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Prospective evaluation of three point of care devices for glycemia measurement in a neonatal intensive care unit

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ABSTRACT

Hypoglycemia, if recurrent, may have severe consequences on cognitive and psychomotor development of neonates. Therefore, screening for hypoglycemia is a daily routine in every facility taking care of newborn infants. Point-of-care-testing (POCT) devices are interesting for neonatal use, as their handling is easy, measurements can be performed at bedside, demanded blood volume is small and results are readily available. However, such whole blood measurements are challenged by a wide variation of hematocrit in neonates and a spectrum of normal glucose concentration at the lower end of the test range. We conducted a prospective trial to check precision and accuracy of the best suitable POCT device for neonatal use from three leading companies in Europe. Of the three devices tested (Precision Xceed, Abbott; Elite XL, Bayer; Aviva Nano, Roche), Aviva Nano exhibited the best precision. None completely fulfilled the ISO-accuracy-criteria 15197: 2003 or 2011. Aviva Nano fulfilled these criteria in 92% of cases while the others were <87%. Precision Xceed reached the 95% limit of the 2003 ISO-criteria for values ≤4.2 mmol/L, but not for the higher range (71%).
Although validated for adults, new POCT devices need to be specifically evaluated on newborn infants before adopting their routine use in neonatology.

1. Introduction

In all facilities caring for newborn infants, screening for hypoglycemia is of utmost importance. Although there is no agreement on the lower normal limit of glycemia in newborn infants, values below 2.5 mmol/L, in particular when recurrent, may have a detrimental impact on neurodevelopmental outcome [1–3]. Therefore, the 'operational threshold', meaning a glycemia level at which an intervention should be performed, is generally defined as glycemia levels ≤2.5 mmol/L [4,5]. Hence, there is an important need of glucose measurement for screening and management of hypoglycemia in neonates, as clinical signs are unspecific or in many cases completely lacking. Three major criteria are required for such measurements in neonatology: 1) use of small blood samples, given the limited total blood volume of neonates (80–100 ml/kg); 2) rapid result availability; and 3) accurate and precise measure. The gold standard for glucose measurement is the hexokinase method used in many hospital laboratories. However, there is often an important time lag between the blood sampling and availability of the result. Furthermore, this method uses typically around 300 μl of blood for each measurement. Point-of-care-testing (POCT) devices like portable blood glucose meters (BGM) respond perfectly to the first two of the three criteria. However, they were primarily developed for self monitoring of glycemia in adult diabetic patients, with the repetitive use of one single device for the same patient [6]. Before using such devices in neonatal intensive care units (NICU), particular issues have to be considered: 1) One such device may be used once or repeatedly for the same or very different patients ranging between extremely preterm babies of <500 g to full term neonates of >4 kg. Therefore, such a device should be able to give precise and accurate results in extremely different clinical situations. 2) Hematocrit, which can potentially confound whole blood glucose measurement, may vary between 20% and 70% in the standard population of a NICU [7]. For these reasons, a new POCT device needs to be carefully investigated before being used in the neonatal population. In general, BGM have shown a trend to overestimate glycemia values in neonates, leading to increased operational thresholds for hypoglycemia screening with such methods, and thus to overtreatment and an increased number of useless blood tests in healthy newborns [8–11]. Although several suggestions for BGM selection in the neonatal population and accuracy criteria for their use have been published, their investigation in well-designed prospective studies in neonates is difficult, regarding the ethical issue for additional blood sampling in this vulnerable population [12–14]. With the help of an electronic patient data acquisition system (DAS), we developed a method, within the

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limits of our standard clinical procedure, to compare the results of different POCT devices with the gold standard hexokinase method, without the need for additional blood sampling [15]. In collaboration with three leading companies producing POCT devices, we tested prospectively their most appropriate BGM for bedside glycemia measurement in newborn infants over a one year period.

2. Materials and methods

2.1. Study design

This prospective study was performed between January 1st and December 31st 2010 in neonatal infants hospitalized at the Clinic of Neonatology of the University Hospital of Lausanne (CHUV). Three of the leading companies in Europe in the field of POCT glucose measurement participated in an equal manner without, however, interfering in any way neither in the planning and implementation of the study nor in the analysis of the results. They were all asked to provide us with twelve devices of their potentially best POCT method for use in neonates. The three tested devices were: Precision Xceed (Abbott AG, Diabetes Care, Baar, Switzerland), Ascensia ELITE® XL (Bayer AG, Diabetes Care, Zurich, Switzerland), and Accu-Chek® Aviva Nano (Roche Diagnostics AG, Rotkreuz, Switzerland). These test devices were randomly allocated to 36 study nurses who received general information about the study and a specific training on how to use their personal BGM which they used during the whole study period. Characteristics of the three POCT devices are summarized in the online supplement (Online supplement — Online-Table 1).

2.2. Patients and sample selection

In accordance with our internal standard operating procedure regarding glucose measurement, the study nurses had to take into account the BGM result. If it was ≤3.0 mmol/L, they had to check glycemia immediately by sending 0.3 mL whole blood to the clinical chemistry laboratory (CCL) of the CHUV. This volume of 0.3 mL whole blood was demanded in order to get the minimal required 60 μL of plasma volume necessary to be able to perform the analysis, even if the hematocrit was as high as 70%. Additionally, any planned glycemia test requested at the CCL was associated with a concomitant POCT measurement. All POCT test results were immediately entered into the bedside electronic DAS (Metavision®, iMDsoft, Tel Aviv, Israel). Those from the CCL were automatically registered within 1 min after validation of the result in the laboratory. Inclusion criteria of glycemia results for study purposes were: 1) blood test performed and introduced into the DAS by one of the study nurses; 2) paired glycemia results from the same blood sampling (first by POCT device, second by the CCL reference method) and 3) time interval <60 min between introduction of the two results into the DAS which corresponds to the maximum allowed turnaround time. This time interval comprises the transfer of the blood sample to the central laboratory, its reception, the centrifugation, the plasma decantation, the analysis itself and the validation of the result. The blood sample was either anticoagulated with fluoride (if only glycemia was demanded) or with heparinate (if other analyses were required). With the computerized search engine of the DAS, all paired results meeting these criteria were selected. The extracted raw data were transferred to an Excel table and manually checked independently by two of the authors to verify the inclusion criteria. For clinical purposes, in some cases, part of the blood sampling was used to measure hematocrit. These values were used to analyze a potential influence of varying hematocrit values on BGM performance. The method used for blood sampling has been described recently [15]. The study was approved by the Ethics Board for Research in Human of the Canton de Vaud. Because no additional blood sampling was necessary for study purposes, no written consent was requested.

2.3. Reference method

The reference method for plasma glucose measurement in the CCL was the hexokinase/glucose-6-phosphate dehydrogenase method (Gluco-quant Glucose/HK, Modular P system, Roche Diagnostics AG, Rotkreuz, Switzerland), considered as gold standard.

2.4. Check of the performance of the POCT devices during the study

To discover any dysfunctional POCT device during the study period, all 36 BGM were tested with the respective control solutions provided by the three manufacturers (three concentration levels for Precision Xceed and Elite XL, and two levels for Aviva Nano) at three time points: at the beginning of the study as part of the teaching and testing process of each study nurse, 6 months later in the middle of the study period and at its end. All of the glucose determinations were within the tolerated range indicated by the manufacturers and no BGM had to be excluded from the study.

2.5. Quality control measurements of the POCT devices

Two within-run imprecision tests were conducted, one in an aqueous and the second in a whole blood matrix. As aqueous matrices, the control solutions (low and high glucose concentration), provided by the manufacturers for their specific device were used. For the whole blood matrix, the following protocol was used: 25 ml of venous whole blood was drawn from a healthy volunteer donor and directly heparinized. The sample was kept three days at room temperature, leading to glycemia close to zero because of the naturally occurring glycolysis. The blood was then separated in 3 aliquots and spiked with different volumes of a concentrated glucose solution (100 mmol/L) in order to generate final glucose concentrations of 2.2 mmol/L, 3.3 mmol/L and 4.5 mmol/L, as assessed by the reference method. For both within-run imprecision tests three devices per company were randomly chosen. Twenty measurements were performed with each device on each of the five test solutions (2 aqueous and 3 whole blood solutions), leading to $n = 60$ for each company and test solution.

2.6. ISO 15197 accuracy criteria: actual (2003) and proposed new (2011)

Accuracy of the three BGM was compared with ISO-criteria 15197, version 2003 and its proposed new version 2011 [14,16]. Tolerated range for ISO criteria 15197:2003 is the following: for ≥95% of samples, the difference of glycemia between POCT and reference method should be within ±0.8 mmol/L for values ≤4.2 mmol/L and within ±20% for values >4.2 mmol/L. With the new ISO criteria 15197:2011, for ≥95% of samples, this tolerated difference should be within ±0.9 mmol/L for values ≤5.5 mmol/L and within ±15% for values >5.5 mmol/L.

2.7. Hematocrit measurements

For blood sampling in which a paired glycemia result and a simultaneous hematocrit value was available, the influence of hematocrit on accuracy of the BGM was assessed as described previously [15]. Hematocrit was determined in the central laboratory of the CHUV on the automated Sysmex Hematology-Analyzer XE-2100 (Sysmex Digitana AG, Horgen, Switzerland).

2.8. Statistics

Statistical analysis was performed using the software Analyse-it for Microsoft Excel, version 2.20 (Analyse-it Software, Ltd. http://www.analyse-it.com, 2009). Agreement between each POCT method and the gold standard was assessed using Passing and Bablok fits and bias plots, with the difference between the compared methods plotted against the reference method (modified Bland–Altman). Performance