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ORIGINAL PAPER

Evaluation of different POCT devices for glucose measurement in a clinical neonatal setting

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Abstract Hypoglycaemia is a major cause of neonatal morbidity and may induce long-term developmental sequelae. Clinical signs of hypoglycaemia in neonatal infants are unspecific or even absent, and therefore, precise and accurate methods for the assessment of glycaemia are needed. Glycaemia measurement in newborns has some particularities like a very low limit of normal glucose concentration compared to adults and a large range of normal haematocrit values. Many bedside point-of-care testing (POCT) systems are available, but literature about their accuracy in newborn infants is scarce and not very convincing. In this retrospective study, we identified over a 1-year study period 1,324 paired glycaemia results, one obtained at bedside with one of three different POCT systems (Elite™ XL, Ascensia™ Contour™ and ABL 735) and the other in the central laboratory of the hospital with the hexokinase reference method. All three POCT systems tended to overestimate glycaemia values, and none of them fulfilled the ISO 15197 accuracy criteria. The Elite XL appeared to be more appropriate than Contour to detect hypoglycaemia, however with a low specificity. Contour additionally showed an important inaccuracy with increasing haematocrit. The bench analyzer ABL 735 was the most accurate of the three tested POCT systems. Both of the tested handheld glucometers have important drawbacks in their use as screening tools for hypoglycaemia in newborn infants. ABL 735 could be a valuable alternative, but the blood volume needed is more than 15 times higher than for handheld glucometers. Before daily use in the newborn population, careful clinical evaluation of each new POCT system for glucose measurement is of utmost importance.

Keywords POCT · Glucose measurement · Neonatal hypoglycaemia · Quality control · Glucometer · Elite XL · Ascensia Contour · Radiometer ABL

Abbreviations

POCT	Point-of-care testing
Elite XL	Glucometer Elite™ XL
Contour	Ascensia® Contour® (5 s)
DAS	Data acquisition system
NICU	Neonatal Intensive Care Unit

Introduction

Blood glucose monitoring is part of standard care in nurseries and neonatal intensive care units (NICU). Hypo-

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glycaemia is a major cause of neonatal morbidity and may induce long-term developmental sequelae, especially when happening repetitively [6, 19]. Therefore, rapid detection and treatment of low glucose values is crucial. However, clinical diagnosis of hypoglycaemia in neonates is a challenge because symptoms are unspecific or completely absent. Precise and accurate methods for rapid assessment of glycaemia are a requisite for institutions taking care of neonates. The hexokinase method, used as reference in this study, is considered as gold standard for the quantification of plasma glucose. This method, however, suffers several drawbacks, like the delayed availability of the result due to transport of the blood sample to the centralised laboratory in distance from the NICU and the time needed to centrifuge the blood sample before analysing it. A second disadvantage is the need for a relatively large volume of blood (typically 300 μL) in regards to the total blood volume of 80–100 mL/kg body weight of newborn infants. Thus, easy to use point-of-care testing (POCT) devices performing measurements at bedside within seconds and requiring small volumes of blood could be ideal alternatives, provided they give accurate results compared to the reference method.

Over the past years, multiple portable glucose meters have been developed and increasingly used in clinical neonatal settings. Measurement of most of these devices is based on an electrochemical reaction using either glucose oxidase or glucose dehydrogenase. The numerous glucose meters available on the market vary in regards to the needed blood volume, their turnaround time (availability of the result), the type of result presentation (whole blood or plasma referenced), the need or not of strip lot calibration, their sensitivity towards oxygen tension or haematocrit values and their susceptibility to interference by various substances like ascorbic acid, acetaminophen, dopamine, paracetamol, mannitol, etc. [7, 18, 29, 31]. Portable glucose meters were originally developed with the focus on adult diabetic patients for self-testing. Compared to the high number of different devices, literature about their use in neonates remains limited and the results in most cases are not very convincing [2, 9, 10, 15–17, 20–23, 25–28].

Glucose monitoring in newborn patients has some specific characteristics: (1) Metabolic adaptation to postnatal life demands in many newborn patients repeated glucose measurements in particular to screen for hypoglycaemic values. Considering the small circulating blood volume in neonates, methods for glucose measurement needing small quantities of blood are of utmost importance. (2) In contrast to older children and adults, the low limit of normal plasma glucose in term newborn infants is very low, somewhere between 1.6 and 2.7 mmol/L during postnatal days 1–3 [1]. The decision limit for treatment intervention is commonly set at 2.5 mmol/L (45 mg/dL) [4]. (3) Haematocrit potentially interferes with glucose measurement [7, 8, 18, 30]. Whereas in adults "normal blood" has a haematocrit close to 43%, it may vary in neonates between 25% and 64% according to gestational and postnatal age and therefore may decrease the accuracy of glucometers [14]. (4) The naturally occurring hyperbilirubinaemia of the newborn infant encompassing the adult normal limits by 10–15 times may also potentially interfere with the measurement and may reduce the POCT performance [7, 8, 11, 29].

In order to test the accuracy of a new handheld POCT glucometer in neonates, we evaluated the Ascensia™ Contour™ (5-s measurement and FAD as coenzyme) in the clinical environment of a NICU with neonates of a wide variation of pathologies and gestational ages. The main focus of this study was on the low glycaemic range. Accuracy was judged by comparison with hexokinase method obtained from the same capillary blood sampling. An identical evaluation was undertaken with the older generation of glucometer of the same company (Elite™ XL) and with the NICU-located bench POCT method, ABL 735, a blood gas analyser with a glucose electrode. Additionally, we studied the influence of haematocrit.

Material and methods

Patients and sample selection

Our internal guidelines request that all glycaemia values ≤3.0 mmol/l measured with a POCT device need an immediate double check with the hexokinase reference method in the central laboratory. Furthermore, control values by the reference method are generously demanded when other chemistry exams are required, as long as no supplementary blood is necessary. We therefore have quite often the opportunity to compare glucose results of the reference method with one of the POCT systems.

All patients hospitalised in the NICU are connected to a data acquisition system (DAS; Metavision®, iMDsoft, Tel Aviv, Israel) which records automatically every minute clinical and laboratory data. Additionally, the nurses introduce manually information about diagnostic and treatment interventions (e.g. blood sampling). We thus know exactly the timing of blood sampling in the NICU and result validation in the central laboratory as well as the results obtained by the different measurement methods. For the period between December 2006 and December 2007, the DAS allowed us to screen retrospectively 29,350 blood glucose values. Our inclusion criteria were: paired glucose values (first with one of the three POCT systems, second with the reference method) performed in the blood sample and registered in the DAS within <60 min. To reduce the bias of different sampling locations and techniques, only

Table 1 Characteristics of the three POCT meters

	Elite XL	Contour	ABL 735
Official name	Old name: Glucometer Elite™ XL New name: Ascensia Elite™ XL	Old name: Ascensia™ Contour™ New name: Contour™	ABL 735
Company	Bayer AG, Diabetes Care, Zurich, Switzerland	Bayer AG, Diabetes Care, Zurich, Switzerland	Radiometer, Copenhagen, Denmark
Approved for neonatal use during study period	Yes (for control, but not for diagnostic)	Yes	Yes
Method of measurement	Glucose oxidase-based amperometric strip	FAD glucose dehydrogenase-based amperometric strip	Amperometric electrode with glucose oxidase membrane
Need for strip lot coding	Yes	No	n/a
Type of sample	Capillary blood	Capillary blood	Heparinized capillary blood
Volume of blood sample	2 μL	0.6 μL	35 μL if only glucose measurement 95 μL if together with blood gas measurements
Analysis time	30 s	5 s	80 s (for 35 μL capillaries) 135 s (for 95 μL capillaries)
Test result	Whole blood referenced	Plasma referenced	Plasma referenced
Test range	1.1–33.3 mmol/L	0.6–33.3 mmol/L	0–60 mmol/L
Haematocrit limits (%)	20–70% (neonatal use: for glucose between 1.1 and 6.7 mmol/L)	0–70%	No information
Internal quality control: Imprecision at low glucose concentration	CV: 3.4% at 2.5 mmol/L	CV: 2.1% at 2.4 mmol/L	CV: 1.9% at 2.4 mmol/L

n/a not applicable, *CV* coefficient of variation

capillary blood samples were selected [12]. A total of 1,324 paired samples, meaning 2,648 capillary blood glucose values, were retained for analysis. The study was accepted by the ethics committee of the University Hospital of Lausanne, and no written consent was demanded.

Sampling method

Softasept® (B. Braun Medical AG, Sempach, Switzerland) was used for disinfection and Accu-Chek® Softclix Pro (Roche Diagnostics, Rotkreuz, Switzerland) for standard heel puncture with reproducible puncture depth. After drying and wiping off the first blood drop, blood collection for glucose measurement was done in the following order: (1) handheld glucometer (Elite XL or Contour), (2) ABL 735 in a heparinised capillary if blood gas analysis was demanded, (3) reference method in a Microvette® CB 300 with lithium heparinate or fluoride as anticoagulants (Sarstedt, Nümbrecht, Germany).

Table 2 Study demographics

	Elite XL	Contour	ABL 735
Number of patients	132	157	133
Number of study samples	472	532	320
Number of samples/patient			
Mean (± SD)	3.6 (±4.8)	3.4 (±4.2)	2.4 (±2.6)
Median (Range)	2 (1–34)	2 (1–30)	1 (1–16)
Reference glycemia (mmol/L)			
Median (Range; mmol/L)	3.2 (0.1–15.9)	3.7 (0.1–23.6)	4.0 (0.1–17.7)
Mean (± SD in mmol/L)	4.1 (±2.45)	4.4 (±2.90)	4.6 (±2.75)
Number of samples with additional haematocrit	116	188	319
Haematocrit values (%)			
Median (Range)	42.0 (26.0–72.1)	44.5 (26.3–74.7)	43.1 (23.9–74.7)
Mean (±SD)	44.3 (±9.9)	46.4 (±10.5)	45.3 (±10.2)

Glucose measurements

During the first 6 months of the study period, we used 30 devices of the Elite XL and during the second 6 months the same number of devices of Contour. As a third POCT system, we used over the whole study period the blood gas analyser ABL 735, located in the NICU. All nursing staff was well trained and experienced in the use of the three POCT meters. The main characteristics of the POCT systems as well as the day-to-day imprecision in the low glucose range are summarised in Table 1.

The reference method for plasma glucose measurement in the central laboratory of the University Hospital of

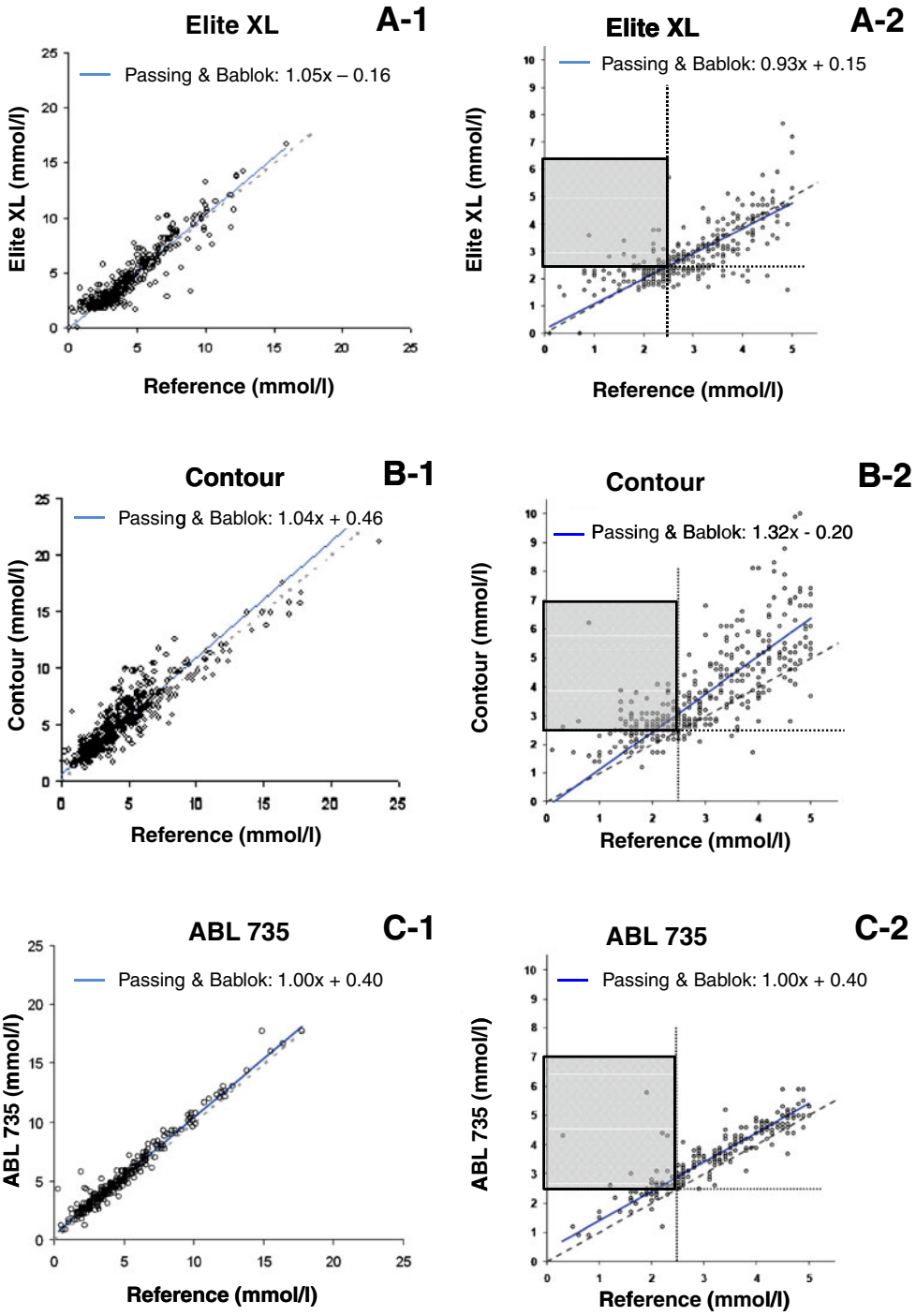

Fig. 1 Passing & Bablok regression analysis between the three POCT glucose meters and the reference method: *A-1*, *B-1*, *C-1* Whole range of glycaemia values; *A-2*, *B-2*, *C-2* Focus on low range glycaemia values (≤5.0 mmol/L, measured by reference method). *Interrupted line* line of identity. *Rectangular striped area* false negative values with a cutoff of 2.5 mmol/L

Lausanne is the hexokinase/glucose-6-phosphate dehydrogenase method (Gluco-quant Glucose/HK method on a Modular P system; Roche Diagnostics). This method, which is standardised on the primary reference method by isotope dilution mass spectrometry, is considered a secondary reference method by the National Committee for Clinical Laboratory Standards [24]. The typical volume of blood sample needed is 300 μL and the turnaround time to the plasma glucose result is usually <1 h. During the whole study period, day-to-day imprecision was 2.3% at 3.3 mmol/L and 2.2% at 20.1 mmol/L. Accuracy was validated by participation to two external quality control surveys (Quality Control Center, Switzerland; Reference Institute for Bioanalytics, Germany).

ISO 15197 accuracy criteria

The International Organization for Standardization (ISO) has defined accuracy criteria for point-of-care glucose meters [13]. They request that 95% of all glycaemia results on POCT systems do not differ by more than ±0.8 mmol/L for glycaemia values ≤4.2 mmol/L or by more than ±20% for glycaemia values >4.2 mmol/L compared to the results measured by the reference method.

Haematocrit measurements

For about one third of the glucose measurements done by one of the two portable glucose meters and for almost 100% of the glycaemia results obtained by the ABL 735 (one value missing), a simultaneous haematocrit value measured by the ABL 735 was available. This enabled us to investigate if haematocrit had an influence on accuracy of the blood glucose measurement by the three POCT systems.

Statistics

Statistics were performed using the software *Analyse-it for Microsoft Excel*, version 2.20 (Analyse-it Software, Ltd. http://www.analyse-it.com, 2009). Agreement between methods was analysed using Passing & Bablok fits and bias plots, with the difference between the compared methods plotted against the reference method (modified Bland–Altman). Performance of the different POCT methods was obtained by ROC curve analysis.

A mixed linear regression was fitted to test the effect of haematocrit on glucose measurement, allowing for the constant to vary randomly across individuals. The significance of the slope was tested by means of the Wald test. This was done using the software STATA, version 10.1. A p value <0.05 was considered statistically significant.

Results

Method comparison

For the 1-year study period, we identified a total of 1,324 paired glucose results fulfilling the inclusion criteria. The results of glycaemia values covered a similar range of glucose concentration in the three POCT groups (Table 2).

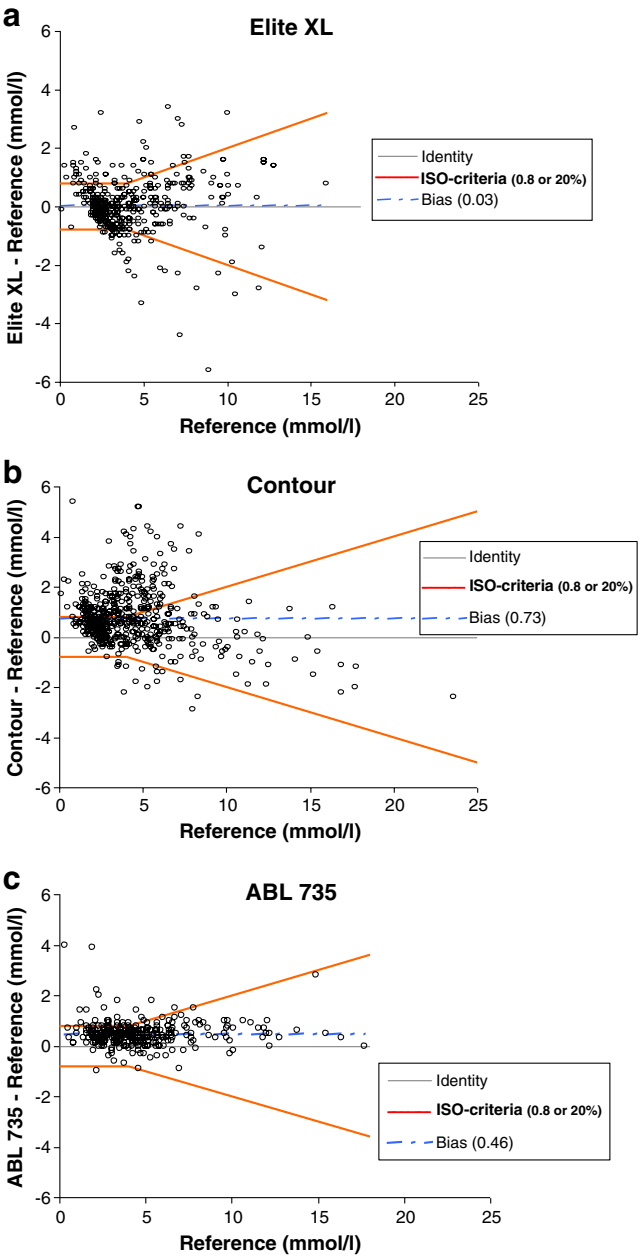

Fig. 2 Bias plots for the three POCT glucose meters: difference of glycaemia values between each of the three POCT systems and the reference method plotted against the reference method with ISO 15197 limits representation

Table 3 Degree of fulfilment of the ISO 15197 accuracy criteria

	Elite XL	Contour	ABL 735
Total samples (*n*)	472	532	320
Number of samples			
With glycaemia ≤4.2 mmol/L	318 (67.4%)	314 (59.0%)	175 (54.7%)
With glycaemia >4.2 mmol/L	154 (32.6%)	218 (41.0%)	145 (45.3%)
ISO criteria fulfilled			
For glycaemia ≤4.2 mmol/L	271/318 (85.2%)	193/314 (61.5%)	157/175 (89.7%)
For glycaemia >4.2 mmol/L	123/154 (79.9%)	140/218 (64.2%)	140/145 (96.6%)
For all glycaemia values	394/472 (83.5%)	333/532 (62.6%)	297/320 (92.8%)

Tolerated range for ISO criteria: ±0.8 mmol/L compared to the reference method (hexokinase-based) for values ≤4.2 mmol/L and ±20% for glycaemia values >4.2 mmol/L

Figure 1 shows the agreement between the three POCT systems and the reference method. Over the whole range of glucose values, the slopes were respectively 1.05, 1.04 and 1.00 for Elite XL, Contour and ABL 735, with intercept values of −0.16, +0.46 and +0.40 mmol/L (A-1, B-1 and C-1 in Fig. 1). These values do change for Elite XL and Contour if we focus on the low range of glycaemia values (≤5 mmol/L), but remain identical for ABL 735 (A-2, B-2 and C-2 in Fig. 1). All POCT systems showed a positive bias compared to the reference method (Fig. 2a–c), ranging from +0.03 mmol/L for Elite XL to +0.73 mmol/L for Contour, whilst ABL 735 was intermediate (+0.46 mmol/L). In terms of accuracy, Contour showed the highest proportion of values outside the ISO 15197 limits (Fig. 2a–c). In our study population, none of the three POCT methods achieved the ISO accuracy criteria, with an overall degree of fulfilment of only 83.5% for Elite XL, 62.6% for Contour and 92.8% for ABL 735 instead of the demanded 95% (Table 3) [13].

Sensitivity and specificity

The goal of neonatal glycaemia screening is the detection of asymptomatic hypoglycaemia which we defined as a glucose value ≤2.5 mmol/L. Taking into account that POCT glucometers tend to overestimate glycaemia values, our actual clinical protocol defines that all glycaemia results ≤3.0 mmol/L must be checked with the reference method in the central laboratory. Table 4 shows the measured sensitivity and specificity for this cutoff value of 3.0 mmol/L and the calculated respective values for a cutoff value of ≤2.5 mmol/L. For both cutoff limits, Elite XL appeared to have the best sensitivity, but the worst specificity of all tested devices. In order not to miss any hypoglycaemia, meaning to reach a sensitivity of 1.0, a cutoff value would be needed to be fixed at ≥5.7 mmol/L for all three POCT systems (Table 4). This, however, is clinically not feasible because far too many measurements would demand a control in the central laboratory (specificity of all three devices ≤0.40; Table 4). We then compared the three methods at a threshold with a clinically reasonable sensitivity of 0.94. The cutoff value would then be of ≤3.0 mmol/L for Elite XL, ≤3.5 mmol/L for Contour and ≤3.3 mmol/L for ABL 735 (Table 4).

Influence of haematocrit

In order to investigate the influence of haematocrit on accuracy of the three POCT systems, we analysed the bias (=difference between POCT and reference glucose results) in relation to the simultaneously measured capillary haematocrit. Table 2 shows sample size and distribution of the haematocrit values for the three groups. Whereas no change in agreement was found in relation to haematocrit for Elite XL (slope 0.001, $p = 0.89$; Fig. 3a), there was a statistically significant increasing difference between Contour and the reference method with increasing haematocrit (slope 0.040, $p<0.001$; Fig. 3b). In other words, Contour showed an increasing overestimation of

Table 4 ROC analysis for the three POCT glucose meters

	Elite XL	Contour	ABL 735
Sample size (*n*)	472	532	320
Prevalence of hypoglycaemia (≤2.5 mmol/L measured by the reference method)	30%	27%	19%
Area under the curve	0.90	0.94	0.96
(95% confidence interval)	(0.87–0.93)	(0.92–0.96)	(0.93–0.99)
Cutoff ≤2.5 mmol/L			
Sensitivity	0.86	0.43	0.55
Specificity	0.80	0.98	1.00
Cutoff ≤3.0 mmol/L			
Sensitivity	0.94	0.82	0.89
Specificity	0.67	0.89	0.95
Sensitivity of 1.0			
Minimal cutoff (mmol/L)	≤5.7	≤6.2	≤5.8
Specificity	0.31	0.40	0.34
Sensitivity of 0.94			
Cutoff (mmol/L)	≤3.0	≤3.5	≤3.3
Specificity	0.67	0.84	0.89

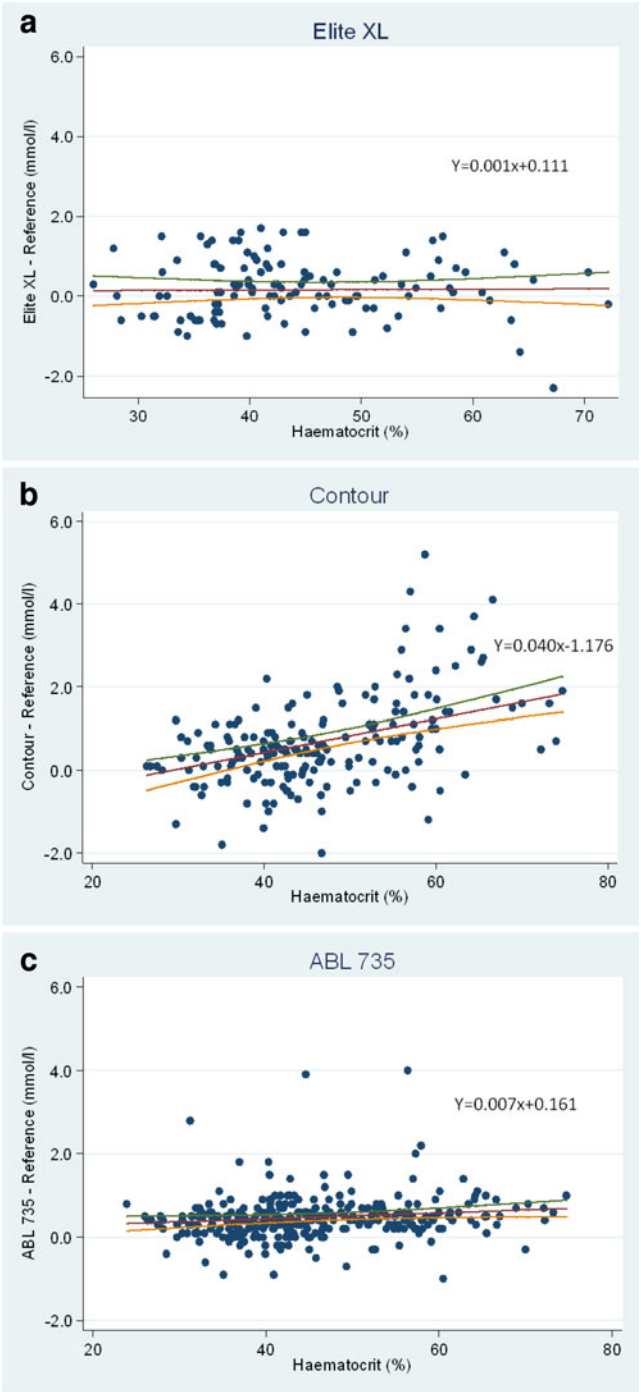

Fig. 3 Effect of haematocrit on POCT glycaemia measurements: difference of glycaemia values between each of the three POCT devices and the reference method plotted against capillary haematocrit with lines of the 95% confidence interval

glucose values in high haematocrit blood samples by 0.4 mmol/L per 10% haematocrit increase. Although statistically significant, the increasing difference measured for ABL 735 (slope 0.007, $p<0.05$) is too small to be of clinical relevance (Fig. 3c).

Discussion

Blood glucose measurements are frequently performed in newborn infants, mainly to detect hypoglycaemia during their first postnatal days. Handheld POCT glucometers are very popular due to the easy and rapid assessment of glycaemia in a small amount of blood, but it is ethically quite challenging to test the accuracy of new glucometers in the neonatal population in randomised trials because of their small circulating blood volume. Thanks to a performing DAS, we were able to screen retrospectively all glucose measurements performed in our NICU over a 1-year period to identify paired glucose results measured in parallel on the same capillary blood sampling by one of three POCT methods as well as by the reference hexokinase method. To our surprise, none of the three tested POCT systems reached the ISO accuracy criteria, with a degree of fulfilment of only 62.6% (Contour), 83.5% (Elite XL) and 92.8% for the blood gas analyser (ABL 735) instead of the required 95% [13]. These results contrast with those of the single neonatal trial performed with this latest generation of Contour devices (results in 5 s, FAD as coenzyme) in which the ISO criteria seemed to be fulfilled [5]. However, for the samples with low glucose concentration (≤4.2 mmol/L), the plasma referenced Contour did not reach either the demanded limit of agreement (93.8%), with inaccuracy being even higher (90%) in very low glycaemia values (≤2.8 mmol/L) [5]. The discrepancy between the two studies could be explained, at least partly, by procedure differences like the different types of reference methods (glucose oxidase-based vs. hexokinase-based). Furthermore, in the study by Dietzen et al., anticoagulated blood from a heparinised tube was taken for glucose measurement with Contour just before plasma separation and measurement with the reference method. Due to our study design with a more clinically oriented approach, we had a higher delay between the two measurements, one on native whole blood with POCT device on clinical ward and the other on plasma in the central laboratory of the hospital. We limited by our inclusion criteria the total turnaround time to 60 min, including transport of blood sample in tubes coated with either fluoride or lithium heparinate to the central laboratory, its reception, plasma separation, glucose measurement, validation and introduction in the DAS. We are thus aware that until plasma separation, glycaemia values may have decreased. However, Chan et al. [3] have shown that such a decrease does not encompass 5% of the initial glucose values when blood remains in a tube coated with fluoride or with lithium heparinate for a total of 60 min. Additionally, as treated the exact same way, differences between Elite XL and Contour can't neither be explained herewith.

A method with a reasonably high sensitivity to detect hypoglycaemic values is of utmost importance in neonates as these episodes may remain clinically asymptomatic. In the absence of a clear consensus about the limit of hypoglycaemia in neonatology, we considered, in accordance to Lucas et al., values of <2.6 mmol/L as hypoglycaemic because these episodes are associated with an increased risk for impaired long-term development, as shown for preterm infants [6, 19]. Due to a significant overestimation of glycaemia results shown for several handheld POCT devices in different studies, real hypoglycaemic episodes might be at risk to be missed with these tools [2, 9, 21, 23, 25]. In order to define clinically relevant and applicable limits for the use of these glucometers, we tested with the help of ROC analysis different strategies regarding sensitivity, specificity and cutoff values (Table 4). Ideally, a glucose meter should have a sensitivity of 1.0 in order not to miss any hypoglycaemia. To reach this goal, a cutoff value would be needed for the three tested POCT devices between 5.7 and 6.3 mmol/L, which is of no clinical practicability. With a pragmatic acceptable sensitivity of 0.94, we calculated a cutoff of ≤3.0 mmol/L for Elite XL, ≤3.5 mmol/L for Contour and ≤3.3 mmol/L for ABL 735 (Table 4). It is to be noticed that Contour with a cutoff of ≤3.5 mmol/L would have a better specificity (0.84) than Elite XL with a cutoff of ≤3.0 mmol/L (0.67). Although ABL 735 would be a valuable alternative in terms of accuracy, its drawback is its higher blood volume requisite (35 μL instead of 2 μL).

Haematocrit has been described to interfere with blood glucose measurements in various handheld POCT devices [11, 12, 18, 30]. In accordance with other studies with Elite XL in neonatal populations, we did not find any influence of the haematocrit value on the accuracy of glucose measurement [11, 12]. In contrast, for the newer glucometer, Contour, we found a statistically significant bias with increasing haematocrit. For every 10% increase of haematocrit, glycaemia was increased by 0.4 mmol/L. A similar haematocrit dependency, although to a lower degree, was already described in the only existing trial report of the Contour in the neonatal population [5].

In regards to these results, we concluded for our clinical daily practice: (1) To stop the use of the glucometer Contour as handheld POCT device. The company was informed about our doubts and has since then discouraged neonatologists in Switzerland to use this device anymore for screening purposes of hypoglycaemia in newborn patients. (2) Although not fully satisfactory because of its low specificity, to return to the older generation of glucometer Elite XL using a cutoff limit of ≤3.0 mmol/L. (3) To change our actual organization and infrastructure to allow POCT glucose measurements on the ABL 735 with the 35 μL capillaries. (4) To launch in the future a prospective trial to test new handheld POCT devices with the specific focus on their neonatal use.

We emphasise the demand that every new POCT device for glucose measurement needs to be carefully tested in clinical trials before its routine use. The validation should be done taking into account the specific characteristics of the patient population (e.g. neonates) and should be focused on the question of interest (e.g. screening for hypoglycaemia or follow-up of insulin treatment). A close collaboration between clinicians, hospital laboratories and companies in such trials is very important.

Conflict of interest The authors state that they do not have any conflict of interest.

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