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Brief reports

NIST calibration alignment is essential when selecting a laboratory reference method for evaluating POC Blood Glucose Monitoring Systems

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Dear Editor,

There has been much discussion about the performance of hospital Blood Glucose Monitoring Systems (BGMS) particularly in critically ill patients and about the evaluation protocols and performance criteria used to assess accuracy [1]. Studies undertaken with the same point-of-care (POC) glucose meters have shown different results and this is often related to the different comparative methods used. Central laboratory analyzer methods for glucose measurement utilize varying enzymatic methods, such as: glucose oxidase/peroxidase method, glucose oxidase/oxygen electrode method, glucose oxidase/dry chemistry method, glucose-6-phosphate dehydrogenase, or hexokinase method. In external quality surveys, data from these different methods on multiple instruments from different laboratories show wide variation in glucose results [2,3]. Therefore, it is important that the comparative method used for performing all glucose method evaluations is standardized and harmonized to an isotope dilution mass spectrometry (IDMS) traceable standard [1,4]. With new performance and system accuracy guidelines emerging from International Organization for Standardization (ISO), Clinical & Laboratory Standards Institute (CLSI) and US Food and Drug Administration (FDA), it becomes imperative that the comparative method in all future evaluations is standardized to a definitive method (traceable to IDMS). This will ensure comparison to a more truthful standardized glucose method. We describe an anomaly that occurred with the calibration of a laboratory hexokinase method with National Institute of Standards and Technology (NIST) certified reference standards before commencing a validation assessment of the performance of BGMS compared to the laboratory method for regulatory submission to the Chinese FDA (CFDA) [5].

The calibration of two laboratory glucose measurement methods, a laboratory hexokinase method (Lab-HK) and a laboratory glucose oxidase method (Lab-GO), were assessed over several time points using primary and secondary NIST standard reference materials (NIST SRM917c and NIST SRM965b). Both laboratory glucose measurement methods were performed on an open channel on the Hitachi 7180 biochemistry analyzer. Seven aqueous glucose levels ranging from 1.39–27.78 mmol/L prepared from NIST standard SRM917c were tested by each glucose method. Four glucose levels of NIST SRM965b (prepared in human serum) with glucose concentration of 1.836 ± 0.027, 4.194 ± 0.059, 6.575 ± 0.094 and 16.35 ± 0.20 mmol/L were also tested. The NIST standards were aliquoted and stored at −80 °C until use, at that time of testing the aliquots were unfrozen and mixed carefully before analysis.

On the third replicate test run we noticed a shift in the calibration with the Lab-HK glucose method. Prior to this the mean % bias for the four NIST SRM965b glucose samples was 0.4%, and 3.9% for the first two test runs and 15.1%, 9.3%, 9.7% for the following three test runs (Table 1). The latter replicates did not meet our mean % bias acceptance level of ± 5% across all levels. This pattern was also seen following testing with the seven NIST SRM917c which gave results with the Lab-HK method of −0.4% and − 0.6% in the first two testing replicates performed before the calibration drift observed with the NIST SRM 965b aliquots. In the test run coinciding with the observation of calibration drift with the SRM 965b samples the mean % bias across all seven SRM 917c aliquots was 7.7% and 12.5% in the next two replicates.

The same NIST 965b (Table 1) and SRM 917c (data not shown) glucose samples tested using the Lab-GO method stayed consistent

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Table 1
Calibration alignment of HK-Hitachi 7180 using NIST SRM965b (glucose in human serum).

Method use on Hitachi 7180	SRM 965b	NIST certified concentration (mmol/L)	Run 1	Run 2	Run 3	Run 4	Run 5
Plasma hexokinase	Level 1	1.836 ± 0.027	1.85	1.94	2.09	1.99	2.01
	Level 2	4.194 ± 0.059	4.22	4.34	4.87	4.66	4.63
	Level 3	6.575 ± 0.094	6.51	6.89	7.6	7.19	7.21
	Level 4	16.35 ± 0.20	16.52	16.59	18.77	17.69	17.88
	Mean % bias across all levels		0.4%	3.9%	15.1%	9.3%	9.7%
	Acceptance criteria ± 5%		Pass	Pass	Fail	Fail	Fail
Glucose oxidase	Level 1	1.836 ± 0.027	1.87	1.9	1.86	1.89	NT
	Level 2	4.194 ± 0.059	4.36	4.32	4.37	4.35	NT
	Level 3	6.575 ± 0.094	6.75	6.73	6.8	6.87	NT
	Level 4	16.35 ± 0.20	16.7	17.21	16.55	16.34	NT
	Mean % bias across all levels		2.7%	3.5%	2.5%	2.8%	NT
	Acceptance criteria ± 5%		Pass	Pass	Pass	Pass	NT

NT = not tested

throughout the testing period with mean % bias across all test runs within the ± 5% mean bias acceptance criteria indicating that the pattern of results seen with the hexokinase reagents was not due to instability of the NIST standards.

Assessing the maintenance log for the laboratory analyzer we noticed that just prior to the third validation test run general maintenance was undertaken resulting in the replacement of both the photometer lamp and cuvettes. Following maintenance verification checks were performed on the photometer as according to the operating manual for the laboratory analyzer to confirm correct functioning. QC testing and an automatic calibration was performed using standard glucose samples provided by Shanghai Center for Clinical Laboratory. Westgard rules were used to confirm QC performance. It is not certain why the calibration shift seen with the NIST standards was observed with the hexokinase method and not with the glucose oxidase method. The latter measurement is the routine method in our hospital whereas the hexokinase which is the most commonly used glucose reference method was implemented for the purposes of the BGMS validation study, and as such the calibration of the Lab-HK method may have been less robust. This unexpected observation with the Lab-HK glucose method could have affected the interpretation of the system accuracy analysis for the BGMS under evaluation and as such we utilized the Lab-GO glucose measurements method for the purposes of the study.

This observation of calibration drift reinforces the need to ensure that NIST glucose standards are used regularly to monitor the calibration of central laboratory glucose methods and in particular when used as the reference method during an evaluation of the system accuracy of Blood Glucose Monitoring Systems.

Author contributions

All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

Authors' disclosures or potential conflicts of interest

There are no disclosures or potential conflicts of interest.

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