Point-of-care glucose monitoring on the neonatal unit

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Aim: This study aims to compare the accuracy and precision of the Nova StatStrip glucometer against the Radiometer ABL gas analyser. Based on the results, to establish if the Nova StatStrip glucometer could be adopted as a reliable alternative for near-patient glucose monitoring on the neonatal unit.

Methods: Seven hundred twenty-eight paired samples were collected prospectively from babies on a neonatal intensive care unit. Analytical performance of the Nova StatStrip glucometer was assessed based on the ISO 15197 criteria and the American Diabetic Association standards. Its performance compared with the Radiometer ABL gas analyser was assessed statistically using Bland–Altman analysis and clinically by use of an error grid.

Results: A percentage of 98.8 of StatStrip values less than 4.2 mmol/L and 97.9% of values greater than 4.2 mmol/L met the ISO criteria. Bland–Altman analysis showed good correlation between the readings. An error grid showed that most infants would be appropriately managed for hypoglycaemic episodes as per local guidelines.

Conclusions: The Nova StatStrip performed well on statistical analysis compared with the Radiometer. Very few hypoglycaemic patients would be missed using the Nova StatStrip glucometer. We would recommend its use on our unit.

Key words: glucometer; hypoglycaemia; neonates; point-of-care testing.

Hypoglycaemia is the commonest metabolic problem in neonates. Recurrent untreated episodes of hypoglycaemia can result in long-term neurological complications.1

The exact definition of hypoglycaemia in neonates remains unclear. Until recently, it has been defined as blood glucose less than 2.6 mmol/L. More recent reviews define a therapeutic objective of blood glucose >2.5 mmol/L and an operational (action) threshold for intervention of <2.0 mmol/L.2 In accordance with this consensus, our unit defines hypoglycaemia in neonates as two consecutive readings of blood glucose less than 2 mmol/L (requiring a feed to be given, and a subsequent blood sugar to be checked), or a single reading of less than 1 mmol/L (requiring treatment with intravenous dextrose).

Blood glucose monitoring is classified as point-of-care testing. Neonatal blood glucose measurement is challenging because of limited availability of blood and because glucose levels are typically lower than in adults. Neonates typically have higher haematocrit levels, which, if not corrected for, lead to lower glucose readings.3 Previously, hand-held glucometers have been developed for use in diabetic patients and have not been used on neonatal units as they are not designed to accurately identify low glucose values. There has been a recent drive for manufacturers to produce newer generation glucometers that could be adopted for such a use. We sought to determine the performance of a new hand-held glucometer (the Nova StatStrip; Nova Biomedical, Waltham, MA, USA) in screening for hypoglycaemia.

Methods

The service evaluation was performed at Jessop Wing Maternity Unit, Sheffield Teaching Hospitals, UK, in conjunction with the

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Clinical Audit Department. As it was part of an assessment for service provision, this was not deemed to be a research project, and no ethical approval was needed. No extra blood samples were taken from the babies, and patient management was not affected in any way. Where discrepant results were noted, the gold standard result was used for determining the necessity of clinical intervention as per unit guidelines.

The ward currently uses a Radiometer ABL735 blood gas analyser (Radiometer, Copenhagen, Denmark) for point-of-care testing. Previous in-house studies show that as our chemistry laboratory is off-site, there is deterioration in glucose when samples are taken in fluoride bottles and sent to the chemistry laboratory for analysis. The Radiometer is thus considered the gold standard for glucose measurements on our unit. It requires 95 µL of blood to run a full spectrum analysis including haematocrit, while 35 µL is needed for glucose analysis. It analyses heparinised whole blood using amperometric electrodes with an enzymatic glucose oxidase sandwich membrane.4 The Nova StatStrip analyses 1.2 µL of whole blood using a modified glucose oxidase and amperometric detection. The patented four-well strip generates a tiny current that is proportional to the glucose concentration but uses comparative wells on the strip to eliminate interference from sugars, drugs and variance in oxygen tension and haematocrit levels. These factors have bedevilled other manufacturers. The strip is built on a thin layer of gold that provides constant conductivity, eliminating the need to calibrate every lot of strips, further reducing risk from incorrect codes.5

Over 3 months from December 2008 to February 2009, paired glucose readings were performed on samples from babies on the neonatal unit and post-natal wards. Samples were collected by doctors, nurses or midwives who would have been otherwise taking a sample of blood to assess gas parameters or check for a glucose reading. Simultaneous measurements were obtained from the Nova StatStrip and one of the two Radiometer gas analysers. Readings were downloaded from both analyser types and paired up allowing a limit of 4 min for pairing. ‘Paired’ samples out of this time limit were excluded. We used a total of four StatStrip meters and one strip lot on the StatStrip. The gas analysers were routinely two-point calibrated every 8 h and one point calibrated every other 4 h. Two quality control checks were run every 24 h, and external quality assessment was run every month.

Where a full blood count was requested at the same time as the gases or chemistry, then the haematocrit value was recovered from the haematology laboratory based at Royal Hallamshire Hospital (Apex System).

We analysed the data using Windows Excel packages and SPSS (version 12.0, IBM, Armonk, NY, USA). Analytical performance of the Nova StatStrip glucometer was assessed using the ISO 15197 criteria. This states that for glucose levels less than 4.2 mmol/L on the gold standard, the equipment being assessed should have a glucose reading within ±0.83 mmol/L of the gold standard reading for a minimum of 95% of the values. For values greater than or equal to 4.2 mmol/L, the reading should be within ±20% of the gold standard reading again for a minimum of 95% of the values.6 We also compared the performance of the StatStrip against stricter American Diabetic Association (ADA) criteria that require less than 10% error for values above 1.6 mmol/L. Glucose values were compared for agreement using a Bland–Altman plot.7 We developed an error grid to put the findings into a clinical context for our local action thresholds.

Results
In total, 728 paired samples were analysed from 87 infants. Two of the readings were recorded on the StatStrip as less than 0.6 mmol/L, which represents the limit of sensitivity of the StatStrip. We decided to use a value of 0.6 mmol/L for these readings for data analysis. The ranges, averages and standard deviation for the individual glucometer readings are shown in Table 1. The limits of agreement using Bland–Altman analysis (given 95% confidence interval) were −1.5 mmol/L to +1.8 mmol/L (Fig. 1) with a bias of 0.15 mmol/L (standard deviation (SD) 0.85 mmol/L). We opted to represent the Bland–Altman plot in a semi-logarithmic form so the spread of the values on the x-axis would be easier to appreciate.

The Nova StatStrip performed well against the ISO 15197 criteria with 98% of the 728 samples fulfilling these criteria as shown in Table 2. As the ISO 15197 criteria differentiate between those specimens above and below 4.2 mmol/L, we analysed these separately and noted 98.79% compliance for those samples below 4.2 mmol/L. Bland–Altman analysis at this lower range detected a bias of 0.18 (SD 0.33) with a 95%
confidence interval of −0.46 to 0.83. Compliance with stricter ADA standards for glucose meters from 1.6 mmol/L to 22.2 mmol/L was unsatisfactory with 78% compliance (565 of 721 samples).

We established the performance of the StatStrip at detecting the three levels of hypoglycaemia, 2.5 mmol/L for the symptomatic infant, 2.0 mmol/L for the infant at risk and 1.0 mmol/L as the value requiring intravenous infusion of dextrose as illustrated in Table 3. Twenty-three readings had a value of less than 2.5 mmol/L on the Radiometer, 10 readings were below 2 mmol/L and two readings had a value less than 1 mmol/L. This is a reasonably small number but probably reflects the overall care of babies on the unit. The overall sensitivity for detecting blood glucose below 2.5 mmol/L was 95.6%. Only two gold standard values were below 1 mmol/L, both of which were correctly identified as being below this threshold. The negative predictive value for all three thresholds approached 100% suggesting a normal result was reassuring. Relatively low positive predictive values at these cutoffs (30% for 1 mmol/L, 36% for <2 mmol/L and 59% for <2.5 mmol/L) suggests values should ideally be rechecked before significant interventions are carried out.

An error grid was constructed based on clinically relevant glucose concentrations to evaluate the impact the Nova StatStrip would have on clinical decisions and management for hypoglycaemic neonates on our unit (Fig. 2). An allowance of 10% error was incorporated as this is considered appropriate. Of 52 samples below 3 mmol/L, 28 fell into the zone considered accurate for clinical purposes, that is management and outcome were not affected. Twenty-three fell into adjacent zones where blood glucose was marginally underestimated. This was regarded as a benign error for clinical purposes resulting in altered management but unaltered outcome. Only one sample fell into the zone of potentially altered outcome where a blood glucose of 1.9 mmol/L was reported as 2.6 mmol/L. No infants fell into a dangerous error category, specifically blood glucose below 1 mmol/L being missed. The error grid showed that the majority of patients would be appropriately managed.

The relationship between haematocrit values and glucose readings was also assessed. Haematocrit readings were available for 131 of the 728 paired samples (Fig. 3). Haematocrit values ranged from 24.2% to 68.8%. The analysis demonstrates that there is a good level of agreement of glucose values across a wide range of haematocrit readings.

### Discussion

Previous hand-held glucometers failed to perform well at low blood glucose readings and higher haematocrit values as seen in neonates. Neonatal erythrocytes have a higher mean corpuscular volume resulting in faster glucose consumption than in adults. Increased numbers of erythrocytes in whole blood sample mechanically impede diffusion of plasma into the reagent layer of the glucometer, or decrease the volume of plasma available to diffuse. Haematocrit changes also alter the viscosity of blood, thus reducing fluid permeability into the reagent layer. These aspects have previously made the use of hand-held glucometers on neonatal units difficult to adopt.

Previous studies assessing performance of hand-held glucometers tended to use the hexokinase methodology in laboratories.

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**Table 2** Nova StatStrip performance based on ISO 15197 criteria

<table>
<thead>
<tr>
<th>Glucose level</th>
<th>ISO 15197 criteria</th>
<th>N</th>
<th>% within ISO criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.2 mmol/L</td>
<td>Within ± 0.83 mmol/L</td>
<td>165</td>
<td>98.79%</td>
</tr>
<tr>
<td>≥4.2 mmol/L</td>
<td>Within ± 20%</td>
<td>563</td>
<td>97.87%</td>
</tr>
</tbody>
</table>


**Table 3** Performance of Nova StatStrip at detecting hypoglycaemia using a series of clinically relevant cutoffs

<table>
<thead>
<tr>
<th>Threshold for cutoff</th>
<th>&lt;1 mmol/L</th>
<th>&lt;2 mmol/L</th>
<th>&lt;2.5 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>2</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>90%</td>
<td>95.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.4%</td>
<td>97.7%</td>
<td>97.8%</td>
</tr>
<tr>
<td>PPV</td>
<td>30%</td>
<td>36%</td>
<td>59%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>99.8%</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, Negative predictive value.

**Fig. 2** Error grid demonstrating overall agreement between Radiometer and StatStrip for clinically relevant thresholds. Zone A represents equivalent clinical management or <10% error. Zone B represents adjacent zone where StatStrip marginally underestimates blood glucose. Zone C represents more significant underestimate. Zone D represents potentially missed hypoglycaemia (adjacent zone), while Zone E represents dangerously overestimated glucose.
as a gold standard process. However, evidence has accumulated suggesting there is an unavoidable decrease in blood glucose even in fluoride-oxalate preserved samples that occurs in the first 30–60 min after phlebotomy. Thus, appropriate near-patient testing models are convenient by providing an answer in a clinically relevant time frame and may prove more accurate than laboratory-based techniques particularly at times of hypoglycaemia.

We established that the Nova StatStrip glucometer, which represents a new generation of hand-held glucometers designed for adaptation to hospital use, meets the ISO 15197 criteria for glucose readings below and above 4.2 mmol/L. Nova StatStrip readings agreed well with those of the Radiometer ABL across the range of glucose values and across a wide range of haematocrit values.

Various criteria exist to define standards in hand-held glucose monitoring. The ISO 15197 criteria are based on adult needs where values below 4.2 mmol/L require intervention, whereas our neonatal guidelines define an action threshold for hypoglycaemia as a glucose reading below 2 mmol/L. The ADA criteria (<10% error for blood glucose above 1.6 mmol/L) were not met by the StatStrip with a 78% success rate. However, this compares favourably with five hand-held glucometers that were assessed in a similar study against ADA criteria with compliance rates that ranged from 20% to 51% with neonatal samples.

Error grid analysis is used to quantify clinical accuracy of blood sugar estimates generated by a glucometer as compared with reference values. The error grid developed was appropriate to our clinical needs and based on UK consensus statements of practice.

We did not regard historical error grids such as the Clarke and Leroux grids to be appropriate to these thresholds of 2.5, 2.0 and 1 mmol/L. We demonstrated that use of the Nova StatStrip would result in very few hypoglycaemic infants being missed but would potentially result in some normoglycaemic infants being classified as hypoglycaemic. These infants would potentially have repeat sampling where not required or additional feeds. We felt that for our clinical purposes, a device that under-read would be safer than one that over-read.

It is apparent that there are three definite outlying values in Figure 1. A review of these readings confirmed they had been correctly paired. We reviewed glucose readings for these same babies just before or just after the outlying values were recorded to establish if there was a trend suggesting which of the analysers could have provided an inaccurate reading. The trend of the readings on the gas analyser on either side of these outlying values was consistent, and where paired samples were available on either side of the outlying values these also correlated well. No problems were noted with the quality control or calibration of the gas analyser around the time of the readings. Hence, our review of the outliers showed that the StatStrip seems to have under-read in all three cases. We however could not discount user error. Three apparently incorrect readings out of 728 represents an error of 0.41% for the StatStrip analyser.

We believe maximum benefit from hand-held glucometers is from their use on post-natal wards. It is not always practical or cost-effective to maintain blood gas machines on these sites. As most full-term infants being tested for hypoglycaemia at these sites are otherwise well, the StatStrip would provide a useful screening tool.

Benefits from an accurate hand-held glucometer include staff not needing to leave the room or ward to process the sample. This is of particular benefit if staff numbers are low and where patients are being isolated. The use of much lower blood volumes for testing is an added benefit. The StatStrip has connectivity features that allow samples to be tracked to a user and to a patient.

Our assessment suggests the StatStrip provides a viable screening tool for hypoglycaemia in newborn infants and its high negative predictive value suggests a normal value is reassuring in the well infant. We could, however, suggest that low blood glucose values are rechecked because of a relatively high false positive rate. We believe this balance is preferable to a device that may potentially miss significant hypoglycaemia, in particular values below 1 mmol/L.

In conclusion, we feel that Nova StatStrip could be considered a suitable alternative for glucose point-of-care monitoring on our unit, particularly on the Special Baby Care Unit and Post-Natal Wards.

Acknowledgements

We would like to thank Nova Biomedics for kindly loaning the department the Nova StatStrip glucometers for the duration of the evaluation. They also provided training for the use of the meters and supplied the consumables. We would like to stress that data collection, data analysis and the write-up are entirely independent of Nova Biomedics.

References


