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Point-of-care determination of neonatal bilirubin with the blood gas analyzer RapidLab 1265

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Abstract

Background: The aim of the study was to evaluate the comparability of the new neonatal bilirubin method on the RapidLab 1265 blood gas analyzer. This point-of-care testing (POCT) device has the option for the determination of neonatal bilirubin, making it potentially valuable for use in neonate intensive care units or in outpatient ambulances.
Methods: We paired 240 patient samples for intermethod comparisons between the new POCT method and the routine laboratory method (Vitros 350 chemistry system with BuBc slide). In parallel, a transcutaneous jaundice meter (JM-103) was applied to the newborns. Low birthweight and premature neonates were excluded from the trial. The turn-around-time (TAT) for the POCT method was also compared with the routine method, and the practicality of the new analyzer was evaluated for clinical purposes.
Results: Bilirubin measurements using the RapidLab 1265 are suitable for the application in newborns. For imprecision, coefficients of variation between 5.6% and 23% were found. The correlation between the Vitros 350 (x) and RapidLab 1265 (y) was $y = 1.0x - 0.1$ ($r = 0.91$), with a mean bias of $+0.1$ mg/dL and a 95% limit of agreement of ± 2.5 mg/dL. As in all POCT methods, the TAT was significantly lower than that of the core laboratory.
Conclusions: In contrast to the JM-103, the results of the RapidLab 1265 correlated closely with the Vitros 350, although occasional results of both methods were more different than expected. In general, the RapidLab 1265 blood gas analyzer provides clinically useful bilirubin results using neonatal whole blood samples, although imprecision data are higher than for the laboratory method. The POCT device is suitable for neonatal intensive care units after thoroughly training the employees that will use the device.
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Keywords: bilirubin measurement; transcutaneous bilirubinometer; neonatal jaundice; oximetry; point-of-care testing.

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Introduction

Clinical aspects

The term icterus neonatorum, or neonatal jaundice, describes the (patho)physiological situation that occurs when the umbilical cord is disconnected after birth (1, 2). The neonate must dispose of the metabolic bilirubin load, which was cleared before birth by the placenta. Neonatal hyperbilirubinemia results from susceptibility to increased bilirubin production and a poor ability to excrete this compound. In particular, preterm infants have higher bilirubin production compared to adults because of higher erythrocyte turnover. Moreover, unconjugated bilirubin is not readily excreted because the ability of the liver to conjugate bilirubin is limited. The unconjugated bilirubin concentrations of physiological jaundice in the first days of life in full-term infants (and slightly longer in preterm infants) peak at 5–6 mg/dL in serum (86–103 μmol/L, conversion factor 17), followed by a decline during the next several weeks to values comparable to values seen in adults (2).

Exaggerated hyperbilirubinemia is defined according to age dependent values ranging from 7 to 20 mg/dL (119–342 μmol/L) with the need for phototherapy, or, in rare cases, blood exchange (3). The causes can usually be identified in such infants and are classified into two groups, one for underlying diseases linked to increased production or bilirubin load on the liver, the other for decreased clearance of bilirubin (1). The clinical correlates of increased serum concentrations of unconjugated bilirubin are acute or chronic encephalopathy. The latter pathology is also termed ''kernicterus'', referring to the typical yellow colour found in the basal ganglia of infants who die from severe jaundice (2). In non-lethal cases considerable neurological dysfunctions may persist. Thus, a quick diagnosis is necessary in order to rapidly implement phototherapy (4).

Clinical chemistry aspects

Bilirubin in serum or plasma represents a variable mixture of isomers and fractions, differing considerably in their phys-

iological and chemical behavior. Bilirubin is measured in most routine laboratory analyzers by various modifications of the Jendrassik-Grof procedure (5, 6). The Vitros 350 dry chemistry analyzer uses two different methods for measurement of bilirubin: one for total bilirubin based on the Jendrassik-Grof procedure (''TBIL'' slide) and another that measures unconjugated and conjugated bilirubin separately (''BuBc slide''). In the latter slide, unconjugated bilirubin migrates together with the bilirubin glucuronides through a barrier layer that retains serum proteins, hemoglobin (Hb) and delta bilirubin. After binding to a chemical mordant, the glucuronides absorb at a maximum of 420 nm, whereas unconjugated bilirubin has a maximum absorbance of 460 nm. Using a two wavelength measurement and an elaborate calculation, it is possible to determine the concentrations of unconjugated and conjugated bilirubin separately (7). Due to lack of interference from Hb, the BuBc slide is preferred for neonatal bilirubin measurements.

The new JM-103 jaundice meter determines the yellow color of the subcutaneous tissue of the neonate. The device measures the difference in the optical densities of reflected light at 450 and 550 nm by the skin in a dual optical path system (8). One beam reaches only the shallow areas of subcutaneous tissue (short optical path), while the other penetrates the deeper layers (long optical path). The differences between the optical densities are detected by photodiodes. Due to the fact that bilirubin is accumulated primarily in the deeper subcutaneous tissue, the described optical measurement of the metabolite is influenced by other skin pigments, such as melanin, and Hb to a lesser extent.

The direct, spectrophotometric measurement of total bilirubin in whole blood can be performed by various blood gas analyzers (e.g., Nova, Radiometer, Roche, Siemens). In the co-oximetry module, total bilirubin is determined simultaneously with the Hb fractions using a multi-wavelength measurement [various wavelengths and ranges are performed by different point-of-care testing (POCT) devices; the RapidLab 1265, e.g., uses 256 wavelengths in the range of 500–680 nm]. Although the absorption spectra of bilirubin and Hb are clearly different, the large difference in concentrations between the two parameters requires a very complex measurement process (9). The total bilirubin concentration is then calculated using a multi-component algorithm (method of least squares) and converted to the serum concentration equivalent. Additional information on the RapidLab 1265 neonatal bilirubin determination is as follows: specificity was checked by interference testing. According to the manufacturer, beta-carotene (2.5 mg/dL in plasma) interferes by +10%, cyanomet-Hb (10% of total Hb) by +93% and methylene blue (50 mg/L) by +66%. Lipids (5% intralipid in plasma) showed no interference. Recovery tests with blood samples spiked with unconjugated bilirubin showed satisfactory results: 93.1% at a bilirubin concentration of 4.6 mg/dL, 104.5% at 12.2 mg/dL, and 108.9% at 42.2 mg/dL.

The aim of this study was to evaluate the practicality and comparability of neonatal bilirubin measurements using the RapidLab 1265 blood gas analyzer from Siemens Healthcare Diagnostics. We did not perform a general analytical validation of the POCT device. The method was compared to our laboratory routine method using the BuBc slide with the Vitros 350 dry chemistry analyzer from Ortho-Clinical Diagnostics. The rationale for the evaluation was to assess whether this device could provide this parameter in an accurate and timely manner. It should be clarified whether the time advantage is clinically relevant.

Materials and methods

Patients

We enrolled 240 consecutive newborns from the pediatric newborn ward in the Klinikum rechts der Isar in the study. Excluded were newborns with a birth weight below 2500 g and/or with lung immaturity, as well as preterm infants <32 weeks of gestation.

For all enrolled patients, the routine capillary blood collection (performed at a birth age of 36–40 h) was increased by 60 μL. For the clinical chemistry analyzer, we used 300 μL lithium heparin tubes (Sarstedt AG; Nümbrecht, Germany; Cat # 20.1309). However, for the blood gas analyzer, 175 μL capillary Multi Cap S tubes were used (Siemens Healthcare Diagnostics; Cat # 2043295). Blood was centrifuged after 30 min at $1500\times g$ for 20 min, and subsequently analyzed in the core laboratory. The surplus 60 μL heparinized capillary blood was used for measurement with the blood gas analyzer. Staff on the ward was instructed to make sure that the transcutaneous measurement with the bilirubinometer was performed and documented within 1 h of blood collection.

The study was in compliance with the Helsinki Declaration and had Institutional Review Board approval from the Ethics Committee of the medical faculty of the Technische Universität München. At least one parent gave written informed consent.

Analyses

We paired the 240 newborn patient samples for intermethod comparisons between the new POCT method and the routine laboratory method. The RapidLab 1265 blood gas analyzer from Siemens Healthcare Diagnostics (Eschborn, Germany) was used as the POCT analyzer, whereas the Vitros 350 full menu, medium seized clinical chemistry analyzer from Ortho-Clinical Diagnostics GmbH (Neckargemünd, Germany) served as the main comparison instrument. The serum sample volume for a single neonatal bilirubin determination (conjugated and unconjugated bilirubin) required for the latter device is 60 μL. The measuring range for the BuBc slide is 0–27 mg/dL.

The RapidLab 1265 is a whole blood analyzer that performs blood gas, electrolyte, metabolite and full co-oximetry analyses from a single sample. It produces results in 60 s or less, allowing critical decisions to be made quickly. Measurement of total bilirubin is accomplished through software design changes introduced in the RapidLab Software Version 2.1. No hardware/mechanical changes were needed when compared to other 1200 series models. The whole blood sample volume for a single bilirubin determination is 60 μL. The measurement range is reported to be 2–60 mg/dL.

Transcutaneous bilirubin was measured by use of the Dräger (formerly Minolta/Air Shields) jaundice meter JM-103 (Dräger Medical AG & Co. KG, Lübeck, Germany). A measurement range 0–20 mg/dL is claimed for this device.

For evaluation of accuracy and precision, the following control materials at different concentrations were used: Vitros 350, Performance Verifier II (lot R7705); RapidLab 1265, AQC cartridges (lots

Table 1 Quality control data for accuracy and precision of bilirubin measurements, as determined by the application of various quality controls (see section Analyses) at different concentrations.

n	Mean, mg/dL	Target value, mg/dL[a]	Standard deviation, mg/dL	CV, %[b]
RapidLab 1265				
68	21.0	20.0	1.2	5.6
67	11.9	12.0	1.1	9.4
64	4.5	5.0	1.0	23.0
Vitros 350				
62	10.01	9.98	0.31	3.15

[a]Target values are instrument-specific; [b]CV values represent between-day imprecision data.

1239960199, 1243425655, and 1246544263). Traceability of the BuBc calibration is accomplished by a masterlot BuBc slide. The performance of this slide was demonstrated in comparison with the HPLC method of Lauff et al. (10). For target bilirubin concentrations, see Table 1.

Statistics

For the calculation of statistical parameters, add-in macro Analyse-It® (Version 2.10, Analyse-it Software Ltd., Leeds, UK) in Windows Excel® was used. Intermethod comparisons were performed using the non-parametric regression analysis of Passing and Bablok (11). Correlation coefficients were calculated according to Pearson. Details of the differences between the three analytical methods are shown using Bland-Altman difference plots (12). Comparison of the means of the bilirubin measurements between the three different methods was calculated using the paired t-test.

Results

General aspects [practicality, turn-around-time (TAT), precision/accuracy]

Operation of the RapidLab 1265 was satisfactory. There was a need for a thorough basic course and an ample familiarization phase for caregivers due to the complexity of the apparatus. In particular, the biosafe automatic sampling system (single sample port) used with a 100 μL heparinized capillary was challenging for some caregivers. However, after familiarization the device proved to be intuitive to operate and needed only minimal maintenance efforts. Long-life ready sensor electrode technology ensured reliable results throughout the study period. This was proven by a quality assurance scheme. The analyzer uses an automated quality control programme. Additionally, every 30 (or 60) min a one point-calibration is performed, and a full calibration every 8 h.

Results for measurement of the bilirubin controls at three concentrations are summarized in Table 1. For purposes of comparison, control measurements with the Vitros 350 are included in the Table.

The total bilirubin analysis with the RapidLab required <2 min from insertion of the capillary to result printout. In contrast, measurement of neonatal total bilirubin in the core laboratory using the Vitros 350 dry chemistry analyzer was completed within, on average, 30 min from arrival of the sample until approval of the final result.

Comparative descriptive data analysis for the three methods

The RapidLab 1265 measurement of bilirubin in whole blood is converted to a serum concentration equivalent. Overall, total serum bilirubin concentrations using the Vitros BuBc slide method and the co-oximetry based method used with the POCT device agreed closely. The RapidLab had a median of 9.7 mg/dL [96.3% confidence interval (CI) 9.2–10.3], whereas the Vitros 350 measured slightly lower at 9.6 mg/dL (96.3% CI 9.1–9.9). The difference between the two methods was not significant ($p=0.3031$) when applying the two-tailed t-test. However, the bilirubinometer measured lower bilirubin concentrations of 8.2 mg/dL that were statistically significantly (96.3% CI 7.6–8.8). Data are summarized in Table 2. Figure 1 additionally shows the distribution of the results as a Box-and-Whisker plot.

Intermethod comparisons using the Passing-Bablok linear regression analysis and the Pearson correlation coefficient

The regression equations, within a range of 2–20 mg/dL, were as follows (all intercepts given in mg/dL):
Vitros (x) vs. RapidLab (y) ($n=205$):

Table 2 Descriptive statistics of all measurements of neonatal total bilirubin.

Method	#	n	Median (96.3% CI)	Mean (95% CI)	2.5th/97.5th percentile
RapidLab	1	235	9.700 (9.200–10.300)	9.782 (9.338–10.225)	2.570/17.050
Vitros 350	2	210	9.600 (9.100–9.900)	9.765 (9.291–10.238)	2.165/17.780
JM-103	3	237	8.200 (7.600–8.800)	8.208 (7.830–8.586)	1.870/14.025

Two-paired t-test: #1 vs. #2: not significant ($p=0.303$); #1 vs. #3: $p<0.001$; #2 vs. #3: $p<0.001$.

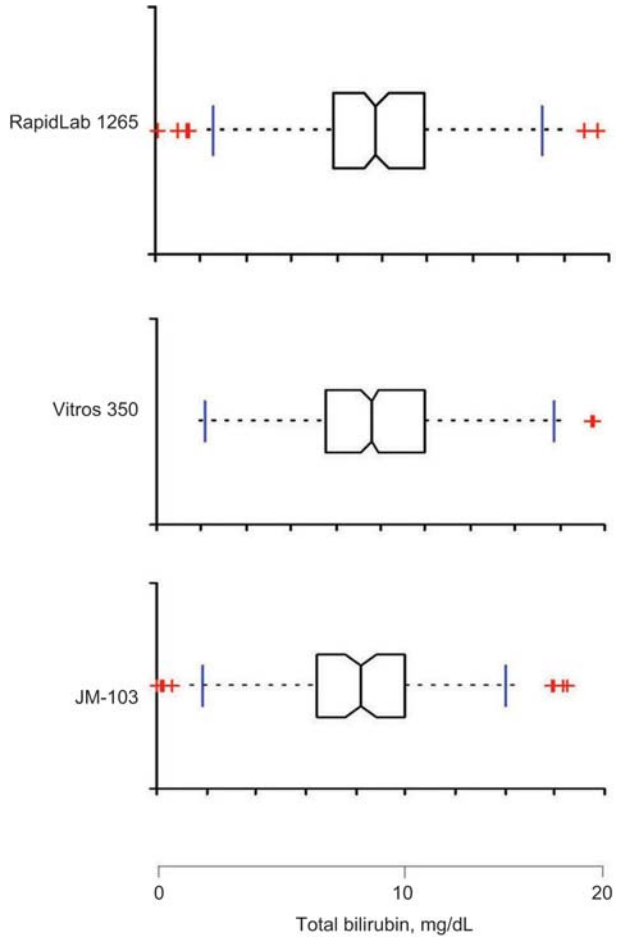

Figure 1 Box-and-Whisker plots of total bilirubin measurements performed with the three devices RapidLab 1265, Vitros 350 and JM-103.

y = 1.0 (CI 0.95–1.03) × x–0.1 (CI –0.43 to 0.39); r = 0.91 (CI 0.89–0.93).
Standard error of the estimate: 1.2833.
Vitros (x) vs. JM-103 (z) (n = 232):
z = 0.86 (CI 0.80–0.92) × x–0.073 (CI –0.67 to 0.46); r = 0.87 (CI 0.84–0.90).
Standard error of the estimate: 1.5589.
RapidLab (y) vs. JM-103 (z) (n = 208):
z = 0.85 (CI 0.79–0.92) × y + 0.0275 (CI –0.58 to 0.66); r = 0.82 (CI 0.77–0.86).
Standard error of the estimate: 1.7764.

The different n values are due to missing data. The CI of the slope of the regression equation, Vitros vs. RapidLab, includes the identity value of 1.0. Also the CI of the intercept includes 0.0. These results demonstrate the comparability between both methods (see also Figure 2). This is not the case for the two other comparisons between the Vitros or RapidLab vs. the bilirubinometer. These methods produce significantly different results. As seen in the descriptive evaluation, the agreement between the Vitros 350 method and the RapidLab 1265 is exceptionally good. However, the agreement between these methods and the bilirubinometer is acceptable only for screening purposes.

Bland-Altman plots as an additional approach for assessing agreement of the three methods

The statement that the RapidLab device is very closely correlated to the laboratory method is also shown in the Bland-Altman plot (Figure 3) which shows little variation throughout the range of 0–20 mg/dL, with nearly perfect agreement since the mean difference line superposes on the zero bias line. The limit of agreement, being defined as the mean difference ± 1.96 × the standard deviation of the differences, was found to be very satisfactory at 2.5 mg/dL.

In contrast, the mean difference lines for the comparison of the transcutaneous bilirubinometer with both the Vitros and the RapidLab method were found to be more than –1.5 mg/dL. The limits are found to be questionable at concentrations > 3.0 mg/dL. Additionally, it can be deduced that the disagreement of at least the JM-103 method strongly depends on the magnitude of measurements. The higher the bilirubin concentration, the larger the disagreement.

Discussion

The current study is the first detailed evaluation of the new bilirubin method on the RapidLab 1265. We used 240 neonatal samples comprising the clinically relevant range up to 20 mg/dL. To our knowledge, there are only a few available data related to performance of the bilirubin measurement using the blood gas analyzer. The results of Hotaling et al. (13) and Dietzen and Wilhite (14) have been published as abstracts only. The RapidLab 1265 offers a variety of critical care testing parameters, such as blood gases, electrolytes and metabolites. All reagents are contained in sealed cartridges, making the device easy to use and maintain. While the analyzer has been on the market for years, the neonatal bilirubin assay received 510(k) approval by the Food and Drug Administration (FDA) in 2008.

The data for the between-run imprecision in Table 1 depicts the fact that the coefficient of variation (CV) trends to be unsatisfactory with values up to 23%. This is in contrast to the finding of Dietzen and Wilhite (14) for the RapidLab, as well as the data of Rolinski et al. (15), Grohmann et al. (16) and Borgard et al. (17) for the Omni S and ABL 735 systems. These authors report CVs that are, even at lower concentrations < 6%. The Vitros 350 shows a CV of approximately 3% at 10 mg/dL, whereas the corresponding CV of the RapidLab is 9.4%. It is impossible to decide whether the high CVs are due to the measurement principle used with the RapidLab. In contrast to RapidLab, the two other devices mentioned above perform measurements using unhemolyzed blood. Also, matrix differences of the control material or handling problems may affect results.

The comparison study shows exceptionally good agreement over the complete measuring range (4.5–20 mg/dL). In the regression equation, y = 1.0 × x–0.1 (r = 0.91), the slope is not significantly different from 1 and the intercept is not different from 0. The 95% CI is approximately ± 2.5 mg/dL, though the manipulation of the 60 μL capillary with the sample requires delicate handling. These results are in prin-

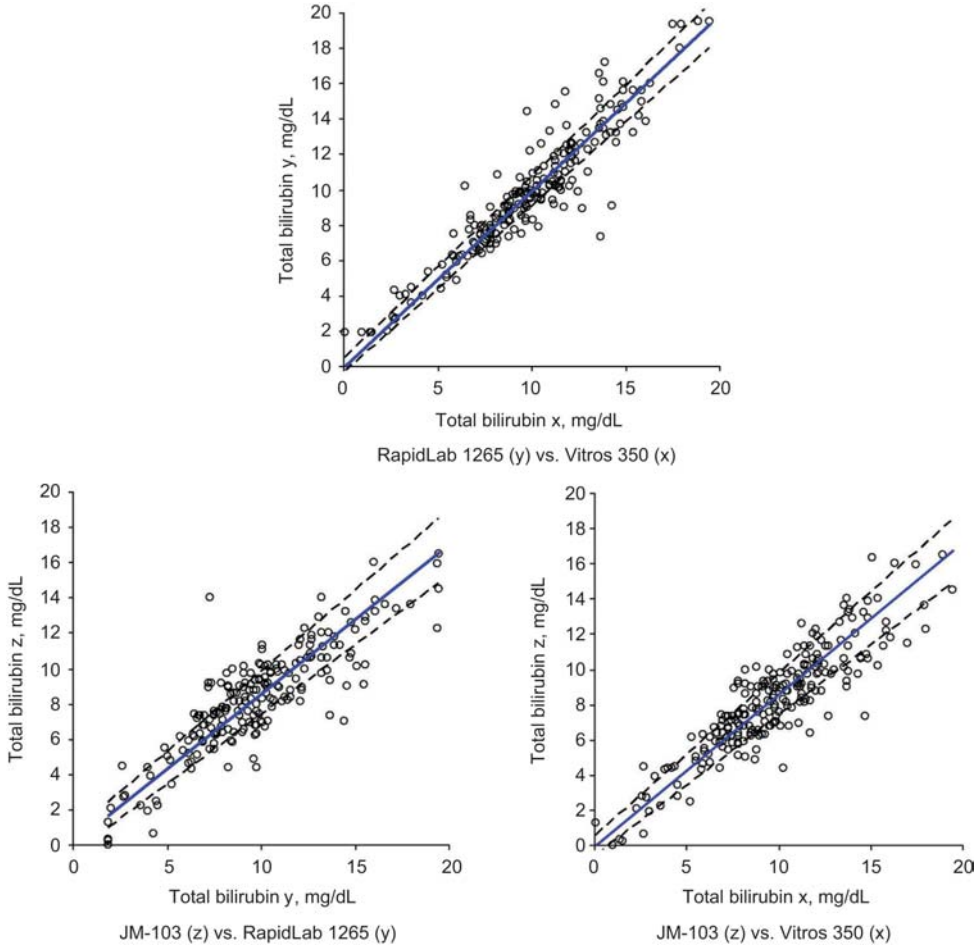

Figure 2 Linear regression lines (Passing-Bablok) for intermethod comparisons between the three devices RapidLab 1265, Vitros 350 and JM-103.
The solid bold line represents the fitted regression line, whereas the dashed lines depict the regression line 95%-confidence band.

ciple comparable to corresponding data of the ABL 735 and the Omni S systems (15–17).

However, despite good correlation, there are discrepancies between single pairs of bilirubin measurements, with three showing differences greater than ±4 mg/dL. Such deviations have been seen also in other studies. In our study, handling problems with the samples might be responsible for these differences.

Our clinical chemistry method is widely used for the analysis of neonatal bilirubin and correlates well with other reliable laboratory methods [e.g., Roche Modular, Dimension RxL (16)]. However, to our knowledge, comparison of the Vitros BuBc method with the original Doumas' reference method (6) for total bilirubin using neonatal samples has not been published. Additionally, the BuBc method cannot be calibrated with the reference standard SRM 916a. In a strict sense, the accuracy of the data thus cannot be judged. Traceability of the BuBc calibration is ascertained by a masterlot BuBc slide that is correlated with the HPLC method of Lauff et al. (10).

In contrast to the RapidLab 1265, the transcutanous bilirubinometer JM-103 generally showed lower values, with a significant mean difference of −1.5 mg/dL and wide scatter. This finding was also described by Grohmann et al. (16). In addition, a study that describes good comparability of results (18), skin test devices generally tend to underestimate bilirubin concentrations (16, 19). Our results are also in accordance with a study performed using the Bilimed bilirubinometer published by Karen et al. (20). This phenomenon is pronounced at high bilirubin concentrations. Thus, these test devices are useful for screening neonates for hyperbilirubinemia, but cannot replace a reliable bilirubin measurement performed using blood (1, 7, 21). If screening by a transcutaneous measurement indicates that the neonate is at increased risk of clinical significant hyperbilirubinemia, a clinical chemistry determination is needed. In the clinical laboratory, the serum fractions of unconjugated and conjugated bilirubin are measured. The TAT in our laboratory is, on average, 30 min, followed by an additional delay of 5 min for electronic reception by the pediatrician. If neonatal bilirubin is measured with a blood gas analyzer, such as the RapidLab 1265, the TAT is reduced dramatically (14, 15). Since the clinical information of the bilirubin serum concentration is usually not as urgent as that of vital parameters,

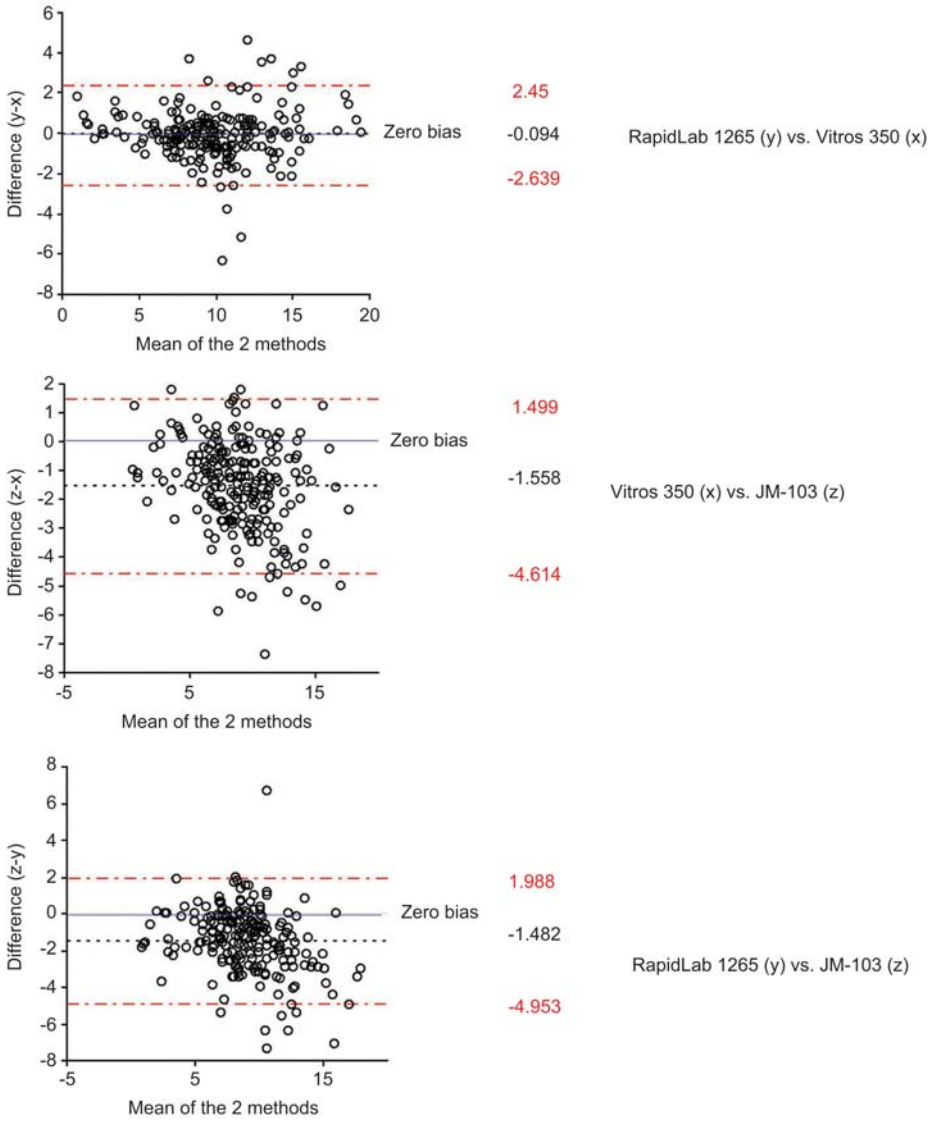

Figure 3 Bland-Altman plots for the intermethod comparisons between the three devices RapidLab 1265, Vitros 350 and JM-103.

such as blood gases, glucose or potassium, this advantage of time is not very relevant in hospitals with sophisticated core laboratories. However, if the clinical chemistry division is not inside the hospital, and the ward-to-laboratory time is considerably long, the POCT device is surely advantageous. Also, in ambulances the RapidLab can be beneficial for neonates at risk of pathological jaundice. Yet, as with any test that is done at the point-of-care (POC), continuous assessment of the competency of the employees using this blood gas analyzer is extremely important. This makes the application of additional parameters within the POC blood gas analyzers complicated. In Germany, a rigorous quality control program [''RiliBÄK'' rules (22)], under the governance of the local POCT coordination, is required.

It remains up to the clinicians whether the time advantage of a rapidly measured neonatal bilirubin is able to optimize clinical procedures, subsequently enhancing the clinical outcome and benefit to the patient. In this context, one should not disregard the economics of such POC tests. The cost-per-reportable-result for the RapidLab bilirubin measurement exceeds the cost of the traditional core laboratory method by an approximated factor of 2–3. This could be justified assuming that the length of stay is reduced significantly. An additional advantage of POCT bilirubin measurements is the low amount of blood needed for analysis, preventing neonatal anemia in long-term intensive care unit patients. This fact also puts the higher costs into perspective.

In conclusion, our study shows that bilirubin measurements performed using the RapidLab 1265 blood gas analyzer appear to be a valuable alternative for the measurements of total bilirubin concentrations traditionally performed in the clinical chemistry laboratory. Results are available within 1–2 min. Thus, the POCT device with the bilirubin option is potentially valuable for use in neonatal

intensive care units or in outpatient ambulances by combining the measurements of vital blood gas parameters and other important metabolites.

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Conflict of interest statement

Authors' conflict of interest disclosure: All authors state that there are no conflicts of interest regarding the publication of this article. Supply of reagents and technical expertise by Siemens played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.
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