RESEARCH ARTICLE

Accuracy of Using a Point-of-Care Glucometer for Cerebrospinal Fluid Glucose Screening in Resource-Limited Countries

Ratchada Kitsommart, MD,[a] Thananjit Wongsinin, MD,[a,b] Uraporn Swasee, BNS,[a] Bosco Paes, FRCPC[c]

ABSTRACT

OBJECTIVES: To explore the accuracy of using a point-of-care (POC) glucometer for cerebrospinal fluid (CSF) glucose screening.

METHODS: A cross-sectional study was conducted. A glucose analysis of CSF samples collected from infants <90 days with suspected meningitis was paired between tests by using a POC glucometer (POC-CSF glucose) and a laboratory glucose analysis (laboratory-CSF glucose). Accuracy and limits of agreement were compared, as well as the glucometer performance to detect a laboratory-CSF glucose level <45 and 60 mg/dL.

RESULTS: Seventy-three CSF samples were analyzed. Subjects' mean gestational age was 32.2 (SD 4.0) weeks, the mean weight was 1947.7 (SD 814.5) g, and the median age was 8 (interquartile range: 2 to 19.5) days. POC-CSF glucose levels ranged from 26 to 126 mg/dL. The mean (±1.96 SD) difference between POC-CSF and laboratory-CSF glucose levels was −1.6 (interquartile range: −12.6 to 9.4) mg/dL. A POC-CSF glucose level <45 mg/dL has a sensitivity and negative predictive value (NPV) to detect a laboratory-CSF glucose level <45 mg/dL of 82% and 94%, respectively. For a laboratory-CSF glucose level <60 mg/dL, a POC glucose level <60 mg/dL provides a sensitivity and NPV of 96% and 90%, respectively, whereas sensitivity and NPV reach 100% at a POC glucose level <70 mg/dL.

CONCLUSIONS: A POC glucometer for CSF glucose can detect a potential abnormal glucose level with an appropriate cutoff level. This may facilitate rapid decisions for empirical antibiotics in suspected meningitis, pending laboratory results in limited-resource settings, but requires robust validation in future studies before implementation.

[a]Division of Neonatology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [b]Department of Pediatrics, Bhumibol Hospital, Bangkok, Thailand; and [c]Division of Neonatology, Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

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Address correspondence to Ratchada Kitsommart, MD, Division of Neonatology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Rd, Bangkok Noi, Bangkok 10700, Thailand. E-mail: rkitsommart@hotmail.com

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The incidence of neonatal meningitis in developing countries is estimated to range from 0.8 per 1000 live births in the first week of life to 6.1 per 1000 live births,[1] but the true global incidence remains undetermined.[2] Early signs and symptoms of neonatal meningitis are subtle and nonspecific, leading inevitably to immediate initiation of antibiotics in critically ill infants to prevent mortality.[3] For those infants who present clinically with sepsis, further investigations, including blood cultures and cultures of fluids from other sterile sites, are routinely conducted to find causative organisms.

Cerebrospinal fluid (CSF) examination is customarily performed as part of a sepsis workup panel because of the inability to accurately interpret signs of central nervous system (CNS) infection in neonates and young infants <3 months of age.[4] A basic CSF analysis is focused on white blood cell counts and differential, biochemical tests, and cultures to determine the presence of infection. Lumbar puncture in neonates is somewhat challenging because of the relatively small spinal cavity and the inability of patients to cooperate during the procedure, which leads to unsuccessful CSF collection or traumatic taps. The incidence of a traumatic lumbar puncture in neonates has been reported to be as high as 48%,[5] making it difficult to interpret white blood cell counts and respective differentials in the diagnosis of CNS infection.[6] Therefore, reliance on only CSF white blood cell counts for a diagnosis of meningitis is not ideal. Low CSF glucose levels (<50%–66% of serum values) and a low CSF-to-serum glucose ratio (<0.4) enhances the likelihood of having a bacterial CNS infection.[7] However, CSF glucose levels in neonates with bacterial meningitis are highly variable (range: 0 to 199 mg/dL), and there is no single value to predict bacterial meningitis.[8] Moreover, laboratory-CSF glucose analyses are not readily available in many low-resource settings, particularly in rural areas.

Bacterial meningitis in neonates is associated with significant morbidity and mortality. Clinical assessment alone is not discriminatory for the presence of severe infections in newborns, nor does it reliably exclude neonatal meningitis.[9] Therefore, decisions regarding the commencement of antibiotics are sometimes made empirically, especially when laboratory results are not readily available in resource-limited settings, which leads to overuse.

With advancements in point-of care (POC) testing, adoption of such technology into clinical practice has become routine, particularly for glucose analysis. POC glucometers are widely used, with acceptable performance in neonatal care. In a previous study, we reported that a POC glucometer had a sensitivity of 59% to 95% and a specificity of 40% to 96% for screening of neonatal hypoglycemia.[10] CSF and plasma are comparable in chemical properties, which lends effectively to a POC assessment of CSF glucose and possible early determination of neonates who may have bacterial versus aseptic meningitis.[7]

Our primary objective for the study was to explore the accuracy of using a quantitative POC glucometer for CSF glucose screening. Our secondary objectives included performance of the POC glucose meter to detect a potential low CSF glucose level, namely a laboratory-CSF glucose level <45 and 60 mg/dL, which are the median and low-normal (95th percentile) levels of the CSF glucose reference range in neonates.[11]

METHODS

This is a prospective cross-sectional study conducted in the intermediate care nursery in a developing country that provides perinatal care for normal and high-risk pregnancies and has ~8000 deliveries annually. The study protocol was approved by the institutional research ethics board. Collected data were coded and de-identified for confidentiality as stipulated by the hospital ethics committee.

CSF specimens are examined for group B *Streptococcus*, *Salmonella* group B, *Streptococcus pneumoniae*, and *Escherechia coli* bacteria in our institution.[12] Viral cultures for enterovirus, herpes simplex virus (HSV), and other potential congenital viruses are performed on CSF specimens when clinically indicated.

The incidence rate of group B *Streptococcus* septicemia in our hospital is 0.2 per 1000 live births.[13] Obstetric practice aligns closely with the American College of Obstetrics and Gynecology guidelines, including intrapartum antibiotic prophylaxis for group B streptococcal disease.[14,15] Infants with signs or symptoms of possible sepsis but without respiratory failure or intractable hemodynamic instability are admitted to the intermediate care nursery. The majority of the population comprises preterm infants with or without noninvasive respiratory support and those who have significant metabolic problems that require close monitoring or intervention (eg, persistent hypoglycemia necessitating central venous line access and investigation of conjugated hyperbilirubinemia) or possible infections. Our approach to infants at risk for early-onset sepsis is based on the American Academy of Pediatrics guideline.[16]

Infants at risk for meningitis have a lumbar puncture performed as part of a septic workup panel if they appear clinically unwell (persistent alterations in cardiorespiratory status or other nonspecific symptoms such as unexplained temperature, glucose instability [either hypoglycemia or hyperglycemia], or feeding intolerance) either with or without specific abnormal neurologic signs. Infants were included if they were <90 days old and if responsible physicians decided to perform a spinal tap for CSF analysis because of concern for infection. Samples were excluded if there was an insufficient CSF volume for routine biochemical analysis. Traumatic samples were not an exclusion criterion.

Once an appropriate CSF sample was procured, a portion was drawn into a hematocrit capillary tube (vol 110 μL), and a drop was placed on a glucose strip before analysis with a glucometer. The process of CSF collection and POC glucose testing was completed within ~5 minutes. The CSF sample was concurrently sent to the laboratory in 3 preservative-free collection tubes for biochemical analysis, cell counts and differential, and a routine bacterial culture. Generally, all test results, except for

the bacterial culture, are reported within a few hours after CSF collection. In our setting, most infants who have lumbar punctures performed as a part of a septic workup receive immediate antibiotic coverage for possible CNS infection if there was clinical concern.

A single glucometer was used to measure glucose levels by using the modified glucose oxidase–based amperometric system (OneTouch StatStrip Glucose Test Strips; LifeScan Europe, Paris, France). For maintenance and quality control of the device and strips, we followed the manufacture instructions and the International Standards Organization (ISO) 22870 accreditation guideline. The instrument was calibrated before each test. Laboratory-CSF glucose levels were measured by using the hexokinase method (COBAS INTEGRA Glucose HK Gen. 3 test; Roche Diagnostics, Indianapolis, IN). For the purposes of the study, CSF glucose was analyzed within 30 minutes after collection.

The following diagnostic criteria were employed. A red blood cell count >500 cells per mm^3 on the laboratory analysis was considered a traumatic tap.[17] According to a recent large study by Thomson et al,[11] the median and 95th percentile levels of CSF glucose concentration in infants <28 days old were 45 and 60 mg/dL, respectively. Therefore, these 2 values were used to assess the performance of the POC-CSF glucose test in the detection of the 2 respective laboratory-CSF glucose levels.

Because we expected the accuracy of the CSF glucose analysis to be similar to blood testing,[7] we calculated a sample size on the basis of our previous study of blood glucose analysis using the same POC glucometer device.[10] By using an estimated mean difference of 4 mg/dL and SD of 8.36 mg/dL with a power of 90% and $\alpha = .01$, a sample size of 65 subjects was needed. We added a 10% compensation for possible dropouts, which resulted in a total sample size of 72 patients.

Demographic data are presented as mean and SD or median and interquartile range (IQR), when appropriate. Agreement of CSF glucose analysis by POC glucometer and laboratory analysis was explored by using Pearson's correlation coefficient and demonstrated by a scatter plot. The accuracy of the CSF glucose analysis by using the POC glucometer (POC-CSF glucose) was compared to standard laboratory-CSF glucose levels by using the mean difference ± 1.96 SD. Bias and error were also evaluated separately between traumatic CSF taps (red blood cell count >500 cells per mm^3) and nontraumatic samples.[18,19] We evaluated the effect of red blood cell counts in traumatic specimens on the accuracy of the test by using Pearson's correlation coefficient to determine the difference between the 2 glucose tests and the red blood cell count. General performance of the POC-CSF testing was explored by using plasma POC glucometer standardizations, the ISO 15197, the Clinical Laboratory Standards Institute (CLSI), and the US Food and Drug Administration (FDA) guidance.[20–23]

We analyzed the performance of the POC-CSF glucose test to detect 2 respective laboratory-CSF glucose levels of 45 and 60 mg/dL using sensitivity, specificity, positive predictive value, and negative predictive value (NPV). All statistical analyses were performed by using SPSS version 18.0 (SPSS Inc, Chicago, IL). Differences were considered statistically significant at $P < .05$.

RESULTS

The study was conducted between April 1, 2017, and October 30, 2018. Seventy-eight CSF samples were collected; 5 patients' samples were excluded because of insufficient volume for the chemistry analysis. Therefore, 73 CSF samples were paired for POC-CSF glucose and laboratory-CSF glucose comparisons. The demographic characteristics of the study infants and CSF samples are shown in Table 1. Fifty-seven samples (78.1%) were collected from preterm infants (<37 weeks' gestation) with a mean gestational age of 32.2 (SD 4.0) weeks. Sixty samples (82.2%) were collected from infants with very low birth weight (<1500 g). The median postnatal age was 8 (IQR: 2 to 19.5) days, and 64 (88%) infants were <28 days. The mean body weight of the cohort on the day of the lumbar puncture procedure was 1947.7 (SD 814.5) g. The number of samples collected within 3 days of life was 22 (30%), the number collected from 4 to 14 days of life was 26 (36%), and the number collected at >14 days of life was 25 (34.2%). The major indication for lumbar puncture was infants who were considered to be septic with possible meningitis (61 infants; 84%) with no or subtle neurologic signs, whereas 12 infants (16%) were clinically considered to have sepsis with abnormal neurologic signs. Traumatic taps (red blood cells >500 cells per mm^3) occurred in 30 samples (41%). Among traumatic samples, the median red blood cell count was 5775 (IQR: 3506 to 16 637.5; range: 970 to 58 000 cells per mm^3). The median laboratory-determined white blood cell count was 6 cells per mm^3 (IQR: 2 to 15 cells per mm^3; range: 1 to 105 cells per mm^3). All CSF cultures were negative for pathogenic bacteria. One sample was positive for HSV, and no bacterial pathogens were detected.

The mean POC-CSF glucose and laboratory-CSF glucose level was 53.5 (SD 16.2) and 55.1 (SD 16.4) mg/dL, respectively. Figure 1 reveals the scatter plot of POC-CSF glucose and laboratory-CSF glucose levels. The correlation coefficient between the tests was 0.9, with an r^2 of 0.9 ($P < .001$). Figure 2 reveals differences between the POC-CSF glucose and laboratory-CSF glucose levels versus the laboratory-CSF glucose level, analogous to the traditional Bland-Altman plots. Overall bias in glucose estimation was −1.6 mg/dL with an error (±1.96 SD; range: −12.6 to 9.4 mg/dL). Such bias (±1.96 SD) in nontraumatic samples (red blood cell count <500 cells per mm^3) was −2.2 (range: −13.3 to 8.9) mg/dL, which decreased to −0.7 (range: −11.4 to 10.0) mg/dL in traumatic (red blood cell count >500 cells per mm^3) samples. It is important to note that the x-axis in the respective plots denotes laboratory-CSF glucose (considered gold standard) and not the average value of POC and laboratory glucose. However, a subanalysis in which average values were used revealed similar results. The correlation coefficient of the difference between the laboratory and POC-CSF glucose levels and red blood cell counts was 0.4 ($P = .53$).

TABLE 1 Demographic Characteristics of Infants and Laboratory-CSF Analysis ($N = 73$)

	Results
Infants characteristics	
Gestational age, wk, mean (SD)	32.2 (4.0)
Male sex, *n* (%)	44 (60)
Body wt, g, mean (SD)	1947.7 (814.5)
Postnatal age, d, median (IQR)	8 (2 to 19.5)
CSF characteristics	
Red blood cell count, cells per mm^3, median (IQR)	242 (10 to 4775)
White blood cell count, cells per mm^3, median (IQR)	6 (2 to 15)
Glucose level, mg/dL, mean (SD)	55.1 (16.4)
Protein level, mg/dL, mean (SD)	125.4 (40.2)

Laboratory-CSF glucose levels ranged from 27 to 137 mg/dL, whereas POC-CSF glucose levels ranged from 26 to 126 mg/dL. Table 2 reveals the general performance of POC-CSF glucose testing using standardizations of the plasma POC glucometer. The test error of all samples was within acceptable limits on the basis of all 3 standardizations.

Table 3 reveals the performance of POC-CSF glucose testing to detect laboratory-CSF glucose on the basis of the stipulated levels. To detect a laboratory-CSF glucose level <45 mg/dL, using a POC-CSF glucose cutoff level of 45 mg/dL provides a sensitivity of 82% with a NPV of 94%. The performance of both increases to 100% at a cutoff level of 50 mg/dL. For a laboratory-CSF glucose level <60 mg/dL, a POC-CSF glucose cutoff level at 60 mg/dL provides a sensitivity and NPV of 96% and 90%, respectively. Both sensitivity and NPV reach 100% at a cutoff glucose level of 70 mg/dL.

DISCUSSION

Neonatal sepsis remains an unresolved issue worldwide despite zealous attempts to diagnose the condition and implement prevention strategies. Because the majority of neonates with concurrent CNS infection have minimal neurologic findings,[24] a CSF examination is accepted as part of the routine workup, especially for late-onset neonatal sepsis.[25] In some institutions, especially in resource-limited settings in our country, the lengthy turnaround time for diagnostic test results is a major impediment to early commencement of antibiotics that may result in substantial morbidity and neurologic sequelae, especially in the presence of meningitis. On the other hand, empirical antibiotics that provide coverage for a broad spectrum of CNS bacterial pathogens leads to overuse. As a consequence, antibiotic resistance has been reported in both community and hospital settings in low- and middle-income countries.[26] Therefore, the World Health Organization has made antimicrobial stewardship a primary initiative to guide proper use of antibiotics in resource-limited health care facilities worldwide despite the numerous challenges posed by the adoption of such intervention programs.

CSF and plasma have common chemical properties. Authors of a few older studies have reported the potential utility of POC-CSF glucose testing combined with leukocyte counts for early detection of meningitis, but performances were suboptimal for clinical application.[27–29] Modern glucometers employ enzymatic assays with up-to-date sampling techniques to avoid the pitfalls encountered in older POC devices, which has significantly improved performance even in neonatal care. We postulated that a modern POC glucometer for CSF glucose analysis would yield an equivalent performance for serum testing and that negative POC test results may allow one to hold off on administering empirical antibiotics and instead choose a "watch and wait" approach while awaiting confirmatory bacterial testing.

Our study reveals potential use of the POC glucometer for CSF glucose analysis. The POC-CSF glucose test revealed high agreement with the routine laboratory-CSF glucose test ($r^2 = 0.9$; $P < .001$). The overall accuracy with a negative bias of 1.6 mg/dL is comparable with our previously reported

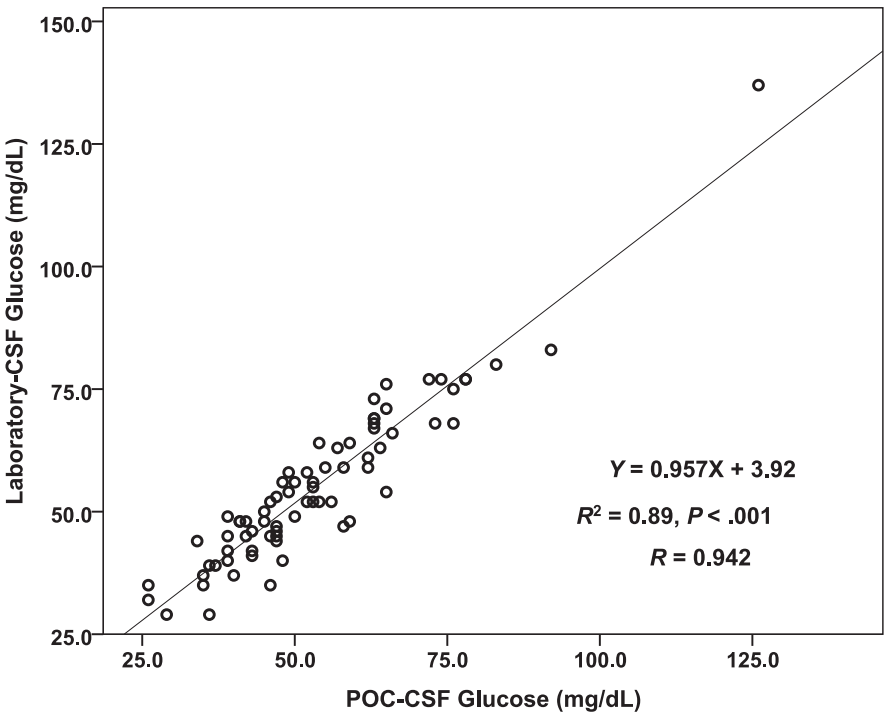

FIGURE 1 Scatter plot between laboratory-CSF glucose and POC-CSF glucose ($N = 73$).

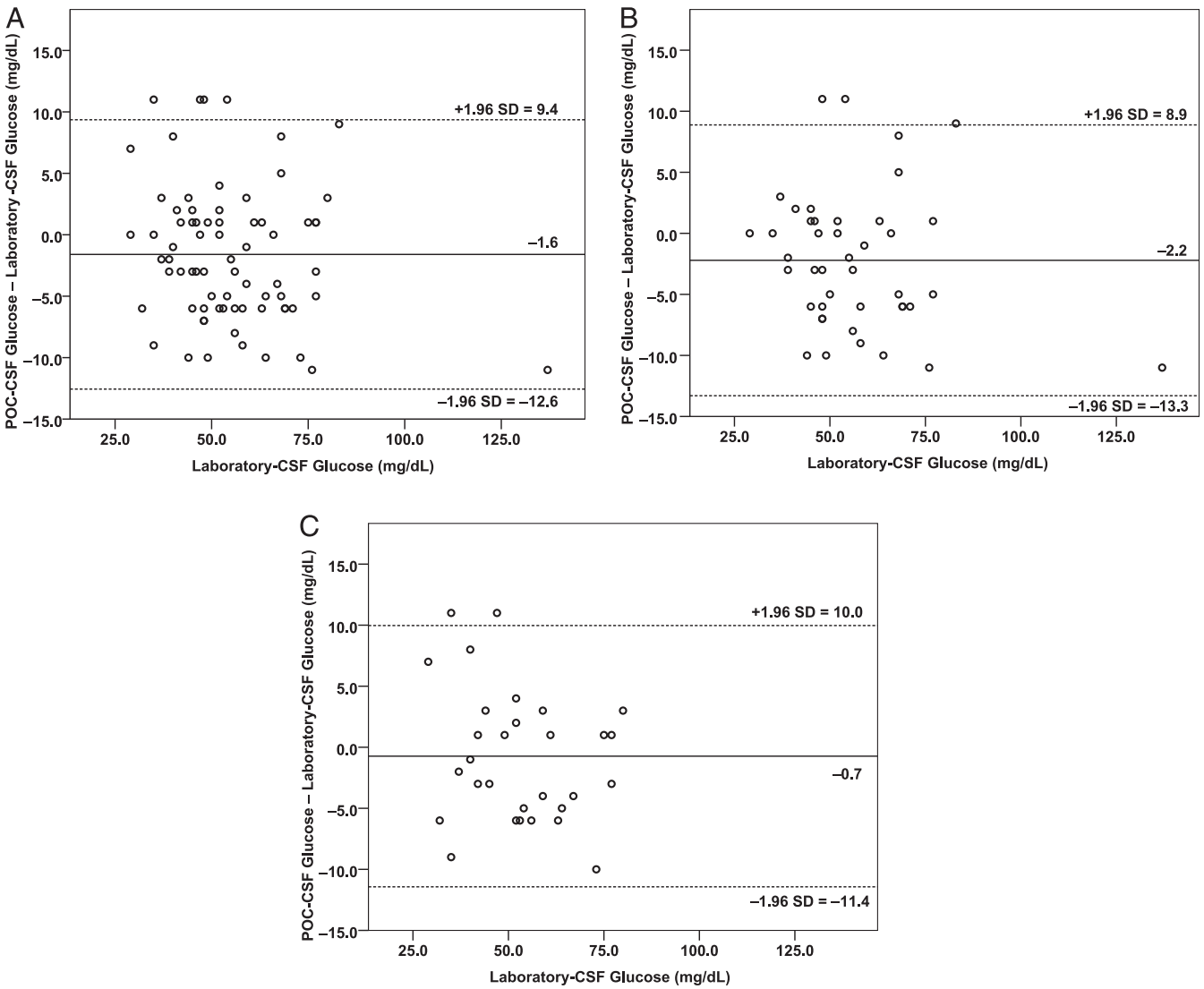

FIGURE 2 Differences between laboratory-CSF glucose and POC-CSF glucose ($N = 73$). A, All CSF samples ($N = 73$). B, Nontraumatic CSF samples (red blood cell count <500 cells per mm^3) ($n = 30$). C, Traumatic CSF samples (red blood cell count >500 cells per mm^3) ($n = 43$).

bias of 3.8 mg/dL in serum POC glucose analysis by using the same POC glucometer. The range of agreement (±1.96 SD) was also comparable between this study and our previous study of plasma POC glucose.[10] Using the same guideline of standard performance of blood POC glucose analysis, the performance error fell remarkably within the acceptable levels according to ISO 15197, CLSI, and FDA standardizations.

Although we thought that the validity of POC testing for CSF glucose may have been altered by traumatic taps because of the impact of red blood cell glycolysis on CSF glucose levels,[30] we did not find significant differences either in bias or the range of error between traumatic versus nontraumatic taps. In our study, 41% of the CSF specimens were traumatic taps, which is in agreement with the 47.7% rate reported by Matettore and Kollmann[5] and other investigators.[6] However, the definition of a traumatic tap varies on the basis of the CSF red blood cell count, ranging from 400 to 10 000 cells per mm^3.[17,31,32] Our selected criterion of >500 cells per mm^3 might be too small to detect an effect of red blood cell contamination, yet the results remain useful in real-life situations when CSF red blood cell counts are relatively low. Moreover, the red blood cell count did not compromise the accuracy of the POC-CSF glucose test.

This study was not conducted to evaluate clinical symptomatology in association with POC-CSF glucose because only 16% of the infants had neurologic signs, and none of the CSF samples were positive for bacterial ($N = 73$) pathogens. One CSF sample was positive for HSV and was concordant with the maternal history of acquired herpes.

We chose laboratory-CSF reference glucose levels ranging from median to high-normal (95th percentile) levels to represent

TABLE 2 Accuracy of POC-CSF Glucose Analysis Relative to Current Standards for the POC Glucose Meter

POC Glucometer Standard	Acceptable Error			Our Study, %
	Reference Glucose Level, mg/dL	Error	Percentage of the Results, %	
ISO 15197 (2013)	<75	Within ±15 mg/dL	95	100
	>75	Within ±20%	95	100
CLSI (2013)	<100	Within ±12 mg/dL	95	100
	>100	Within ±12.5%	95	100
	<75	>15 mg/dL	<2	0
	≥75	>20%	<2	0
FDA (2016)	<75	Within ±12 mg/dL	95	100
	<75	Within ±15 mg/dL	98	100
	≥75	Within ±12%	95	100
	≥75	Within ±15%	98	100

operational thresholds. In our study, a POC-CSF glucose level ≤70 mg/dL in the majority yielded laboratory-CSF glucose values in the <95th percentile of the normal reference (60 mg/dL). When we selected a POC-CSF glucose level <70 mg/dL alone as being abnormal, 10 (14%) neonates could wait for laboratory confirmation of laboratory glucose sensitivity.

Because the clinical diagnosis of meningitis and timely laboratory interpretation pose challenges, authors of several studies have reported on the performance of POC white cell blood counts and glucose on CSF samples to facilitate a rapid diagnosis of bacterial infection.[33,34] However, in the respective studies, urine reagent strips were used, which provide a semiquantitative analysis with relatively wide ranges of both leukocyte counts and glucose levels. Moreover, the microscopic and chemical properties of CSF in young infants, especially in neonates aged <28 days, are different from those in older children and adults. The normal reference values of white blood cell counts are higher and glucose levels are lower than infants beyond the neonatal period.[11] Therefore, urine reagent strips may not be able to discriminate abnormal CSF levels in the neonatal population. In a recent study, Mazumder et al[34] chose a cutoff CSF glucose level of 50 mg/dL, which was likely due to the semiqualitative technique employed. The investigators reported a sensitivity and NPV for glucose of 48.2% and 82.6%, respectively. To our knowledge, this is the first study in which the accuracy of using a modern POC glucometer for CSF glucose screening in neonates is evaluated in a systematic way. The results represent a quantitative assessment compared to urine reagent strips and can be performed at the bedside.

TABLE 3 Performance of POC-CSF Glucose Testing by Using the POC Glucometer to Predict Low CSF Glucose Levels (<45 or <60 mg/dL) ($N = 73$)

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
CSF glucose level <45 mg/dL					
POC-CSF glucose cutoff, mg/dL					
45	82	88	67	94	86
50	100	68	49	100	75
CSF glucose level <60 mg/dL					
POC-CSF glucose cutoff, mg/dL					
60	96	87	94	90	93
65	98	57	83	93	85
70	100	43	80	100	82

PPV, positive predictive value.

There are some limitations that bear consideration. We were unable to elucidate the performance of the test for culture-proven meningitis because no pathogens were detected in the CSF study samples. Garges et al[8] reported that the incidence of meningitis among late-preterm and term infants was 1% when a lumbar puncture was performed as part of the sepsis workup. Therefore, the selection of an operational CSF glucose level at median or 95th percentile levels would be a reasonable surrogate regarding acute intervention with antibiotics. However, additional studies are necessary to clearly determine if a POC-CSF glucose result should or would change practice, and more data are needed to draw firm conclusions about its place in the diagnostic and treatment algorithms for suspected meningitis.

In our study, all CSF samples were not routinely tested for viruses. Therefore, high red blood cell counts could be a marker of HSV meningitis. However, none of the infants received antiviral agents, and none deteriorated clinically with signs of herpetic skin, eye and mouth, disseminated, or CNS disease. The majority of the samples in this study were collected from preterm infants with subtle signs of infection, such as temperature instability or feeding intolerance, in whom a lumbar puncture was performed as part of a septic workup for sepsis. Hence, clinical assessment alone in this population is of limited value in the prediction of CNS involvement.[25,35]

CONCLUSIONS

Laboratory analysis of CSF glucose, white blood cell counts, and microbiology tests remain the gold standard for diagnosis of meningitis. However, the reliability of a POC glucometer when compared with laboratory analysis suggests that it may be valuable in the decision to administer empirical treatment of CNS infections in resource-limited settings if confirmed in future studies. Decisions regarding urgent antibiotic therapy for suspected CNS infection should be based on the severity of illness and, in some life-threatening scenarios, may override both POC and laboratory test results. To support antibiotic stewardship and avoid resistance, antibiotics should be rapidly discontinued if the infant is considered stable and laboratory test results for presumed meningitis are negative.

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