RESEARCH PAPER

Validity of Two Point-of-Care Glucometers in the Diagnosis of Neonatal Hypoglycemia

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Objective: To estimate validity of two point-of-care glucometers for the diagnosis of neonatal hypoglycemia and to determine the glucometer's cut-off values for which standard laboratory confirmatory test are no longer needed.

Design: Prospective study.

Settings: A tertiary care, university hospital in Bangkok, Thailand.

Participants: The study included 180 blood specimens from 166 high-risk neonates aged between 1-24 hours.

Results: On average, most of the blood glucose read-outs from the Nova StatStrip and SureStep were higher than laboratory plasma glucose throughout the glucose range with mean differences (SD) of 11.2 (8.4) mg/dL and 13.7 (6.8) mg/dL, respectively. Sensitivity of Nova StatStrip and SureStep were 62% and 53.3%, respectively. Specificity and positive predictive value of both glucometers were 100%. Negative predictive values of both glucometers were approximately 85%. The cut-off levels with 100% negative predictive values were 63 mg/dL and 62 mg/dL for Nova StatStrip and SureStep, respectively.

Conclusions: None of the glucometers in this study has sufficient validity to replace laboratory testing in diagnosing hypoglycemia. Confirmatory plasma glucose for diagnosis of hypoglycemia is needed when POC readings are between 39 and 63 mg/dL for Nova StatStrip and between 39 and 62 mg/dL for SureStep.

Key words: *Glucometer, Neonatal hypoglycemia, Point-of-care test.*

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Hypoglycemia in neonates is an emergency condition requiring immediate treatment to prevent serious outcomes [1]. Most of hypoglycemic infants are asymptomatic; hence, screening is needed for high-risk infants. There are many portable glucometers available for point-of-care (POC) testing. However, accuracy testing of these machines is usually done in older children and adults with diabetes mellitus. Operational glucose levels in newborn period run in a lower range than those in diabetic patients [2]. The number of accuracy studies in newborn infants is increasing, with promising results [3-7]. At Siriraj Hospital, POC glucose testing is done using the OneTouch SureStep Hospital Test Strips. Presently, there is no data available on their validity in neonates. The Nova StatStrip has recently been launched, and reported to have demonstrable accuracy with interference corrections [8]. We performed this study to estimate validity of two POC glucometers for the diagnosis of neonatal hypoglycemia and to determine the glucometers' cut-off values for which standard laboratory confirmatory tests are no longer needed.

METHODS

This was a prospective study approved by the Ethics Committee of the Faculty of Medicine, Siriraj Hospital and informed consents were obtained prior to the study. The study was conducted at Siriraj Hospital, which is a tertiary care university hospital. We consecutively recruited high-risk newborn infants aged between 1 and 24 hours from the High-risk nursery and the Intermediate care unit. The patients included small for gestational age, large for gestational age, infant of diabetic mother, and low birth weight infants. Critically ill infants in the NICU were excluded due to possible multiple medication administration. The study was conducted only during office hours, in order to limit the POC glucose testing to that of trained operators, which were two pediatric residents and a technician.

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This was a split-sample design using single venous blood sample from a peripheral vein for both the glucometers and the reference laboratory. Two glucometers were used in the study. The first one was the OneTouch SureStep Hospital Test Strips (LifeScan, Inc., a Johnson & Johnson Company, Milpitas, CA, USA), with a photometric glucose oxidase system. The other was the Nova StatStrip (Nova Biomedical, Waltham, Massachusetts, USA), with a modified glucose oxidase-based amperometric system. The POC glucose testing was done by trained operators immediately after the blood was drawn. Cuvette tube with sodium fluoride as a stabilizer was used for reference laboratory plasma glucose testing. A Roche Modular P 800 (Roche Diagnostics (Thailand) Ltd.) with enzymatic colorimetric assay using hexokinase enzyme was used for measuring reference plasma glucose. The reference laboratory had International Standard Organization (ISO) 15189 certification. The quality control materials were run according to manufacturer's recommendations. The laboratory plasma glucose tests had a bias of 1.75% and imprecision (%CV) of 1.62%. The blood specimens were tested for plasma glucose within one hour after being drawn. The readers of the index tests (POC glucometers) and the reference standard were blinded to the results of each other at the time they read the results from the device. Hypoglycemia was defined as laboratory plasma glucose less than 40 mg/dL [9].

Demographic data, hematocrit level on the same day of blood glucose testing, and time difference between blood sampling and blood test were recorded. Sample size calculation was based on sensitivity and specificity of at least 93% with acceptable error of 7%. According to the incidence of hypoglycemia in high-risk infants at our hospital (30%), we required at least 174 tests.

Statistical analysis: The SPSS 17.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Differences of glucose level between POC glucose testing and laboratory testing were presented as mean difference. Following the standard DIN EN ISO 15197, the differences were presented as percentage within ± 15 mg/dL and percentage within ± 20% of the reference method for plasma glucose <75 mg/dL and ≥75 mg/dL, respectively [10]. The differences were also presented as percentage within ±15 mg/dL of the reference method for plasma glucose <99 mg/dL per National Committee for Clinical Laboratory Standards (NCCLS) recommendation [11] and percentage within ±10% for plasma glucose ranging from 30 to 400 mg/dL [12].

Sensitivity, specificity, positive and negative predictive values (PPV and NPV) for detection of hypoglycemia were determined. ROC curves of both glucometers were plotted. The pre-test probability (prevalence) of hypoglycemia in high-risk neonates at our hospital was 30%. We calculated PPV and NPV from sensitivity and specificity because the incidence of hypoglycemia in this study was 51%, which was higher than our population.

RESULTS

The study period was between December 1, 2008 and May 31, 2009. There were 166 infants (61% males) recruited with 180 sets of blood specimens. Mean (SD) gestational age and birthweight were 37.1 (2.8) weeks and 2,799.6 (837.3) grams, respectively. Mean (SD) hematocrit on the day of the study was 52.0% (7.2%). Range (minimum, maximum) and median age (P25, P75) at blood drawn were 23 (1, 24) and 1.0 (1.0, 1.0) hour, respectively. Approximately 31% and 91% of the blood specimens had glucose measurement performed at the laboratory within 30 minutes and 60 minutes of blood drawn, respectively. Mean (SD) time difference between blood drawn and laboratory plasma glucose measurement was 44.5 (24.7) minute.

Of 180 samples, 92 (51%) were diagnosed with hypoglycemia. Blood glucose levels measured by different methods are shown in ***Web Table* I**. Differences between blood glucose from each POC glucometer and from laboratory plasma glucose were normally distributed, thus 95% of the measurements had differences between mean plus and minus 1.96 SD. On average, most of the blood glucose read out from the Nova StatStrip and SureStep were higher than laboratory plasma glucose throughout the glucose range with mean differences (SD) of 11.2 (8.4) mg/dL and 13.7 (6.8) mg/dL, respectively (***Fig.* 1**). Results presented following the standard DIN EN ISO 15197, NCCLS and ADA are in ***Web Table* II**.

When using POC glucometer to diagnose hypoglycemia, the sensitivity of Nova StatStrip was higher than SureStep but both were less than 70%. The specificities and PPV were 100% for both POC glucometer testings. Negative predictive value of both POC glucometers were less than 90% (***Table* I**).

From ROC curve (not shown), cut-off levels that would yield the best sensitivity and specificity for both POC glucometers were less than 52 mg/dL, with NPV of approximately 97% (***Table* I**). To diagnose blood glucose of less than 45 mg/dL, the sensitivity of both glucometers were 72% and 61%, respectively (***Table* II**). From ROC curve (not shown), cut-off levels that would yield the best sensitivity and specificity for Nova StatStrip and SureStep to diagnose blood glucose of less than 45 mg/dL

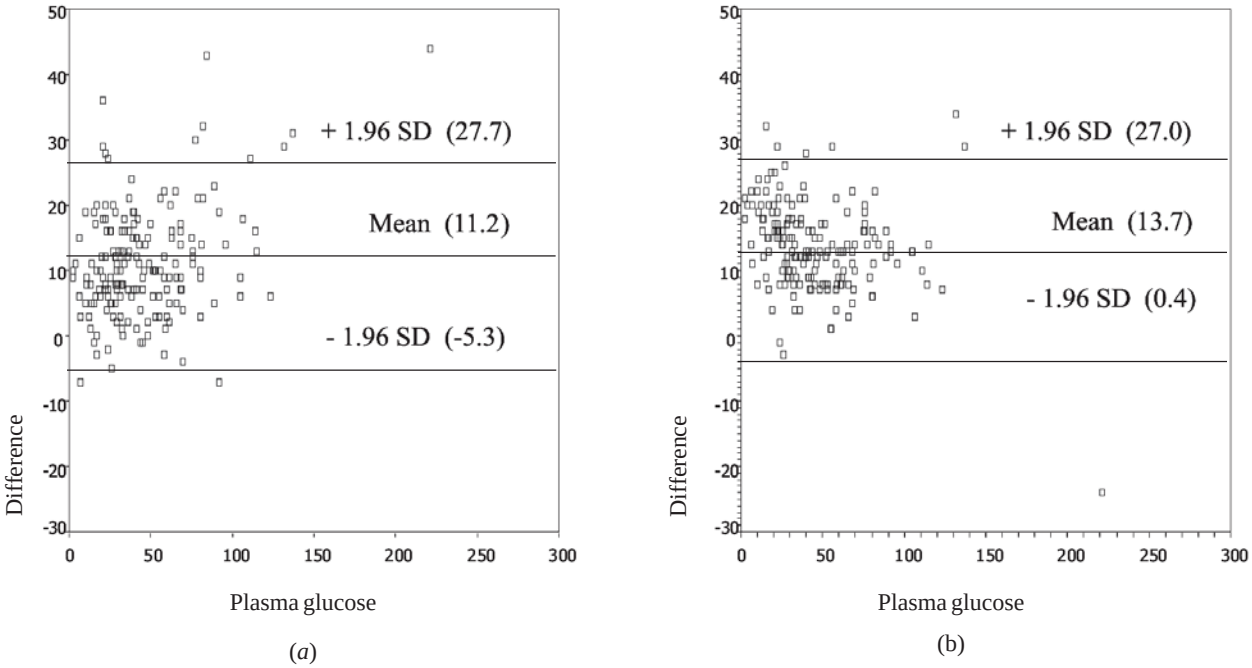

FIG. 1 *Scatter plots of differences between laboratory plasma glucose and (a) Nova StatStrip and (b) SureStep.*

were less than 60 mg/dL and less than 55 mg/dL, respectively (***Table* II**).

DISCUSSION

Our results agree with previous studies which concluded that glucose reagent strips should be considered only as a screening test, not as a diagnostic test, due to their questionable reliability [2,6,7]. Though, the difference of glucose level between both POC glucometers and laboratory is normally distributed, 95% of the differences lie in a wide range (between -5.3 and 27.7 mg/dL for Nova StatStrip and between 0.4 and 27.0 mg/dL for SureStep), and are not acceptable for clinical purposes.

Validity of POC glucometer also depends on pre-analytical processes. Using sample tubes containing sodium fluoride (NaF) has been recommended in order to minimize ex-vivo glycolysis [13, 14]. Such a method was adopted in our study. Though fluoride is the best available preservative for blood glucose measurement, the antiglycolytic action may delay for up to 4 hours [15]. The mean plasma glucose concentration could decrease by 4.3% at 1 hour and by 4.6% at 2 hours in blood kept in tube containing NaF [15,16]. Our results are not applicable for different glucose preservative used or different glucose measurement process.

Mann, *et al*. [17] found that error rates for low hematocrit between 25% and 34% ranged from 16.4% to 18.4%. Hematocrit of the infants recruited in our study ranges from 27% to 65% which is within the operational range of accuracy (25-65%) for both POC glucometers. There were only three specimens with hematocrit less than 34% in our study. Hence, glucometer error

TABLE I SENSITIVITY, SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR DETECTING DIFFERENT PLASMA GLUCOSE LEVELS*

Cut-off level of plasma glucose (mg/dL)	*Nova StatStrip*				*SureStep*			
	Sn	*Sp*	*PPV*†	*NPV*†	*Sn*	*Sp*	*PPV*†	*NPV*†
< 40	62.0	100	100	85.7	53.3	100	100	83.4
< 52	92.4	90.9	82	96.6	93.5	95.5	89.3	96.8
Nova StatStrip<63	100	65.9	55.7	100	–	–	–	–
SureStep< 62	–	–	–	–	100	70.5	59.3	100

** Data are presented as percentage; † Positive predictive value (PPV) and negative predictive value (NPV) were calculated from sensitivity (Sn), specificity (Sp) and 30% incidence of hypoglycemia; Hypoglycemia: plasma glucose <40 mg/dL.*

WHAT IS ALREADY KNOWN?

- Point-of-care glucometer should be considered only as a screening test, not as a diagnostic test in diagnosing neonatal hypoglycemia.

WHAT THIS PAPER ADDS?

- Each individual glucometer needs its own validity study and operational cut-off values for the decision to send laboratory plasma glucose for confirmation.

secondary to low hematocrit should not be a major problem in this study.

Based on the standard DIN EN ISO 15197: at blood glucose concentrations <75 mg/dL, ≥95% of the blood glucose results should fall within ±15 mg/dL of the reference method and at blood glucose concentrations ≥75 mg/dL, ≥95% of the blood glucose results should fall within ±20% [10]. Nova StatStrip was more accurate than SureStep at glucose level <75 mg/dL, although neither of them met the minimum requirement of DIN EN ISO 15197.

NCCLS recommended that discrepancies in blood glucose measurements should be less than 15 mg/dL when actual glucose concentrations were less than 99 mg/dL. Subsequently, 75.3% of Nova StatStrip fulfilled such standard, compared to 61.8% of SureStep [11]. Moreover, using the ADA standard, none of the POC glucometers tested demonstrated satisfactory accuracy. Nova StatStrip and SureStep had only 22.6% and 9.6% of their tests achieved a total error of less than 10% at glucose concentration ranging from 30 to 400 mg/dL [12].

In clinical practice, sending for confirmation plasma glucose in all cases would add to the expense, considering how often glucose levels are assessed in newborns. Using POC glucometer alone, we may miss 38% and 47% of hypoglycemia (POC glucose level <40 mg/dL) by Nova StatStrip and SureStep, respectively. With ROC analysis, the cut-off level with the best sensitivity and specificity of both POC glucometers are 52 mg/dL. At this cut-off level, we will still miss approximately 6-8% of hypoglycemia. For POC glucose reading of less than 40 mg/dL, we could be confident of the diagnosis of hypoglycemia without sending confirmatory plasma glucose. Thus, confirmatory plasma glucose for diagnosis of hypoglycemia would be required when POC glucose readings are between 39 and 63 mg/dL for Nova StatStrip and between 39 and 62 mg/dL for SureStep.

Practically, different blood glucose levels are used as the "operational threshold" and the "therapeutic objective" [2]. Mostly accepted therapeutic goal is to keep blood glucose higher than 45 mg/dL [2,13]. For this purpose of defining blood glucose less than 45 mg/dL, the cut-off levels that confirmatory blood glucose is not necessary would be different. Confirmatory plasma glucose for diagnosis of blood glucose less than 45 mg/dL is needed when POC glucose readings are between 44 and 63 mg/dL for Nova StatStrip and between 44 and 69 mg/dL for SureStep.

The clinical application of our study is limited to clinically stable infants without medications that might interfere with glucose measurement. The participants in this study were infants aged between 1 and 24 hours. If the POC glucose measurement is done in older infants,

TABLE II SENSITIVITY, SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR DETECTING DIFFERENT PLASMA GLUCOSE LEVELS* (FOR THERAPEUTIC GOAL OF PLASMA GLUCOSE AT 45 MG/DL).

Cut-off level of plasma glucose (mg/dL)	*Nova StatStrip*				*SureStep*			
	Sn	*Sp*	*PPV*†	*NPV*†	*Sn*	*Sp*	*PPV*†	*NPV*†
<45	71.7	98.6	95.8	89.1	61.3	100	100	85.8
< 60	98.1	86.5	75.7	99.1	–	–	–	–
< 55	–	–	–	–	92.5	98.6	96.7	96.8
Nova StatStrip <63	100	78.4	66.5	100	–	–	–	–
SureStep <69	–	–	–	–	100	71.6	60.2	100

** Data are presented as percentage; † Positive predictive value (PPV) and negative predictive value (NPV) were calculated from sensitivity (Sn), specificity (Sp) and 30% incidence of hypoglycemia.*

the clinicians must be aware of the possibility of hyperbilirubinemia interfering with glucose measurement.

Both POC glucometers in this study did not meet the minimum requirement of DIN EN ISO 15197, NCCLS, and ADA. A degree of caution should be exercised in the interpretation of POC glucose measurements as they may not possess sufficient accuracy to replace laboratory plasma glucose results. Individual devices may need their own operational cut-off values for sending plasma glucose for confirmation.

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