Reliability of Glucometer Blood Glucose Readings in Neonates
Shayan Pavaskar, Sidduraj Rangesh, Dhanam Venkatachalam Suresh, Santhanakrishnan Ramakrishnan*

Abstract

Aim: To assess the agreement between bedside glucometer readings and laboratory blood glucose estimation in neonates

Materials and Methods: This prospective observational study was performed in the tertiary NICU of a private hospital in a tier 2 city in south India. The study duration was 5 months, and it included 100 neonates who required blood glucose testing and an intravenous cannula insertion as part of their routine clinical care. Venous blood samples of the neonates were sent to the laboratory for plasma glucose estimation and simultaneously tested for whole blood glucose using the Accu-Chek® Performa glucometer.

Results: There was a lack of agreement between the 2 methods, with a difference of up to 40 mg/dL. The venous blood glucose estimation using a glucometer may be 33 mg/dL above or 13 mg/dL below the values of plasma glucose concentration obtained from the laboratory test. The 95% confidence interval for the upper limits of degree of agreement was 28.7 to 36.6 mg/dL, and for the lower limits of agreement, it was 8.7 to 16.6 mg/dL.

Conclusions: Not all glucometers can be relied upon to accurately monitor neonatal blood glucose. Only glucometers approved for use in the neonatal population must be used for desired accuracy.

*Correspondence
Dr Santhanakrishnan Ramakrishnan
Consultant Neonatal Pediatrician
Department of Pediatrics & Neonatology
SKS Hospital & Postgraduate Medical Institute
23, SKS Hospital Road, Alagapuram
Salem 636004, Tamil Nadu
India
E-mail: ramakrishnan.s@skshospital.org
Introduction
Point of care (POC) glucose testing is widely used in neonates to determine blood glucose concentration. Laboratory estimation of plasma glucose concentration by the hexokinase method is routinely recommended.\(^1\) The major disadvantages of laboratory plasma glucose estimations are the requirement of a larger blood volume and delay in availability of results for timely intervention.\(^2\) Therefore, POC glucose testing devices are widely used. Glucometers were originally designed for glucose monitoring in adults with diabetes.\(^3\)

A prefeed blood glucose concentration of < 45 mg/dL during the first 48 hours of life and < 60 mg/dL after 48 hours of life is defined as hypoglycemia in neonates.\(^4\) Hence, a glucometer may not be reliable in extreme ranges of blood glucose concentrations, for example, < 60 or > 180 mg/dL.

Most studies comparing glucometer values and laboratory plasma glucose estimation results have used correlation and regression analyses to describe the relationship between the two.\(^5\)-\(^11\) However, correlation describes the relationship between 2 variables and not the differences between them.\(^12\) Bland and Altman proposed a correct alternative analytical method to evaluate the bias between 2 quantitative laboratory methods and to estimate an agreement, with limits of agreement including its 95% confidence intervals (CIs).\(^12\),\(^13\)

We conducted this study to assess the performance of a glucometer, the Accu-Chek\textsuperscript® Performa (Accu-Chek Extra Care, Roche Diabetes Care India Pvt Ltd, Mumbai, Maharashtra, India), against the gold standard laboratory plasma glucose estimation using the statistical method described by Bland and Altman. Along with a description of our analyses, results and interpretation, and conclusions, we also provide information about glucometers specific for neonatal use and alternative bedside methods for glucose monitoring.

Aim
To assess the agreement between glucometer readings and laboratory blood glucose estimation in neonates

Materials and Methods
All neonates, including term and preterm, who were admitted to the NICU of SKS Hospital & Postgraduate Medical Institute (Salem, Tamil Nadu, India) and who fulfilled the inclusion criteria were enrolled for this prospective, comparative study. Institutional ethics committee approval and parental consent were obtained before their enrollment.

A sample size of 100 was chosen considering the current admission rate, with an aim to complete the study within 6 months and for an allowance of 50% consent refusal for participation in the study. Neonates who required blood investigations at admission, including glucose testing, and an intravenous cannula insertion as part of their routine clinical care were included. Their venous blood sample was sent to the laboratory for plasma glucose estimation. Simultaneously, a venous blood sample was tested at bedside for whole blood glucose concentration using the Accu-Chek\textsuperscript® Performa glucometer. Accu-Chek\textsuperscript® Performa is an ISO 15197:2013–certified product.

The Accu-Chek\textsuperscript® Performa analyzes glucose concentration in the whole blood on a disposable dry reagent strip containing an electrode and glucose oxidase. Plasma from the whole blood diffuses through a porous membrane, separating out the erythrocytes. Glucose in the sample is oxidized to glucuronic acid, and electrons from this reaction are transferred to the electrode’s surface through an electrochemical mediator, generating a current that is measured by the system.\(^14\) The glucometer was calibrated before the study and at periodic intervals as per the standard laboratory guidelines.
Trained nursing staff performed the glucometer measurements.

In our institute, laboratory plasma glucose estimation is done using the glucose oxidase and peroxidase method (Roche cobas® 6000 analyzer; Roche Diagnostics International AG, Rotkreuz, Switzerland). The oxidation of glucose in the sample is catalyzed by glucose oxidase to form hydrogen peroxidase and glucoronate, which is followed by an oxidative coupling catalyzed by peroxidase in the presence of dye precursors to produce a dye. The intensity of the dye is measured through spectrophotometry. Routine quality control check was followed for the analyses.

Confidentiality of the study neonates was maintained by assigning numbers to the neonates. Identity details such as the neonate’s name, date of birth, name of the birthing hospital, and sex were not stored in the same computer where data were stored and analyzed.

Statistical analyses

The statistical method described by Bland and Altman was used for comparing the 2 clinical measurements. Microsoft Excel for Windows (Microsoft Corporation, WA, USA) was used for data storage and basic analyses. GraphPad Prism version 8 (GraphPad Software, CA, USA) was used for advanced statistical analyses. Birth weight and gestational age distribution were described as median and range. The average (mean) of differences (biases) between the blood glucose concentrations estimated by the 2 methods was calculated. From the standard deviation (SD) of the bias, 95% limits of agreement were calculated. Standard error of the bias and its 95% CI were then calculated, from which 95% CIs for the upper and lower limits of agreement (degree of agreement) were obtained.

Results

Of the 150 NICU admissions during the 5-month study period (January 2019–May 2019), 135 neonates required blood sampling and blood glucose testing at admission. The parents of the 135 neonates were approached for participation in this study, of whom 101 consented. One of the neonate’s result was not included in the analyses because the glucometer displayed a “high” reading.

The median gestational age was 36 weeks and 2 days (range: 27 wk and 3 d–40 wk), and the median birth weight was 2600 g (range: 960–4500 g) (Table 1).

We first plotted the data and analyzed it to gauge the degree of agreement between the laboratory and the glucometer measurements (Figure 1). Although this provided a rough estimate of agreement, detailed statistical analyses were done.

A plot of the difference between the blood glucose measurements obtained using the glucometer and the standardized laboratory method versus the average blood glucose measurements obtained using these 2 methods is shown in Figure 2.

It is clear from Figure 2 that there is no obvious agreement between the differences in the readings and the mean. The average of differences between the glucometer and the laboratory measurements (mean) constitutes

| Table 1. Gestation and Birth Weight Distribution of the Study Population |
|-------------------------------------------------|-----------------|
| Description | Median (Range) |
| Gestation, wk + d | 36 + 2 (27 + 3 to 40 + 0) |
| Birth Weight, g | 2600 (960–4500) |

Figure 1. Blood Glucose Measurements Obtained Using the Glucometer Plotted Against Measurements Obtained Using the Standard Laboratory Method. Correlation coefficient \( r = 0.94; P < .0001. \)
The bias. For our data, the bias was 10.03 mg/dL; the SD of the bias was 11.61 mg/dL. One would expect the differences to fall around ± 2 SD from the bias. The 2 SD of the bias was 23 mg/dL. Hence, 95% limits of agreement, which is bias ± 2 SD, fell between 32.7 mg/dL (upper limit of agreement) and − 12.7 mg/dL (lower limit of agreement) (Table 2).

Limits of agreement are estimates of the population; another set of samples from the same population may provide different results. Standard errors and CIs help assess the precision of the estimated limits of agreement, as shown in Table 3.

**Discussion**

We evaluated the agreement between the readings for blood glucose concentrations in neonates using 2 methods: the glucometer, which used venous whole blood, and the laboratory estimation, which used plasma. This comparison will help the clinicians in deciding whether venous whole blood glucose readings displayed on a glucometer could be reliably interpreted to aid prompt treatment decisions.

Usually capillary blood samples are used on glucometer reagent strips to obtain the blood glucose readings. However, in many neonatal units, capillary, venous, or arterial blood samples are used interchangeably. Although the capillary samples are routinely used for bedside glucose analysis, such a technique has limitations. Júnior et al.\(^1\) demonstrated that a capillary glucose strip showed the poorest correlation and agreement compared with an arterial glucose strip in patients with septic shock and those who were receiving noradrenaline. Most neonates admitted to our NICU were extra- mural referrals who were invariably sick. We used noradrenaline often when dopamine and dobutamine failed to optimize blood pressure. All these may affect the quality of capillary blood glucose readings. We only included neonates in whom withdrawal of venous blood samples was clinically indicated, as it would be unethical to prick a neonate to obtain a capillary sample for study purposes only. Reddy et al.,\(^10\) in their study involving term and preterm neonates, clearly demonstrated that blood glucose estimation using venous blood

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**Table 2. Bland–Altman Plot Statistics for Limits of Agreement**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bias, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average of Differences Between the Glucometer and the Laboratory Blood Glucose Measurements (Bias), d</td>
<td>10</td>
</tr>
<tr>
<td>Standard Deviation of Bias, s</td>
<td>11.61</td>
</tr>
<tr>
<td>95% Limits of Agreement, Bias ± 2 SD</td>
<td>− 12.7 to + 32.7</td>
</tr>
<tr>
<td>Upper Limit of Agreement</td>
<td>32.7</td>
</tr>
<tr>
<td>Lower Limit of Agreement</td>
<td>− 12.7</td>
</tr>
</tbody>
</table>

**Table 3. Bland–Altman Plot Statistics for Precision of Estimated Limits of Agreement**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, n</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Degrees of Freedom, (n−1)</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>t Value for 99 Degrees of Freedom</td>
<td>1.984</td>
<td></td>
</tr>
<tr>
<td>Standard Error of Bias/ Mean (SE d)</td>
<td>(\frac{\sqrt{s^2}}{n})</td>
<td>1.15</td>
</tr>
<tr>
<td>Standard Error of Bias/ Mean ± 2 SD</td>
<td>(\frac{\sqrt{3s^2}}{n})</td>
<td>2.01</td>
</tr>
<tr>
<td>95% CI for Bias</td>
<td>(\frac{(d - (t \times SE d))}{(d + (t \times SE d))})</td>
<td>9.32–13.89</td>
</tr>
<tr>
<td>95% CI for Upper Limit of Agreement</td>
<td>28.72–36.68</td>
<td></td>
</tr>
<tr>
<td>95% CI for Lower Limit of Agreement</td>
<td>− 16.66 to − 8.71</td>
<td></td>
</tr>
</tbody>
</table>
samples with bedside glucometers designed for capillary blood testing is accurate across a wide range of blood glucose readings. Boyd et al\(^5\) demonstrated that in patients above 12 years of age there was a clinically insignificant difference of 0.33 mmol/L (5.9 mg/dL) between bedside venous glucometer and capillary glucometer readings. Based on these reasons, we decided to compare venous whole blood glucometer readings with laboratory plasma glucose readings.

Bland et al\(^13\) critically appraised the utility of correlation for clinical measurements in their study. Applying the authors’ critical logic to our study, for the data in Figure 1, we obtained a correlation coefficient \(r = 0.94\) (\(P < .0001\)). Correlation is a measure of strength of the relationship and not the agreement between 2 measurements. Also, correlation depends on sample data range, where a wider range would provide greater correlation and vice versa. As blood glucose readings from our study had to be analyzed across the entire data range, it would invariably result in a high correlation. Hence, we found it appropriate to use the Bland–Altman analysis.

Current consensus states 50 mg/dL as a cutoff for neonatal hypoglycemia during the first 48 hours of life. Williams,\(^16\) in his review article, narrated that reagent strip screening detects only approximately 85% of true cases of hypoglycemia and 75% of true cases of normoglycemia among neonates. He recommends that reagent strip tests are unsuitable for diagnosing neonatal hypoglycemia and should not be used.

In our study, although Figure 1 shows that there may be an agreement between the 2 methods, detailed analyses failed to show precise agreement. Figure 2 reveals lack of agreement between the 2 methods, with a difference of up to 40 mg/dL. This information was not evident from Figure 1, which clearly shows a linear relationship between the 2 methods.

The inference from the statistics shown in Table 3 suggests that venous blood glucose estimation using a glucometer may be 33 mg/dL above or 13 mg/dL below the plasma glucose estimations obtained from a standard laboratory. Also, the data from Table 4 demonstrate that if the experiment is repeated with a different set of participants at another time period, with the same analytical technology, on 95% of the occasions, the glucometer readings would be higher than the laboratory blood glucose measurements by 28.72 to 36.66 mg/dL. Similarly, the glucometer readings may be 8.7 to 16.6 mg/dL lower than the laboratory blood glucose readings.

Based on our statistics, an actual laboratory plasma glucose concentration of 40 mg/dL may be analyzed by a glucometer as 73 mg/dL, thus falsely missing a diagnosis of asymptomatic hypoglycemia, considering it unsuitable to screen blood glucose concentrations in the neonatal population. Also, a wider CI for the upper and lower limits of agreement questions the accuracy of a glucometer as a bedside screening tool in detecting neonatal hypoglycemia, particularly at lower glucose readings (< 60 mg/dL).

A framework of practice guidelines issued by the British Association of Perinatal Medicine\(^17\) suggests that most handheld glucometers report results as “plasma glucose equivalents”. Only some devices measure true whole blood (which may be 10%–15% lower than corresponding plasma glucose value) by rupturing the blood cells and measuring combined plasma and cellular glucose. They claim that all current handheld glucometers are prone to inaccuracy, particularly around low blood glucose range up to 40 mg/dL.

**Conclusions**

Overall, our results show that there is lack of agreement between venous whole blood glucose estimation using a glucometer and laboratory plasma glucose estimation. It is important to choose the correct type of glucometer or any other POC blood glucose testing device in the neonatal population. A routine ward-based glucometer not approved for neonatal use may not provide accurate blood glucose readings. Using correlation as the main statistical method to compare these 2 methods may erroneously imply that glucometers may safely be used as a screening tool to monitor neonatal blood glucose concentrations.
The strength of our study is the fact that we have used the correct statistical methodology to compare 2 clinical measurement methods, the Bland–Altman analysis. This not only gives information about the correlation but also about the agreement, degree of agreement, and the precision of the limits of agreement. Interpreting other studies on neonatal blood glucose estimation was difficult because correlation was the main statistical methodology used.

Certain limitations are that our study compared only venous whole blood glucometer readings against the gold standard plasma laboratory blood glucose estimation. Simultaneously comparing the capillary whole blood glucometer readings, using the Food and Drug Administration (FDA)–approved glucometer suited for hospitalized neonates, would have been even more informative. The principal investigator in our study was not blinded to the blood glucose measurements and the clinical information of the neonate.

It is recommended that the ward-based blood gas biosensor be considered the reference standard for measuring blood glucose, based on the accuracy and speed of result availability. Warm, well-perfused, heel-prick capillary samples or a free-flowing venous or arterial sample may be used to analyze bedside blood glucose concentrations.17

If these recommendations are not feasible because of economic reasons and if handheld glucometers are used to screen for low blood glucose, it is advised to use devices complaint with the ISO 15197:2013 standards.17

The FDA has approved highly accurate handheld glucometers such as Nova StatStrip® Hospital Glucose Monitoring (Nova Biomedical, MA, USA) system for use in hospital settings, particularly in neonates.18 These devices appear to be as accurate as the gold standard laboratory analytical methods; they use minimal blood volume and provide instant results. Other anticipated methods currently under research include continuous interstitial glucose monitors and POC devices that measure alternative components such as lactate and ketones.4

References


**Authors’ Affiliations**

Dr Shayan Pavaskar, Senior Pediatric DNB Resident; Dr Siddhuraj Rangesh, Junior Consultant Pediatrician; Dr Dhanam Venkatachalam Suresh, Consultant Pediatrician; Dr Santhanakrishnan Ramakrishnan, Consultant Neonatal Pediatrician, Department of Pediatrics and Neonatology, SKS Hospital & Postgraduate Medical Institute, Salem 636004, Tamil Nadu, India