Comparison of Whole Blood Total Bilirubin Determination in Neonates

Managing the care of newborn patients requires integration of multidisciplinary professionals, skills, and processes. Patients' needs fluctuate constantly, and the necessity for accurate and fast results is urgent. Real-time dissemination of information allows clinicians to make critical clinical decisions in a timely manner. In this article, we look at a new alternative for monitoring bilirubin in newborns.

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Background

About 60 percent of newborn babies display mild jaundice (yellowing of the skin) within the first two days after birth due to shortened lifespan of red blood cells coupled with slow maturation of liver glucuronyl transferase activity. Mild jaundice is usually not detrimental. However, some newborns develop severe jaundice from high levels of unconjugated bilirubin circulating in the blood. If left untreated, unconjugated bilirubin may deposit in the basal ganglia and brainstem, causing irreversible neurologic damage, a condition known as kernicterus. Kernicterus can cause cerebral palsy; problems with hearing, vision and teeth; and mental retardation. Some newborns have a higher risk of developing elevated bilirubin concentrations than others. Risk factors include prematurity, family history, bruising at birth, jaundice in the first 24 hours of life, unrecognized maternal-fetal Rh incompatibility and other causes of severe hemolysis (e.g., glucose-6-phosphate dehydrogenase deficiency).

Simple and non-invasive phototherapy is the first approach to reduce high levels of neonatal bilirubin. However, if phototherapy does not lower the baby's bilirubin blood levels, an exchange transfusion may be required. As untreated hyperbilirubinemia may cause severe permanent health problems, all newborns should be checked for jaundice. The practice guidelines of the American Academy of Pediatrics include provisions for measurement of total bilirubin to evaluate the degree of jaundice and the necessity for intervention.

Because of the complication of collection, limited blood volume and higher hematocrit, testing neonatal blood can be challenging. Large reagent-based chemistry analyzers require the separation of plasma from the red blood cells prior to analysis. Blood gas analyzers offer an alternate method for assessing the risk of kernicterus using direct multiwavelength spectrophotometry on small volumes of whole blood. Additionally, blood gases, pH, electrolytes, metabolites, total hemoglobin and CO-oximetry can be measured simultaneously on the same whole blood specimen.

We present a neonatal whole blood total bilirubin performance evaluation of two blood gas systems: the RAPIDLab® 1245 from Siemens Healthcare Diagnostics compared to the RADIOMETER ABL 735, a member of the RADIOMETER ABL 700/800 family of systems. The ABL 735 uses an on-board sonicator to hemolyze the red blood cells for CO-oximetry and optical bilirubin analysis. The RAPIDLab 1245 performs the optical measurements directly on unhemolyzed whole blood.

Materials and Methods

Whole blood samples were collected from babies less than 100 days of age in the neonatal and pediatric intensive care units of St. Louis Children's Hospital, St. Louis, Missouri, USA. The protocol was approved by the Human Subjects Committee of Washington University, St. Louis, Missouri, USA. Whole blood, originally drawn from these patients via heparinized arterial lines, was measured first on the ABL 735 (Radiometer, Copenhagen, DE) and results reported. Remaining whole blood volume from the same draw was then analyzed on the RAPIDLab 1245 system within 10 minutes of the ABL 735 analysis. The same two blood gas analyzers were used throughout the nine-week study. Paired bilirubin values from the two analyzers were compared on all neonatal samples that were greater than the analyte detection limit (2.0 mg/dL) of the RAPIDLab. Any samples exhibiting preanalytical error were removed from the analysis.

Imprecision was evaluated using aqueous quality control (QC) material measured in duplicate daily. Manual QC was run according to manufacturers' directions with one QC sample tested per vial using the respective manufacturer-recommended adapters. Radiometer QUALICHECK™ was used on the ABL 735, and Siemens RapidQC™ Complete was used on the RAPIDLab 1245 system. The optional automatic quality control material (AQC) available on the RAPIDLab 1245 was also tested for imprecision.

Results

Imprecision

A minimum of 50 manual aqueous QC samples per level were measured on each blood gas analyzer throughout the study. Two levels (representing low and high bilirubin ranges) were run on the ABL 735, and three levels (low, mid, and high) were analyzed on the RAPIDLab 1245. Mean bilirubin concentration (in mg/dL), total standard deviation (Total SD), and coefficient of variation [%CV = 100 x (Total SD/Mean Concentration)] were calculated. The Total SD and %CV incorporate within-run and day-to-day imprecision. Based on the data in Table 1, the imprecision of the manual quality control material for the two platforms was similar and ranged from 2.2% to 7.0% CV. In addition, the performance of the control materials on the RAPIDLab 1245 was comparable across the two different types of quality control application (manual versus automatic quality control).

Accuracy

A total of 77 paired clinical neonatal whole blood specimens were evaluated. Age of the patients ranged from birth to 100 days old. Total bilirubin levels ranged from 2.2 to 16.7 mg/dL, per the ABL 735. Four samples were excluded (1 rejected due to the >10 minute elapsed time criteria and 3 rejected due to ABL 735 sampling errors). The total bilirubin values of the 77 pairs were graphically compared. The ABL 735 total bilirubin results represent the x-axis and the RAPIDLab 1245 total bilirubin values represent the y-axis in Figure 2.

Linear regression analysis of the neonatal total bilirubin data was performed to provide estimates of proportional (slope) and constant (intercept, in mg/dL) bias, along with estimates of relative error (standard error of the estimate, referred to as root mean square error or Syx) and agreement (correlation coefficient, r^2) between the two instrument models. Regression analysis yielded the following relationship:

RAPIDLab = (1.01 x ABL) – 0.48

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Device	Material	Mean Conc. (mg/dL)	N	Total SD	CV (%)
ABL	Qualicheck	4.2	140	0.29	7.0
ABL	Qualicheck	22.3	140	0.49	2.2
RAPIDLab	Complete	5.1	53	0.19	3.7
RAPIDLab	Complete	12.4	50	0.39	3.1
RAPIDLab	Complete	19.8	51	0.94	4.7
RAPIDLab	AQC	5.0	32	0.21	4.2
RAPIDLab	AQC	11.9	33	0.32	2.7
RAPIDLab	AQC	20.0	12	1.03	5.2

1 **Quality control precision statistics**

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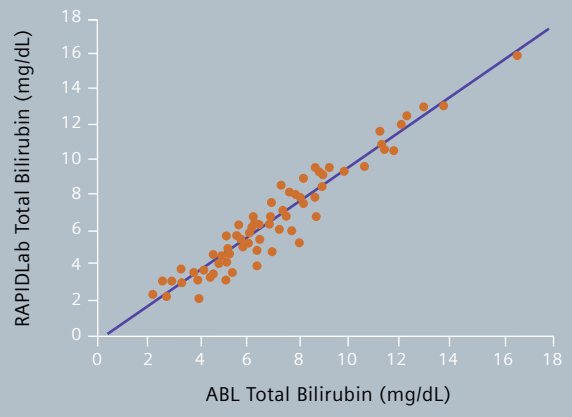

2 **Neonatal total bilirubin concentration using the RAPIDLab 1245 vs. the ABL 735**

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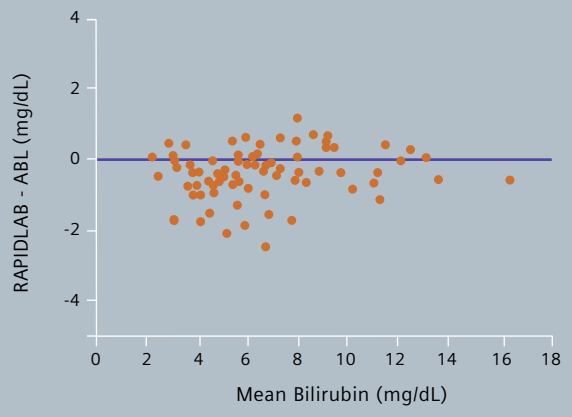

3 **Bland-Altman plot of neonatal whole blood total bilirubin (bias vs. mean)**

The Syx was 0.79 and r^2 was 0.93. The results indicate good total bilirubin correlation between the two blood gas instrument platforms.

Total bilirubin bias was determined (RAPIDLab 1245 – ABL 735). Average bias was –0.4 mg/dL and ranged from –2.7 to 1.3 mg/dL. A Bland-Altman plot (Figure 3) displaying bias against mean [(RAPIDLab bilirubin + ABL bilirubin)/2] indicates a consistent pattern across the entire range.

Conclusion

As demonstrated in the hospital setting using diverse clinical specimens from neonates, whole blood total bilirubin analysis on the Siemens RAPIDLab 1245 blood gas analyzer is accurate and precise when compared to the Radiometer ABL 735. Analysis of unhemolyzed whole blood using the RAPIDLab 1245 or RAPIDLab 1265 is a clinically acceptable method for monitoring the development of pathologic concentrations of bilirubin in neonates.

Results and Conclusions

Imprecision of controls on the RAPIDLab was 3.7%, 3.1%, and 4.7% (CV) at 5.1, 12.4, and 19.8 mg/dL (n=50), respectively. Similarly, imprecision of the ABL was 7.0% and 2.2% (CV) at 4.2 and 22.3 mg/dL (n=140), respectively. Whole blood bilirubin values ranged from 2.2 to 16.7 mg/dL. Linear regression of the RAPIDLab vs. the ABL (see Figure 2) yielded the following statistics: slope, 1.01; intercept, –0.48; r, 0.964; Syx, 0.79. Absolute bias between the RAPIDLab and the ABL averaged 0.4 mg/dL (range: –2.7 to 1.3 mg/dL). Whole blood bilirubin analysis on the RAPIDLab 1245 and RAPIDLab1265 is substantially equivalent to that on the ABL 700/800 system family and provides a new alternative for monitoring bilirubin in newborns.

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