Neonatal hemoglobin affects the accuracy of whole blood bilirubin measurement on GEM Premier 4000 blood gas analyzers

Yun Huang a,b,*, Robert Dean a, Yvonne Dubbelman a, Anne Vincent a, Faiza Khurshid c,d

a Clinical Laboratories, Kingston General Hospital, 76 Stuart Street, Kingston, ON, Canada
b Department of Pathology and Molecular Medicine, Queen’s University, 76 Stuart Street, Kingston, ON, Canada
c Neonatal-Perinatal Medicine, Kingston General Hospital, 76 Stuart Street, Kingston, ON, Canada
d Department of Pediatrics, Queen’s University, 76 Stuart Street, Kingston, ON, Canada

ARTICLE INFO

Keywords:
Whole blood bilirubin
Neonates
Hyperbilirubinemia and blood gas analyzer

ABSTRACT

Objectives: Whole blood bilirubin measured on blood gas analyzers is accepted by physicians in neonatal hyperbilirubinemia management since it requires a small sample volume. The accuracy of bilirubin measurement on blood gas analyzers is instrument dependent and remains controversial.

Design and Methods: Bilirubin in adult and umbilical cord whole blood samples, spiked with an unconjugated bilirubin standard, and non-spiked adult plasma samples was measured on a blood gas analyzer (GEM 4000) and a Core Laboratory Chemistry analyzer (Architect c16000) respectively. We also investigated the linear regression for neonatal and adult hemoglobin measured on the blood gas analyzer and the Core Laboratory hematology analyzer (Alinity h-Series).

Results: Plasma bilirubin measured on the blood gas analyzer and the chemistry analyzer was statistically identical. Adult whole blood bilirubin showed slightly increased proportional bias. When umbilical cord whole blood samples were used, the Deming regression showed GEM bilirubin = 1.233(Architect) (95% CI 1.199 to 1.266)-44.43 μmol/L (95% CI -53.6 to -35.2). The regression was significantly different from that in plasma (p < 0.001) or adult whole blood (p < 0.001) samples. 36.1% neonatal samples with bilirubin levels > 50 μmol/L showed that the bias% was above laboratory standards. In addition, the regression of neonatal hemoglobin measurement between the GEM and the Alinity was significantly different from adult hemoglobin (p < 0.01).

Conclusions: Neonatal whole blood bilirubin measurement on blood gas analyzers may be affected by neonatal hemoglobin. The method should be validated using neonatal whole blood samples or samples with a similar matrix before the analyzers are implemented into neonatal hyperbilirubinemia management.

1. Introduction

Physiological Jaundice is seen in 60–70% of newborns. In the management of neonatal hyperbilirubinemia, it requires frequent blood bilirubin level monitoring to reduce the incidence of severe hyperbilirubinemia (kernicterus) [1]. Since the whole blood bilirubin measurement on a blood gas analyzer requires a small sample volume, has a quick turnaround time, and is included in a multi-test panel,
it provides a convenient approach for neonates. However, the Bhutani’s hour-specific bilirubin nomogram that is being used to assess the risk of hyperbilirubinemia was established by serum bilirubin measured on a diazo based assay [2]. To use whole blood bilirubin measurements in Bhutani’s nomogram, the bilirubin accuracy on blood gas analyzers should be comparable to serum bilirubin. It is difficult for routine clinical laboratories to verify the accuracy of neonatal whole blood bilirubin measurements with the limited availability of neonatal blood samples. Adult plasma or whole blood samples used in the validation are not able to confirm neonatal whole blood bilirubin measurements due to the uniqueness of physiological characteristics in neonatal red blood cells (RBCs) [3]. Neonatal RBCs show a larger size and contain a higher level of fetal hemoglobin (HbF) than adults [3]. HbF in adults is normally reduced to less than 0.6% of the total hemoglobin and is concentrated in a small number of RBCs, termed F-cells [4].

Some validation studies using neonatal whole blood samples provided conflicting correlations between blood gas analyzers and chemistry analyzers [5–9], which confused physicians in interpreting whole blood bilirubin results for patient management. The common causes of bias are a lack of standardized plasma bilirubin reference methods [10,11] and the difference in methodologies between blood gas analyzers using multiple-wavelength photometry and chemistry analyzers using diazo based assay [5–9]. Other factors contributing to the bias include neonatal hemoglobin interference [5,8], calculation of plasma equivalency on blood gas analyzers [8,9], increased conjugated bilirubin or delta bilirubin in samples [7], and variable blood albumin levels [12].

In our Neonatal Intensive Care Unit (NICU) we observed inconsistent blood bilirubin results between the blood gas analyzer and the Core Laboratory chemistry analyzer. This study was conducted to verify the accuracy of neonatal whole blood bilirubin measurement on the blood gas analyzer to establish its clinical utilization. We used adult plasma samples, adult whole blood sample pools and umbilical cord blood sample pools (with the similar cell matrix and Hb F as neonatal blood samples). The whole blood samples were spiked with commercial unconjugated bilirubin across the whole measuring range. The accuracy of neonatal hemoglobin measurement on the blood gas analyzer was investigated as well.

2. Methods and materials

2.1. Measurement principles

GEM Premier 4000 blood gas analyzer (Instrumentation Laboratory) [13,14]: RBCs are lysed by a chemical reagent. Total bilirubin and hemoglobin are measured by multiple-wavelength optical absorbance in hemolyzed whole blood samples. The sample spectrum is measured simultaneously at about 2000 wavelengths between 480 and 650 nm and is compared to on-board standards based on Beer Lambert’s Law. Plasma equivalent bilirubin = bilirubin in whole blood hemolysate/(1-hematocrit), hematocrit = total hemoglobin (g/dL) x 0.03. The measuring range of bilirubin on GEM 4000 is 5–684 μmol/L, and 30–230 g/L for hemoglobin. According to the instrument manual HbF is automatically corrected in the measurement of CO-Oximetry in every sample by identifying the spectral patterns associated with HbF [13]. The level of total bilirubin can be used to aid in assessing the risk of kernicterus in neonates [14].

Architect c16000 chemistry analyzer (Abbott Diagnostics): Bilirubin in plasma samples couples with a diazo reagent in the presence of a surfactant to form azobilirubin. The increase of absorbance at 548 nm due to azobilirubin is directly proportional to the total bilirubin level. The measuring range of plasma bilirubin on Architect c16000 is from 1.71 to 427.5 μmol/L. Hemolysis up to 20 g/L does not affect the measurement of total bilirubin at 18.3 μmol/L and 240.8 μmol/L respectively.

Alinity h-Series Hematology System (Abbott Diagnostics): RBCs are lysed by a chemical reagent, hemoglobin is converted to a chromogen and measured by absorption spectrophotometry at the wavelength of 540 nm. The measuring range of hemoglobin is from 10 g/L to 250 g/L.

2.2. Materials

Unconjugated bilirubin standard (product number B4126, molecular weight 584.7) was purchased from Sigma-Aldrich. The stocks were prepared in sodium hydroxide solution as manufacturer’s instruction and were aliquoted and protected from light.

2.3. Study procedures

The study was approved by the Queen’s University Health Sciences & Affiliated Teaching Hospital Research Ethics Board.

2.3.1. Bilirubin method comparison between the GEM4000 and the Architect c16000 using adult heparinized plasma samples

In the initial validation of the GEM4000 blood gas analyzer, split adult patient plasma samples were measured for bilirubin on the GEM and the Architect respectively within 30 min to verify the measurement of bilirubin on the GEM.

2.3.2. Bilirubin method comparison between the GEM 4000 and the Architect c16000 using adult heparinized whole blood sample pools

Adult whole blood samples were used to verify the correlation between whole blood bilirubin measurement on the GEM and plasma bilirubin measurement on the Architect. After the adult whole blood samples spiked with different amounts of unconjugated bilirubin were measured on the GEM, the samples were centrifuged immediately to collect plasma for bilirubin measurement on the Architect.

2.3.3. Bilirubin method comparison between the GEM 4000 and the Architect c16000 using umbilical cord heparinized whole blood sample pools

Umbilical cord whole blood samples were used to verify the accuracy of neonatal whole blood bilirubin measurement on the GEM.
After the umbilical cord whole blood samples spiked with different amounts of unconjugated bilirubin were measured on the GEM, the samples were centrifuged immediately to collect plasma for bilirubin measurement on the Architect.

2.3.4. The comparison of hemoglobin measurement between the GEM 4000 (adult heparinized whole blood) and the Alinity h-Series (adult EDTA whole blood)

Since patient hemoglobin level was used in the calculation of plasma equivalent bilirubin, the accuracy of hemoglobin measurement on the GEM was investigated. In a one-month period, 20 pairs of adult patient hemoglobin results measured on the GEM and the Core Laboratory Alinity within a 9-h interval were randomly selected and extracted from the laboratory information system for hemoglobin method comparison.

2.3.5. The comparison of hemoglobin measurement between the GEM 4000 (neonatal heparinized whole blood) and the Alinity h-Series (neonatal EDTA whole blood)

Similarly, in a four-month period 28 pairs of neonatal patient hemoglobin results measured on the GEM and on the Alinity within 30 min interval were random selected and extracted from the laboratory information system for hemoglobin method comparison.

2.4. Data analysis

Deming regression analysis between the two methods and the distribution of method bias% were performed in EP Evaluator (Data Innovations, version 12). The two methods were considered statistically identical if the 95% confidence interval (CI) of slope crossed 1 and the 95%CI of intercept crossed 0. The difference of the regression between the groups was determined by General Linear Model and univariate analysis on SPSS (IBM SPSS statistics, version 26). P < 0.05 indicated a significant difference.

3. Results

3.1. Bilirubin comparison between the GEM4000 and the Architect c16000 using adult plasma samples

Thirty-nine adult plasma samples with bilirubin levels ranging from 4 to 460 μmol/L were measured on the GEM and the Architect respectively, which had no hemoglobin interference. Deming regression showed a good correlation between the two methods with a correlation coefficient (r) 0.9952, slope 1.005 (95% CI 0.972–1.038), and intercept 1.33 (95% CI -4.88–7.55) (Fig. 1A). This indicated that the two methods were statistically identical. When sample bilirubin levels were greater than 50 μmol/L, the average bias was 0.65 μmol/L and the distribution of bias% was evenly between −14.44% and 12.72% (Fig. 1B).

3.2. Bilirubin comparison between the GEM 4000 and the Architect c16000 using adult whole blood sample pools

Forty-one adult whole blood samples were spiked with different amounts of unconjugated bilirubin ranging from 7 to 610 μmol/L. Deming regression analysis of bilirubin measurements between the GEM and the Architect showed a good correlation (r 0.9977), identical intercept 0.90 (95% CI of intercept −5.4–7.3), and non-identical slope 1.045 (95% CI 1.022–1.068) (Fig. 2A). There was no significant difference of regression between the adult plasma samples and the whole blood samples (p > 0.05), hence the adult whole blood bilirubin measurement on the GEM was comparable with the Architect. When sample bilirubin levels were greater than 50 μmol/L, the average bias was increased to 14.4 μmol/L, and the distribution of bias% was evenly between −6.2% and 20.1% (Fig. 2B).

Fig. 1. Bilirubin comparison between the GEM 4000 and the Architect c16000 using adult plasma samples. A: Deming regression, B: Distribution of bias%.
3.3. Bilirubin comparison between the GEM 4000 and the Architect c16000 using umbilical cord whole blood sample pools:

Fifty-one umbilical cord whole blood samples were spiked with different amounts of unconjugated bilirubin ranging from 25 to 550 μmol/L. The two methods still correlated well with r 0.996, however, the Deming regression showed poor statistical identity between the two methods with a slope 1.233 (95% CI 1.199–1.266) and intercept -44.43 (95% CI -53.6–-35.2) (Fig. 3A). Furthermore, univariate analysis showed a significant difference of regression between the umbilical cord whole blood samples and the plasma samples (p < 0.001), and the adult whole blood samples (p < 0.001) respectively. In addition, the GEM overestimated bilirubin level when it was above 270 μmol/L. When sample bilirubin levels were greater than 50 μmol/L, the average bias was 15.5 μmol/L. However, the distribution range of bias% (-39.2%–22.18%) was increased comparing to the adult whole blood samples. Also, the bias% was increased with the increase of bilirubin (Fig. 3B). In 36 umbilical cord samples with bilirubin levels greater than 50 μmol/L, 13 (36.1%) samples had the bias% between the GEM and the Architect greater than 16% (laboratory total allowable error). The neonatal whole blood bilirubin measurement on the GEM was not comparable with the Architect.

3.4. The comparison of adult hemoglobin measurement between the GEM 4000 and the Alinity h-Series

Twenty pairs of adult hemoglobin results from 20 patients were measured on the GEM and the Alinity, ranging from 69 to 172 g/L. Adult hemoglobin measurement on the GEM showed statistically identical as the Alinity. Deming regression was Hb GEM = 1.037 x (Alinity) - 3.2 g/L with r 0.9924, 95% CI of slope 0.973–1.100, and 95% CI of intercept -11.0–-4.7 (Fig. 4A). The average bias was 1.3 g/

---

![Fig. 2. Bilirubin comparison between the GEM 4000 and the Architect c16000 using adult blood samples](image1)

A: Deming regression, B: Distribution of bias%.

![Fig. 3. Bilirubin comparison between the GEM 4000 and the Architect c16000 using spiked umbilical cord blood sample pools](image2)

A: Deming regression, B: Distribution of bias%.

---
between /C0 bilirubin on Roche Cobas C601 result is closer to the true value since no reference method is available [10,11]. In method validation studies the bilirubin measurements on different diazo assay-based chemistry analyzers were compared, such as analyzers from Roche diagnostics, Ortho Clinical Diagnostics, or Siemens Healthcare Diagnostics [9,15]. The linear regression analysis identified a good correlation (r > 0.990) between these chemistry analyzers, but different slopes and intercepts. In Lano’s study [3] Passing-Bablok linear regression analysis showed that bilirubin on Roche Cobas C601 = 0.97 (Vitros 350) – 2.4 μmol/L, with statistically identical slope and intercept. While in Grohmann’s study [15] the linear regression analysis showed that bilirubin on Hitachi 912 = 1.019 x (Dimension RXL) + 3.254 μmol/L, Dimension RXL=0.943 x (Vitros 250) – 2.629 μmol/L, and Vitros 250=–1.045 x (Hitachi 912) –1.516 μmol/L. The average bias between the measured results and the assigned value of a quality control material on Hitachi 912, Dimension RXL and Vitros 250 was –8.0, 12.1 and –4.1 μmol/L respectively. In our laboratory we used an Abbott Architect c16000 (Diazo assay) to measure plasma bilirubin. In a recent survey of Proficiency Testing Abbott architect chemistry analyzers showed the lowest bilirubin result among all method groups. At total bilirubin 89 μmol/L, the biases between the means of measurements on the analyzers and the assigned value were from –5 to 8 μmol/L for four groups of chemistry analyzers including Abbott Architect, Roche Cobas, Siemens Dimension, and Ortho Vitros.

Similarly, 28 pairs of hemoglobin results from 12 neonates in NICU were measured on the GEM and the Alinity. The range of neonatal hemoglobin was 98–176 g/L. Deming regression was Hb GEM = 1.217 (Alinity) - 3.01 g/L, with r 0.9598, 95% CI of slope 1.078–1.355, and 95% CI of intercept –49.3––11.0, which was not statistically identical (Fig. 5A). One sample showed a bias up to –24.3% that might be due to inadequate sample mixing in capillary tube when the sample was measured on the blood gas analyzer. The regression of hemoglobin between the adult whole blood and the umbilical cord whole blood samples was significantly different (p < 0.01), which might affect the calculation of neonatal whole blood bilirubin on the GEM. In addition, the GEM showed a trend to overestimate neonatal hemoglobin level when it was above 140 g/L. The average bias was –0.5 g/L, the distribution of bias% was between –6.31 and 9.71%, and the bias% was slightly increased with the increase of hemoglobin (Fig. 5B).

### 4. Discussion

The bilirubin measurement on chemistry analyzers has been showing challenges in laboratory practice, it cannot determine which result is closer to the true value since no reference method is available [10,11]. In method validation studies the bilirubin measurements on different diazo assay-based chemistry analyzers were compared, such as analyzers from Roche diagnostics, Ortho Clinical Diagnostics, or Siemens Healthcare Diagnostics [9,15]. The linear regression analysis identified a good correlation (r > 0.990) between these chemistry analyzers, but different slopes and intercepts. In Lano’s study [3] Passing-Bablok linear regression analysis showed that bilirubin on Roche Cobas C601 = 0.97 (Vitros 350) – 2.4 μmol/L, with statistically identical slope and intercept. While in Grohmann’s study [15] the linear regression analysis showed that bilirubin on Hitachi 912 = 1.019 x (Dimension RXL) + 3.254 μmol/L, Dimension RXL=0.943 x (Vitros 250) – 2.629 μmol/L, and Vitros 250=–1.045 x (Hitachi 912) –1.516 μmol/L. The average bias between the measured results and the assigned value of a quality control material on Hitachi 912, Dimension RXL and Vitros 250 was –8.0, 12.1 and –4.1 μmol/L respectively. In our laboratory we used an Abbott Architect c16000 (Diazo assay) to measure plasma bilirubin. In a recent survey of Proficiency Testing Abbott architect chemistry analyzers showed the lowest bilirubin result among all method groups. At total bilirubin 89 μmol/L, the biases between the means of measurements on the analyzers and the assigned value were from –5 to 8 μmol/L for four groups of chemistry analyzers including Abbott Architect, Roche Cobas, Siemens Dimension, and Ortho Vitros.

Blood gas analyzers from Radiometer (ABL series) have been used in several published validation studies with neonatal whole blood samples. The correlation coefficient between ABLS and chemistry analyzers were from 0.876 to 0.987 [6,7,9]. Rolinski’s study (2001) showed bilirubin on ABL 735 = 1.002 x (Hitachi 917) - 4.0 μmol/L, with 95% CI of slope 0.914–1.090, 95%CI of intercept –22–14 μmol/L [6]. Another study (Peake et al., 2001) showed bilirubin on ABL735 = 0.986 x (Hitachi 917) - 0.4 μmol/L [5]. While conjugated and delta bilirubin were excluded, bilirubin on ABL735 = 0.99 (Vitros 250) + 3.4 μmol/L [6]. In 2018 the regression analysis (Lano et al.) showed bilirubin on ABL 90 = 1.03 (Roche Cobas 601) – 3.5 μmol/L, with 95% CI of slope 1.00–1.06, 95%CI of intercept –6.4––0.5 μmol/L; and bilirubin on ABL 90 =0.98 (Vitros 350) –5.7 μmol/L, with 95% CI of slope 0.93–1.04, 95%CI of intercept –11.8–8. μmol/L [9]. No significant interference on whole blood bilirubin measurements resulted from hematocrit, hemoglobin F, PO2 and pH in the samples was reported on ABLS [5,6]. However, one study showed imperfect correlation between neonatal whole blood bilirubin measured on the GEM 4000 and plasma bilirubin on the Vitros 350, GEM =1.43 (Vitros 350) –61.13 μmol/L, with 95% CI of slope 1.36–1.50, and 95%CI of intercept –73.8–50.5 μmol/L. Additionally, the GEM underestimated bilirubin at low levels and overestimated bilirubin at high levels. It also identified that the GEM underestimated bilirubin at high hemoglobin levels [8].

**Fig. 4.** Hemoglobin comparison between the GEM 4000 and the Alinity h-Series using adult blood samples
A: Deming regression, B: Distribution of bias%.

L, and the distribution of bias% was evenly between –5.62 and 5.60% (Fig. 4B).

### 3.5. The comparison of neonatal hemoglobin measurement between the GEM 4000 and the Alinity h-Series

In method validation studies the bilirubin measurements on different diazo assay-based chemistry analyzers were compared, such as analyzers from Roche diagnostics, Ortho Clinical Diagnostics, or Siemens Healthcare Diagnostics [9,15]. The linear regression analysis identified a good correlation (r > 0.990) between these chemistry analyzers, but different slopes and intercepts. In Lano’s study [3] Passing-Bablok linear regression analysis showed that bilirubin on Roche Cobas C601 = 0.97 (Vitros 350) – 2.4 μmol/L, with statistically identical slope and intercept. While in Grohmann’s study [15] the linear regression analysis showed that bilirubin on Hitachi 912 = 1.019 x (Dimension RXL) + 3.254 μmol/L, Dimension RXL=0.943 x (Vitros 250) – 2.629 μmol/L, and Vitros 250=–1.045 x (Hitachi 912) –1.516 μmol/L. The average bias between the measured results and the assigned value of a quality control material on Hitachi 912, Dimension RXL and Vitros 250 was –8.0, 12.1 and –4.1 μmol/L respectively. In our laboratory we used an Abbott Architect c16000 (Diazo assay) to measure plasma bilirubin. In a recent survey of Proficiency Testing Abbott architect chemistry analyzers showed the lowest bilirubin result among all method groups. At total bilirubin 89 μmol/L, the biases between the means of measurements on the analyzers and the assigned value were from –5 to 8 μmol/L for four groups of chemistry analyzers including Abbott Architect, Roche Cobas, Siemens Dimension, and Ortho Vitros.
In our study we verified that adult plasma bilirubin results measured on the GEM were statistically identical as the Architect. This good correlation was similar to the neonatal plasma results in Peake’s study showing that the Passing-Bablok linear regression of bilirubin was \( ABL_{735} = 0.996 \times (\text{Hitachi 917}) - 3.3 \mu\text{mol/L} \) [5]. When adult whole blood samples were used for method comparison, the bilirubin measurement on the GEM was partially non-identical as the Architect. However, the regression between the adult whole blood samples and the plasma samples had no statistical difference. When umbilical cord whole blood samples were used for method comparison, the regression between the two methods was poor with a slope of 1.233 and an intercept of \(-44.4 \mu\text{mol/L}\), and the regression was significantly different from the adult plasma samples (\( p < 0.001 \)) and from the adult whole blood samples (\( p < 0.001 \)). 36.1% of neonatal samples had a bias greater than laboratory standards when the bilirubin levels were greater than 50 \( \mu\text{mol/L} \). Therefore, the accuracy of neonatal whole blood bilirubin measurements on the GEM was not verified as indicated in the manufacture’s reference [13]. Although all types of blood gas analyzers use multiple-wavelength optical absorbance for whole blood bilirubin measurements, the calibration related to neonatal bilirubin measurements may not be the same [9]. The comparison between different types of blood gas analyzers would be helpful to understand the influence of algorithm of HbF correction on the accuracy of neonatal whole blood bilirubin measurement, this has not been available in the literature search.

When plasma equivalent bilirubin results are reported on GEM blood gas analyzers, the measured hemoglobin results are converted to hematocrit to correct sample dilution of RBCs [13]. In this study Deming regression showed adult hemoglobin measurements on the GEM and the Alinity were statistically identical and the bias% was evenly distributed in a narrower range (–5.62 to 5.60%). While for neonates, Deming regression showed poorer slope (1.037 adult vs. 1.217 neonate), intercept (–3.2 adult vs. –30.1 neonate), and correlation coefficient (0.9924 adult vs. 0.9598 neonate). The regression between the adult samples and the neonatal samples was significantly different (\( P < 0.05 \)). In two studies the comparison of hemoglobin measurements between the GEM series and the Core Laboratory hematology analyzers showed no significant difference [16,17]. However, both studies used the samples from different patient populations. One study used patient samples randomly collected from the Intensive Care Unit [16] and the other used anonymous samples from different units [17]. Although Hb F and Hb A (majority of adult hemoglobin) have a slightly different light absorption spectra, it is important enough to be taken into account in the multi-component analysis of hemoglobin derivatives [18,19]. The inaccurate neonatal hemoglobin on the GEM observed in this study may also account for the bias of bilirubin measurements between blood gas analyzers and chemistry analyzers as seen in Wang’s study [8].

We used umbilical cord whole blood sample pools that have a similar cell matrix including HbF as neonatal whole blood in this study. However, the commercial unconjugated bilirubin spiked in the sample pools may not exactly represent the bilirubin in patient blood samples measured on blood gas analyzers and chemistry analyzers [13]. It was difficult to investigate the interference of bilirubin measurement on blood gas analyzers without fully understanding the design or calibration of the analyzers. Standard methods are required to confirm superiority of one data to the other. Currently the bias between blood gas analyzers and chemistry analyzers are unavoidable. If the analyzer is validated appropriately, blood sample saving should be a goal that is achievable and beneficial. Neonatal bilirubin levels measured on three types of analyzers, including transcutaneous bilirubin devices, blood gas analyzers and chemistry analyzers were compared to each other in Grohmann’s study [15]. A strategy based on the accuracy of the methods to avoid repeated blood sampling for neonatal bilirubin measurement was recommended accordingly.

5. Conclusions

Whole blood bilirubin measurement on blood gas analyzers should be validated with neonatal samples or samples with a similar matrix before it is used in the management of neonatal hyperbilirubinemia due to the special properties of neonatal hemoglobin. The whole blood bilirubin measurement may not be able to replace the serum bilirubin measurement in Bhutani’s nomogram, but it can be
used for monitoring blood bilirubin level and for reducing blood sampling when the analyzer is set up appropriately.

Author statement

Yun Huang: Conceptualization, Methodology, Formal analysis, Writing-Original draft, Writing-Review and editing.
Robert Dean: Methodology, Validation.
Yvonne Dubbelman: Methodology, Validation.
Anne Vincent: Methodology, Investigation, Writing-Review and editing.
Faiza Khurshid: Conceptualization, Methodology, Writing-Review and editing.

Declaration of competing interest

There are no known conflicts of interest associated with this publication.

References

[1] Canadian Pediatric Society, Guidelines for Detection, Management and Prevention of Hyperbilirubinemia in Term and Late Preterm Newborn Infants, Posted, 2007. and reaffirmed: Feb 28, 2018.
[2] V.K. Bhutani, L. Johnson, E.M. Sivieri, Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns, Pediatrics 103 (1) (1999 Jan) 6–14.
[3] O. Linderkamp, G.B. Nash, P.Y. Wu, H.J. Meiselman, Deformability and intrinsic material properties of neonatal red blood cells, Blood 67 (5) (1986 May) 1244–1250.
[4] J. Rochele, J.E. Craig, S.L. Thein, Fetal hemoglobin levels in adults, Blood Rev. 8 (4) (1994 Dec) 213–224.
[5] M. Peake, B. Mazzachi, A. Fudge, R. Bais, Bilirubin measured on a blood gas analyser: a suitable alternative for near-patient assessment of neonatal Jaundice? Ann. Clin. Biochem. 38 (Pt 5) (2001 Sep) 533–540.
[6] B. Rolinski, H. Küster, B. Ugele, R. Gruber, K. Horn, Total bilirubin measurement by photometry on a blood gas analyzer: potential for use in neonatal testing at the point of care, Clin. Chem. 47 (10) (2001 Oct) 1845–1847.
[7] O.P. Laterza, C.H. Smith, T.R. Willkie, M. Landt, Accurate direct spectrophotometric bilirubin measurement combined with blood gas analysis, Clin. Chim. Acta 323 (1–2) (2002 Sep) 115–120.
[8] L. Wang, A.Y. Albert, B. Jung, K. Hadad, M.E. Lyon, M. Basso, Limitations and opportunities of whole blood bilirubin measurements by GEM premier 4000®, BMC Pediatr. 17 (1) (2017 Mar) 92.
[9] L.M. Lano, A.W. Lyon, L. Wang, R. Ruskin, M.E. Lyon, Comparative evaluation of neonatal bilirubin using Radiometer whole blood co-oximetry and plasma bilirubin methods from Roche Diagnostics and Ortho Clinical Diagnostics, Clin. Biochem. 53 (2018 Mar) 88–92.
[10] Dina N. Greene, Joy Liang, Daniel T. Holmes, Ann Resch, Thomas S. Lorey, Neonatal total bilirubin measurements: still room for harmonization, Clin. Biochem. 47 (12) (2014 Aug) 1112–1115.
[11] R. Klauike, H.J. Kytzia, F. Weber, D. Grote-Koska, K. Brand, G. Schumann, Reference measurement procedure for total bilirubin in serum re-evaluated and measurement uncertainty determined, Clin. Chim. Acta 481 (2018 Jun) 115–120.
[12] D.E. Van Imhoff, P.H. Dijk, C.W. Weykamp, C.M. Cobbaert, C.V. Hulzebos, BARTrial Study Group, Measurements of neonatal bilirubin and albumin concentrations: a need for improvement and quality control, Eur. J. Pediatr. 170 (8) (2011 Aug) 977–982.
[13] Instrumentation Laboratory, GEM Premier 4000 Reference Guide, November 2015. Version 3.
[14] Instrumentation Laboratory, GEM Premier 4000 Operator’s Guide, March 2015. Version 3.
[15] K. Grohmann, M. Roser, B. Rolinski, I. Kadow, C. Müller, A. Goerlach-Grav, M. Nauck, H. Küster, Bilirubin measurement for neonates: comparison of 9 frequently used methods, Pediatrics 117 (4) (2006 Apr) 1174–1183.
[16] M. Oyaert, T. Van Maerken, S. Bridges, S. Van Loon, H. Laverge, V. Stove, Analytical and pre-analytical performance characteristics of a novel cartridge-type blood gas analyzer for point-of-care and laboratory testing, Clin. Biochem. 53 (2018 Mar) 116–126.
[17] C. Oris, Y. Clavel, M. Jabaudon, A. Pialat, H.A. Mohamed, F. Loret, V. Sapin, D. Bouvier, Method validation of a set of 12 GEM® Premier™ 4000 blood gas analyzers for point-of-care testing in a university teaching hospital, Pract. Lab. Med. 10 (2017 Dec) 21–33.
[18] W.G. Zijlstra, A. Buurenma, W.P. Meerswes-van der Roest, Absorption spectra of human fetal and adult oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin, Clin. Chim. Acta 37 (9) (1991 Sep) 1633–1638.
[19] N. Fogh-Andersen, O. Siggaard-Andersen, F.C. Lundsgaard, P.D. Wimberley, Spectrophotometric determination of hemoglobin pigments in neonatal blood, Clin. Chim. Acta 166 (2–3) (1987 Jul 15) 291–296.