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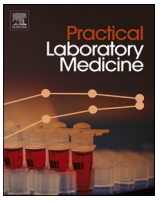

Added value of a connected glucose meter for glycorrhachia assessment

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ABSTRACT

Objectives: The aim of this study was to demonstrate the performance and added value of rapid glucose determination in cerebrospinal fluid using a connected glucometer.
Design and Methods: Intra-assay and inter-assay accuracies were calculated using residual clinical samples. Accuracies were measured by comparing the results obtained with the glucometer to those from the central laboratory on a large routine chemistry platform.
Results: The intra-assay coefficients of variation were between 6.1% and 6.2% for low values (18 mg/dL) and between 5.6% and 6.8% for high values (58 mg/dL). The inter-assay coefficients of variation were between 9.4% and 16.3% for the low values (18 mg/dL) and between 5.7% and 8.7% for the high values (pool; ±75 mg/dL). The regression equation by comparison to the central laboratory was $y = 4.08 + 0.82\ x$, with a coefficient of determination (r^2) of 0.95.
Conclusions: The measurement of glycorrhachia with a connected glucometer before the analysis in the central laboratory allows a rapid orientation in the deferential diagnosis of a meningitis of viral vs bacterial origin. The response time is fast (6 s) and requires only a small amount of fluid (1.2 μL), which is important in infants, especially since lumbar puncture is an integral part of the investigation of the origin of a fever in this population.

1. Introduction

Bacterial meningitis has a significant prevalence with overrepresentation in children, mainly under 2 years. It is a severe clinical challenge in diagnosis and treatment, while symptoms are often unspecific but clinical consequences of the disease can be severe. Therefore, diagnosis as early as possible is mandatory. A decreased concentration of glucose in cerebrospinal fluid (CSF) is a strong indicator for bacterial meningitis. Glucose testing in CSF is usually performed in the central laboratory on clinical chemistry analyzers after sample centrifugation. This requires a significant amount of sample volume exceeding 100 μL. In addition, turn-around-time to the availability of the result is extended, which can significantly delay time to therapy start.

Nowadays point-of-care (POC) devices are available on the market with excellent performance features regarding reference correlation, measuring ranges and precision. They require a minimal sample volume (1.2 μL) and provide results in seconds.

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The objective of this study was to evaluate a handle blood glucose monitoring system (BGMS), StatStrip GLU/KET meter (Nova Biomedical, Waltham, MA), for its performance in CSF compared to the reference lab analyzer. We tested intra-assay and inter-assay variation, strip-lot differences and correlated the method to the lab reference analyzer (cobas 8000, Roche Diagnostics, Mannheim, DE), using the LEAP checklist wherever applicable [1].

2. Materials and methods

2.1. Study settings

The study took place in a 550-bed public hospital group distributed on four sites, including a daytime polyclinic.

2.2. Evaluation of the analytical performances of Nova Biomedical StatStrip GLU/KET

Evaluation of the precision was performed in accordance with the Clinical and Laboratory Standards Institute (CLSI) EP 15-A3 document [2]. The acceptance criteria were defined according to the performance of reported by the manufacturer.

2.2.1. Intra-assay precision

The intra-assay assessment of the precision was performed using two CSF samples from the routine. The high glucose value sample issued from a woman aged 42 suffering from dysesthesia of the lower limb due to multiple sclerosis. The low glucose value sample originated from a 50-year-old woman having an epidural abscess due to methicillin-resistant *Staphylococcus aureus*. The target values measured using a routine biochemistry platform cobas 8000 were 58 mg/dL and 18 mg/dL respectively.

2.2.2. Inter-assay precision (in-between-days)

The low-value sample was the same as for the intra-assay precision. Because of limited volumes, the high value sample was obtained by pooling of 3 different samples. The intra-assay precision was assessed by 20 measurements of each level using two different strip lots. For the inter-assay evaluation, we performed glucose measurements twice daily of each level using two different strip lots during 20 consecutive days.

2.2.3. Accuracy and laboratory correlation

The method accuracy was evaluated by testing consecutive clinical CSF samples subsequent to the glucose determination on the routine biochemistry module of the central laboratory between March 4 and September 18, 2021. Analysis was performed in duplicate using the two same strip lots as for the precision evaluation. We also evaluated for the biological parameters of the patients (white blood cells count, red blood cells count, protein and lactate), as well as demographics, indication of CSF puncture and the requesting site. Blood cell counts in CSF above 1600/μL were reported as "1600/μL".

2.2.4. Statistical analysis

Statistical analysis was performed using MedCalc version 10.4.0.0 (MedCalc Software, Ostend, Belgium). Paired samples were compared with a Wilcoxon test. A P-value <0.05 was considered statistically significant.

Table 1
– Evaluation of the precision intra-assay (A) and inter-assay (in-between-days) (B)
a = 1st run/morning; b = 2nd run/morning; c = 1st run/afternoon; d = 2nd run/afternoon.

	A. Intra-assay precision			
	Strip Lot 1		Strip Lot 2	
	Low	High	Low	High
Target (mg/dL)	18	58	18	58
Median (mg/dL) [95% CI]	12.0 [11.0–12.6]	52.0 [50.0–58.0]	11.5 [11.0–12.0]	49.0 [47.0–52.0]
CV	6.2%	6.8%	6.1%	5.6%

	B. Intra-assay precision			
	Strip Lot 1		Strip Lot 2	
	Low	High	Low	High
Median (mg/dL) [95% CI]	13.0 [12.0–14.0][a]; 13.0 [13.0–14.0][b]; 13.5 [12.2–14.0][c]; 13.0 [12.0–15.0][d]	73.0 [70.0–75.0][a]; 75.0 [73.2–78.0][b]; 75.0 [72.0–77.8][c]; 75.0 [74.0–78.8][d]	13.0 [13.0–14.0][a]; 13.0 [12.0–15.0][b]; 13.0 [12.2–13.0][c]; 14.0 [12.2–14.8][d]	76.0 [73.2–77.0][a]; 76.0 [73.2–79.0][b]; 75.0 [72.2–76.8][c]; 74.0 [72.2–76.7][d]
CV	9.5%[a]; 9.7%[b] 8.8%[c]; 12.2%[d]	5.7%[a]; 7.0%[b] 6.6%[c]; 8.3%[d]	9.4%[a]; 16.3%[b] 9.5%[c]; 12.2%[d]	8.7%[a]; 7.9%[b] 8.5%[c]; 8.1%[d]

3. Results

3.1. Study settings and study population

During the clinical evaluation, from March 4, 2021 till September 18, 2021, 72 CSF samples were selected, from patients aged 0.0 (birth) to 94.2 y. o. (median; 95% CI: 44.2; 28.8–53.7), among those 32 males and 40 females. The requesting units were mainly the hospitalization wards (40.3%) and the emergency rooms (37.5%). The most encountered indications of lumbar punctures were an investigation of neurological disease (41.7%) and the investigation of fever in infants (27.8%). Median CSF glucose (95% CI; min-max) was 61.0 mg/dL (59.0–65.8; 18.0–175.0) and the median white blood cells count ranged from 0 to 720/μL (median: 1/μL).

3.2. Intra assay precision

Table 1A summarizes the evaluation of the intra-assay precision testing. The low Glucose sample revealed a median of 12 mg/dL (11.0–12.6) and 11.5 mg/dL (11.0–12.0) respectively for two different strip lot numbers in use and CVs of 6.2% and 6.1% respectively. The high Glucose sample revealed a median of 52 mg/dL (52.0–58.0) and 49 mg/dL (47.0–52.0) respectively for two different strip lot numbers in use and CVs of 6.2% and 6.1% respectively. The lot-to-lot variation (Wilcoxon test) was not significant for low values ($P = 0.19$), but slightly significant for high values ($P = 0.03$).

3.3. Inter-assay precision (in-between-days)

Table 1B summarizes the evaluation of the inter-assay (in-between-days) precision testing. The in-between days evaluation over 20 days did not show any significant differences between the results obtained with the 2 lots ($P = 0.90$; Wilcoxon test) nor between the results of the morning and the afternoon ($P = 0.83$; Wilcoxon test).

These results agree with the acceptation criteria and are in line with the CVs provided by the manufacturer.

3.4. Accuracy and laboratory correlation

Fig. 1 shows the correlation of the StatStrip Glu test strip compared to the cobas 8000. The median delay between the two methods was 1 day (95% CI: 0.57–1.21 days). The Glucose test strip showed a good correlation to the clinical chemistry reference method with a correlation coefficient of 0.95 ($y = 0.82\ x + 4.08$) in the Passing-Bablok regression analysis. The Bland-Altman chart showed a trend to slightly negative bias of −7.6 (median) for high glucose values (>100 mg/dL).

4. Discussion

Meningitis is associated with significant mortality rates and may cause severe long-term comorbidities. In their 2021 fact sheet on Meningitis, the World Health Organization (WHO) states meningitis as a *"global public health challenge"*. They estimate an overall mortality of 10%, and a 20% severe incidence rate. The GBD 2016 Meningitis Collaboration states in its report an increase in incidence rates globally from 2.5 million cases in 1990 to 2.82 million cases in 2016, with a death rate decrease of 21% in the same time frame. So meningitis prevalence still remains high with an overrepresentation in children, mainly under 2 years, and in underdeveloped countries, as the sub-Saharan Africa [3,4]. Hypoglycorrhachia is a strong indicator for the bacterial form of meningitis, whereas a normal CSF glucose level is more common in viral meningitis. A quickly available hypoglycorrhachia at the patient's bed may alarm the clinician about a bacterial meningitis. However, the Gram stain result, the culture and the white blood cells count remain mandatory to confirm the suspected diagnosis. Reference ranges for normal CSF glucose levels are described for example by Tietz et al.

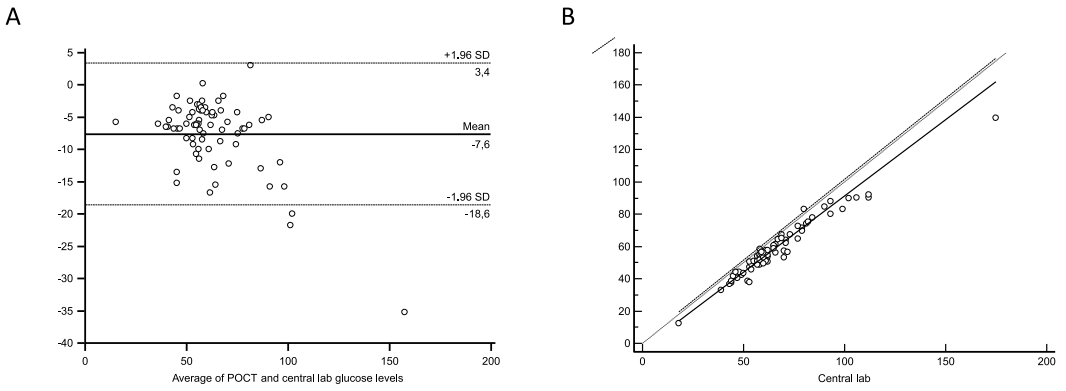

Fig. 1. Bland-Altman plot (A) and Passing-Bablok regression (B) comparing the mean results of CSF glucose measured with POCT and the comparison method in the central lab (regression line [solid line]; confidence interval for the regression line [dashed lines]; identity line [dotted line].

at 60–80 mg/dL for adults, and 40–70 mg/dL for infants. Normally CSF glucose levels are directly related to blood glucose levels. Several authors describe a ratio of 0.6, showing variations from 0.42 to 1.1 due to age dependency [5–7]. Some authors have already assessed the use of POC for glucose determination in CSF in resource-limited countries with urinary strips or with non-connectivity blood glucose monitoring systems. [8,9] Although meningitis is not a major public health problem in developed countries, more and more hospitals are forced to work in a network with only one central laboratory. As a result, hospitals without a permanently open laboratory are obliged to transport clinical biology samples via shuttles, which delays the response of results. However, diagnosis by POC instruments is becoming increasingly accessible and makes it possible to obtain fast results for the most urgent parameters. It is therefore advisable to use glucose meters for the measurement of glycorrhachia, since these connected instruments are widely available in almost all departments of hospitals. Rousseau et al. suggest shorten the door-to-antibiotics time for treating bacterial meningitis, which is critical for patient management [10]. But in addition, the measurement of glucose in the CSF using a POC instrument requires only 6 s and 1.2 μL of this precious sample, while the large biochemistry platforms of the central laboratory have a time-to-result of almost 1 h and consume a large amount of sample (100 μL). Indeed, if the analysis on a common biochemistry analyzer requires only 2 μL of sample per parameter, including glucose, the dead volume is estimated at 100 μL [11]. This is a significant saving especially when it comes to small children. Furthermore, lumbar puncture is an integral part of the etiological evaluation of fevers of undetermined origin in infants. This is a widely practiced procedure in our institution, which has a significant pediatric emergency department.

In this study, we evaluated the performance of the StatStrip GLU/KET for glucose measurement in CSF. Although several studies have been published on the use of portable blood glucose meters in this indication, this is the first study on the evaluation of StatStrip and, to our knowledge, the first study conducted on connected blood glucose meters. The evaluations conducted by Kitsommart et al. Alkhalifah et al. and Rousseau et al. involved not connected blood glucose systems for outpatients [9,10,12]. Working on connected instruments has many advantages, such as the rapid transmission of the results in the patient files, the management of quality controls and the control of reagent lots and of the users. In addition, the middleware ensures full traceability of information. Nowadays POC devices for measuring glucose in the hospital bedside are available on the market with excellent performance features regarding reference correlation, ranges and precision. Alkhalifah et al. described an overestimation in glucose results in CSF using a POC glucose meter [12]. In our study, we observed an underestimation in comparison to the central lab results. However lower results are encountered mainly for high CSF glucose levels (above 100 mg/dL). Removing those clinically insignificant results permitted to obtain a slope of 0.94. The accuracy is thus acceptable for key-values in the diagnosis of meningitis.

5. Conclusion

Even in cases where glucose results in the CSF from the central laboratory may be available within a reasonable time, the use of BGMS to obtain a rapid response is a significant added value in the different departments of a hospital. Especially emergency departments, which represent the main actors in the diagnosis of meningitis and encephalitis will benefit here. Besides the fact that the required sample volume is very small and the time to result is only a few seconds, the advantage is that these BGMS are widely used for routine blood glucose monitoring and are therefore immediately available throughout the hospital.

Informed consent

According to Belgian Health Public Law (article 3§2 of the Law of May 7, 2004 relating to experiments on humans), this type of study did not require specific informed consent or ethics committee approval.

CRediT authorship contribution statement

Laurent Blairon: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **Marie Tré-Hardy:** Investigation, Methodology, Visualization, Writing – review & editing. **Sophie Collignon:** Data curation, Formal analysis, Investigation, Writing – review & editing. **François Coenen:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Ingrid Beukinga:** Supervision, Visualization, Writing – review & editing. **Roberto Cupaiolo:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The reagents required for the precision evaluation were provided free of charge by Nova Biomedical. However, the study was conducted independently and without any conflict of interest.

Data availability

Data will be made available on request.

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