictive value (NPV) were calculated for both the Advantage and Precision-G machines for the diagnosis of hypoglycaemia (≤ 2.6 mmol/L). Data were entered into and analysed with Microsoft Excel 97 (Microsoft Corporation, Washington, USA) and Minitab for Windows (version 11; Minitab Inc., State College, USA) software.

**RESULTS**

A total of 108 samples were collected from 47 neonates. TBG was measured on 83 occasions. The 25 unavailable results from the ABL 620 were due to: insufficient sample (11), capillary sample insufficient and specimen clotted in tube (4), operator error (2), measurement aborted reason unknown (4), and
broken capillary tube (2). On two occasions a reason was not given. Results for the Advantage Glucose Meter were unavailable on one occasion and a reason was not reported. Results for the Precision-G Glucose Meter were unavailable on two occasions. One was due to insufficient sample and the other due to machine failure. The Precision-G glucose meter had one reading recorded at < 1.1 and as this was not an absolute value it was not included in the data analysis.

Haematocrit was measured on 88 (81%) of the samples collected. Data was unavailable because of insufficient specimens, including clots and broken capillary tubes (17), operator error (2) and a malfunction of the ABL 620 on one occasion. The mean (SD) haematocrit was 0.60 (0.08) I/L with a range from 0.42 to 0.78 I/L.

There were 82 and 81 blood glucose levels measured by the Advantage and Precision-G glucose meters, respectively, paired with a TBG. Comparisons between the Advantage Glucose Meter and TBG are summarized in Table 1. The means of absolute blood glucose values are not significantly different for all measurements. The mean (SD) percentage difference between measurements was 4.5% (12.5), which is close to zero. Figure 1 shows the percentage difference between measurements plotted against the TBG ($r^2 = 0.223$, $P < 0.001$). This shows that the Advantage Glucose Meter under-read more with higher TBG and this seemed to be more pronounced at TBG > 4 mmol/L. The differences between measurements for TBG ≤ 4 mmol/L and > 4 mmol/L (see Table 1) were analysed. The mean (SD) percentage difference between measurements for TBG: > 4 mmol/L was 0.6% (13.9). The mean (SD) percentage difference between measurements for TBG > 4 mmol/L was 8.6% (8.8). In the clinically important range of TBG, from 2 to 3 mmol/L, the mean (SD) percentage difference was −4.0% (14.4). Figure 2 shows the percentage difference between measurements plotted against HCT. The fitted line plot was almost horizontal with a coefficient of determination ($r^2$) of 0.02 ($P = 0.27$); therefore the HCT did not influence the degree of difference between measurements. The overall performance of the Advantage Glucose Meter in diagnosing hypoglycaemia (for all measurement pairs and for measurement pairs over the clinically important range where the TBG is: ≤ 4.0 mmol/L) is summarized in Table 2. The regression equation for the prediction of TBG from the Advantage glucose meter reading is:

### Table 1

|                  | Advantage Glucose Meter | Precision-G glucose meter | P value* | Difference †
<table>
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<tr>
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<tr>
<td>TBG mmol/L (%)</td>
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<td></td>
</tr>
<tr>
<td>All pairs, n = 82</td>
<td>4.0 (1.10)</td>
<td>3.7 (0.95)</td>
<td>0.14</td>
<td>4.5 (12.5)</td>
</tr>
<tr>
<td>TBG ≤ 4, n = 44</td>
<td>3.1 (0.61)</td>
<td>3.1 (0.57)</td>
<td>0.64</td>
<td>0.6 (13.9)</td>
</tr>
<tr>
<td>TBG &gt; 4, n = 38</td>
<td>5.0 (0.64)</td>
<td>4.5 (0.67)</td>
<td>0.0032</td>
<td>8.6 (8.8)</td>
</tr>
<tr>
<td>TBG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pairs, n = 81</td>
<td>4.0 (1.13)</td>
<td>3.4 (1.02)</td>
<td>0.0002</td>
<td>15.4 (12.4)</td>
</tr>
<tr>
<td>TBG ≤ 4, n = 43</td>
<td>3.1 (0.62)</td>
<td>2.7 (0.56)</td>
<td>0.00008</td>
<td>13.5 (11.6)</td>
</tr>
<tr>
<td>TBG &gt; 4, n = 38</td>
<td>5.0 (0.64)</td>
<td>4.1 (0.86)</td>
<td>&lt; 0.0001</td>
<td>17.5 (13.0)</td>
</tr>
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</table>

TBG, total blood glucose. *Student’s t-test. † The difference between paired measurements as a percentage of the total blood glucose (TBG), i.e. ($TBG – Advantage$)/$TBG$ × 100. ‡ The difference between paired measurements as a percentage of the TBG, i.e. ($TBG – Precision-G$)/$TBG$ × 100.

![Fig. 1](image1.png) Percentage difference between the total blood glucose (TBG) and the Advantage glucometer readings versus the TBG, with fitted line plot (bold line) and 95% confidence intervals (faint lines). $y = 5.264x – 16.477; r^2 = 0.2229$.

![Fig. 2](image2.png) Percentage difference between the total blood glucose and the Advantage glucometer readings versus the haematocrit, with fitted line plot (bold line) and 95% confidence intervals (faint lines). $y = 0.2178x + 18.1; r^2 = 0.0161$. 


\[
\text{TBG}_{\text{mmol/L}} = 0.026 + (1.06 \times \text{ADV}_{\text{mmol/L}}) \\
\quad r^2 = 0.82 \quad P < 0.001 \quad s = 0.486,
\]

allowing the calculation of a predicted TBG with approximate 95% prediction intervals of ± 0.97 mmol/L.

Comparisons between the Precision-G glucose meter and TBG are summarized in Table 1. There was a greater difference between the means of absolute blood glucose values for all the measurements. The mean (SD) percentage difference between measurements was 15.4% (12.4). Figure 3 shows the percentage difference between measurements plotted against the TBG \( (r^2 = 0.04, P = 0.07) \). Therefore the Precision-G glucose meter tended to under-read more with higher TBG but this was not statistically significant. Analysis of the percentage differences between measurements for TBG ≤ 4 mmol/L and > 4 mmol/L is shown in Table 1. The mean (SD) percentage difference between measurements for TBG ≤ 4 mmol/L was 13.5% (11.6) mmol/L. The mean (SD) difference between measurements for TBG > 4 mmol/L was 17.5% (13.0). In the clinically important range of TBG from 2 to 3 mmol/L, the mean (SD) percentage difference was 10.0% (13.7). Figure 4 shows the difference between measurements plotted against haematocrit. The fitted line plot is almost horizontal with \( (r^2) \) of 0.06 \( (P = 0.03) \); therefore the HCT only slightly influences the degree of difference between measurements. The overall performance of the Precision-G glucose meter in detecting hypoglycaemia (for all measurement pairs and for measurement pairs over the clinically important range where the TBG is ≤ 4.0 mmol/L) is shown in Table 2. The regression equation for the prediction of TBG from the Precision-G glucose meter reading is:

\[
\text{TBG}_{\text{mmol/L}} = 0.773 + (0.96 \times \text{PRE}_{\text{mmol/L}}) \\
\quad r^2 = 0.75 \quad P < 0.001 \quad s = 0.567,
\]

allowing the calculation of a predicted TBG with approximate 95% prediction intervals of ± 1.13 mmol/L.

At the completion of the study, the nursing staff were asked to compare the ABL 620, and the Advantage and Precision-G glucose meters with regard to their user acceptability. There was an overall preference for the Advantage Glucose Meter for its ‘ease of use’ and convenience, with 13/13 (100%) nurses rating it the easiest to use and the most convenient. The ABL 620 was the least preferred for convenience and ‘ease of use’. Problems encountered by the nursing staff when using the ABL 620 included: difficulty in collecting blood into the capillary tubes, difficulty with the technical detail required in working the machine and the inconvenience of the machine’s location.

Table 2  Test performance characteristics for the Advantage and Precision-G glucose meters for detection of neonatal hypoglycaemia (< 2.6 mmol/L), for all measurement pairs and for measurement pairs where the TBG is ≤ 4.0 mmol/L

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Positive LR</th>
<th>Negative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pairs</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Advantage</td>
<td>89</td>
<td>99</td>
<td>89</td>
<td>99</td>
<td>65</td>
<td>0.11</td>
</tr>
<tr>
<td>Precision-G</td>
<td>100</td>
<td>88</td>
<td>50</td>
<td>100</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Pairs TBG: ≤ 4.0</td>
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</tr>
<tr>
<td>Advantage</td>
<td>89</td>
<td>97</td>
<td>89</td>
<td>97</td>
<td>31</td>
<td>0.11</td>
</tr>
<tr>
<td>Precision-G</td>
<td>100</td>
<td>74</td>
<td>50</td>
<td>100</td>
<td>3.8</td>
<td>0</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; positive LR, likelihood ratio of a positive test; negative LR, likelihood ratio of a negative test.
They reported that with the Precision-G glucose meter, entering patient information was more arduous, and the machine more cumbersome. The median (IQR) ‘ ease of use’ rating for the three methods were: 1.0 (1.0–1.0) for the Advantage, 2.0 (1.5–3.0) for the Precision-G, and 3.0 (2.5–5.0) for the ABL 620. These differences are statistically significant, \( P < 0.001 \), Kruskal–Wallis test. Post-test, Mann–Whitney tests revealed significant differences between the Advantage and the ABL 620 (\( P < 0.0001 \)), and the Advantage and the Precision-G (\( P = 0.0014 \)).

On nine of 83 (11%) occasions where the TBG was measured with the ABL 620, the result was delayed by \( \geq 5 \) min. No such delays were experienced with the Advantage and the Precision-G glucose meters.

**DISCUSSION**

Two glucose electrochemical meters were compared for evaluation against a glucose oxidase analyser. Both glucose meters were specifically recommended by their manufacturers for use in neonates. The Advantage Glucose Meter was more accurate and had similar precision compared with the Precision-G glucose meter with a mean percentage difference closer to zero and a similar (SD). This mean difference of 4.5% (0.2 mmol/L) for the Advantage Glucose Meter was also similar to that found by Perkins et al.\(^{12} \) The accuracy of the Advantage was better for measuring blood glucose levels less than 4 mmol/L. The mean difference of 15.4% (0.6 mmol/L) found for the Precision-G meter would be unacceptable in clinical practice and this machine was even more unreliable for TBG values above 4 mmol/L with mean (SD) of 17.5% (13.0).

Hypoglycaemia in neonates is diagnosed as a plasma blood glucose of less than 2.6 mmol/L. Controversy remains regarding the definition of hypoglycaemia\(^ {7,13-15} \) but it has become a safe clinical practice to maintain blood glucose levels above 2.6 mmol/L.\(^ {8,13,14} \) The purpose of cot-side glucose meters should be to determine hypoglycaemia in at-risk neonates, however, it has been observed that cot-side glucose meters overestimate hypoglycaemia\(^ {6,15} \) and neonates are treated unnecessarily for the incorrect diagnosis.\(^ {1,2,16} \) Missed hypoglycaemia occurs less frequently.\(^ {8,15} \) The Advantage Glucose Meter was very specific and had adequate sensitivity, which would result in a rare over-diagnosis of hypoglycaemia. The Precision-G glucose meter was significantly less specific and with a sensitivity of 100% and a positive predictive value of only 50%, over-diagnosis of hypoglycaemia would occur frequently. The positive test likelihood ratio is superior for the Advantage Glucose Meter in the diagnosis of hypoglycaemia. The negative test likelihood ratios are good for both glucose meters.

The Advantage and Precision-G glucose meters are similar in that they use electrochemical technology to determine the glucose result. They differ from older systems, which use photometric technology. Our results show better sensitivity and specificity of the electrochemical glucose meters in the detection of neonatal hypoglycaemia, as compared with other glucose meters which rely on reflectance based technology.\(^ {1,2,17} \)

Cot-side glucose meters have been shown to give erroneously low readings of glucose levels in the context of high haematocrit value\(^ {11} \) and this creates a problem when neonatal haematocrit samples vary between 0.4 and 0.7 I/L. In this study, no influence by haematocrit was found for the Advantage Glucose Meter for the haematocrit range between 0.42 and 0.78 I/L. There was only a slight effect on the Precision-G by haematocrit.

A secondary objective of our study was to determine which of the three machines would be acceptable for first-line blood glucose measurement within our nursery. A key component of this is the user acceptability. The ABL 620 is known to be an accepted method to determine true blood glucose in neonates.\(^ {9,10} \) However, there were a number of problems encountered by the nursing staff using this machine. There were several ‘insufficient specimens’ for the ABL 620. This may have been because blood was collected firstly for the glucose meters, and might not occur in the clinical setting if blood was collected for only one machine. The nursing staff also found the ABL 620 difficult to use. The Advantage and Precision-G glucose meters were easy to use with minimal technical problems, but there was a clear preference for the Advantage Glucose Meter. This preference for the Advantage Glucose Meter may be because they were already familiar with its use. Both the ABL 620 and Precision-G glucose meter were introduced as new instruments. The ‘ ease of use’ comparison is subject to considerable bias because of this, and thus, should be interpreted with caution. The ‘ ease of use’ comparison would be more valid if the staff had equal or no prior experience with each instrument. In choosing a device to determine blood glucose in neonates, it is important to take into consideration not only its precision and accuracy but also its user acceptability. Nursing staff are the most frequent users of glucose meters and thus, their input was valuable in the process of evaluating a glucose meter.

We conclude that the Advantage Glucose Meter is most suitable for use as the first-line screening device for neonatal hypoglycaemia. It is significantly more accurate than the Precision-G glucose meter with similar precision, and has a high degree of user acceptability. Measurement of the TBG with the ABL 620 was, at times, slower and is technically demanding.

**ACKNOWLEDGEMENTS**

We would like to thank the nursing staff of the Level 2 Special Care Baby Unit, Nambour General Hospital, Nambour, Queensland, for their contribution in the clinical measurements and data collection.

**REFERENCES**


