Screening for Hyperbilirubinemia in Japanese Very Low Birthweight Infants Using Transcutaneous Bilirubinometry

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Objectives To assess the accuracy of transcutaneous bilirubin (TcB) measurements at 5 different body sites in Japanese very low birthweight (VLBW) infants and to determine a cut-off value of TcB to detect total serum/plasma bilirubin (TB) levels ≥10 mg/dL (171 μM).

Study design In a prospective multicenter study, 85 Japanese VLBW infants were enrolled from 5 neonatal intensive care units during the study period. A total of 383 blood samples from infants not receiving phototherapy or ≥24 hours postphototherapy were analyzed. TcB was measured at the forehead, sternum, upper back, lower abdomen, and waist within 1 hour of blood collection. Linear regression analysis and Bland-Altman plots were used to compare TcB values at each site with TB levels. The TcB cut-off value for detecting TB ≥10 mg/dL was determined by receiver operating characteristics curve analysis.

Results TcB significantly correlated with TB, but the coefficient of determination varied among the sites (forehead: 0.5294, sternum: 0.6488, upper back: 0.6321, lower abdomen: 0.5430, waist: 0.7396). At a TcB value ≥8, the sensitivity was 100% at the sternum and upper back, 85% at the waist, 84% at the forehead, and 64% at the lower abdomen to detect TB ≥10 mg/dL.

Conclusions In Japanese VLBW infants, the accuracy of TcB measurements varies according to body site. TcB ≥8 on the sternum or upper back is more reliable than that on the forehead, lower abdomen, or waist to detect TB levels ≥10 mg/dL. *(J Pediatr 2016;168:77-81)*.

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Clinical kernicterus has been observed in Japan, with an incidence of 1.8 per 1000 live births <30 weeks of gestational age (GA).[1] We previously found that total serum/plasma bilirubin (TB) levels in most very low birthweight (VLBW) infants with kernicterus peak after 1 week of age (median age: 28 days).[2] This finding indicates that VLBW infants should be continuously monitored for hyperbilirubinemia during their neonatal intensive care unit (NICU) stay, in contrast to monitoring for one week after birth as currently practiced in Japan.

Transcutaneous bilirubin (TcB) measurements taken at the forehead and sternum are a noninvasive screening method for hyperbilirubinemia. These measurements are clinically useful for identifying term or late preterm infants with hyperbilirubinemia because TcB values correlate with TB levels, except for in Black infants.[3-6] Previous studies in preterm or VLBW infants have shown that TcB significantly correlates with TB levels, with a slightly weaker correlation coefficient than in term infants.[7-13] However, TcB measurements are not routinely used for screening for hyperbilirubinemia in this vulnerable population throughout the world. The major reasons might be that TcB in VLBW infants underestimates TB compared with that in term infants,[10,14] and the most accurate body site has not been determined.

CV	Coefficient of variation
GA	Gestational age
NICU	Neonatal intensive care unit
NPV	Negative predictive value
PPV	Positive predictive value
R^2	Coefficient of determination
ROC	Receiver operating characteristics
TB	Total serum/plasma bilirubin
TcB	Transcutaneous bilirubin
VLBW	Very low birthweight

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We assessed the accuracy of TcB measurements at 5 different body sites in Japanese VLBW infants, and then determined a cut-off TcB value for detecting TB levels ≥10 mg/dL (171 μM), when phototherapy is initiated in VLBW infants per Japanese guidelines.[15,16]

Methods

We performed a multicenter prospective study of 85 VLBW infants who were born from April 2013 to December 2014 and admitted to the NICU at Kobe University Hospital, Kakogawa West Municipal Hospital, Takatsuki General Hospital, Hyogo Prefectural Kobe Children's Hospital, and Japanese Red Cross Society Himeji Hospital, Japan. We received institutional review board approval from Kobe University Hospital (1450) and written informed consent from the parents.

Before enrollment of patients, the following protocol was established. In VLBW infants not receiving phototherapy or ≥24 hours postphototherapy, blood was collected for TB measurements based on the clinical indication by neonatologists at each hospital, and TcB measurements were then taken at some or all of 5 different body sites: forehead, sternum, upper back, lower abdomen, and/or waist. All TcB measurements were taken within 1 hour of blood sampling. Blood was collected by venipuncture, then shielded from exposure to light, and measured within 1 hour after blood sampling.

TcB was measured 3-6 times at each body site using the JM-105 jaundice meter (Konica Minolta, Inc, Tokyo, Japan) according to the manufacturer's instructions. The median value was designated as the TcB value at each measurement site. TB levels were measured by spectrophotometry using a UB-Analyzer (Arrows Co, Ltd, Osaka, Japan).[17,18] TB values that were measured using this device correlate with those measured by high-performance liquid chromatography, which is the gold standard method for determination of TB.[4]

Validation of TcB Measurements by Examiners

To determine the consistency of TcB values, 3 independent examiners (neonatologist, resident doctor, and nurse) performed 6 replicates of TcB measurements at 5 different body sites in a VLBW infant and results were compared among users. The mean TcB values and coefficients of variation (CVs) were then calculated.

Data and Statistical Analyses

Linear regression analysis was used to determine the correlation between TcB at each body site and TB levels.[6] The regression equation and coefficient of determination (R^2) were calculated using the results between the TcB and TB values. In addition, R^2 were compared between 0 and 7 days of age and thereafter. Bland-Altman plots (mean ± 2 SD) were used to determine the difference between TcB at each body site and TB levels.[6] TcB cut-off values for detecting TB levels ≥10 mg/dL for each body site were analyzed by receiver operating characteristics (ROC) curve analyses. The sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated and determined for the TcB cut-off value and the best measurement site. Validation of TcB measurements by examiners was analyzed by the Kruskal-Wallis test. All analyses were conducted using Excel Statistics (Statcel 3; Social Survey Research Information Co, Ltd, Tokyo, Japan). Statistical significance was determined when $P < .05$.

Results

A total of 85 VLBW infants not receiving phototherapy or ≥24 hours postphototherapy were enrolled because TcB values did not correlate with TB levels during phototherapy (n = 35, $R^2 = 0.1662$).

Median GA and birthweight were 29 weeks (range, 22-36 weeks) and 1154 g (range, 470-1490 g), respectively (Table I). Forty-two percent of infants were small for GA, which indicated that birthweight was below the 10th percentile compared with mean values at the same GA in Japanese infants.[19] All of the infants were of Japanese descent. Two infants were diagnosed with hemolysis with positive Coombs tests or elevations of carboxyhemoglobin (ABO incompatibility and unknown cause). A total of 383 blood samples from all 85 infants were analyzed (median age: 20 days; range: 1-117 days).

Precision of TcB Measurements by Examiners

The CVs for TcB measurements at each body site taken by each examiner are shown in Table II (available at www.jpeds.com). Although most CV values were more than

Table I. Background characteristics in VLBW infants (n = 85)

	n	%
Birth weight		
<500 g	2	2.4
500-999 g	28	32.9
1000-1499 g	55	64.7
GA (wk)		
22-27	25	29.4
28-33	52	61.2
34-36	8	9.4
Male	44	51.8
Small for GA	36	42.4
Delivery mode		
Vaginal	6	7.1
Cesarean	79	92.9
History of childbirth		
Nullipara	42	49.4
Multipara	43	50.6
Nationality		
Japanese	85	100
Hemolysis	2	2.4
Postnatal age at blood sampling (n = 383)		
1-7 d	92	24.0
8-14 d	59	15.4
15-117 d	232	60.6