Noninvasive Transcutaneous Bilirubin as a Screening Test to Identify the Need for Serum Bilirubin Assessment

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Hyperbilirubinemia is a common problem in the newborn infant. It can progress to develop kernicterus unless intervention is initiated. Severity and decision for management are usually based on serum bilirubin (TsB) which needs blood sampling. Transcutaneous bilirubin measurement is a noninvasive technique and the result correlates closely with TsB. A new transcutaneous bilirubinometer, Minolta AirShields Jaundice Meter, JM103, has been introduced. The objectives of this study were: 1) To evaluate the accuracy of transcutaneous bilirubin (TcB) measured by JM 103, when compared to TsB, used clinically in a hospital setting (Leica Unistat Bilirubinometer) and 2) To develop a cut-off point of TcB level which indicated the need for serum bilirubin assessment.

Three hundred and eighty eight term and near-term newborn infants with 460 paired TcB-TsB specimens were studied from August to November 2003. Birth weight was 3117.57 $\pm$ 424.82 grams. TsB ranged from 4 to 19.6 mg/dL($\bar{x}$ 10.5, SD 2.46). The correlation coefficient between TcB and TsB was significant (r 0.8, $p < 0.001$). TcB showed a tendency to underestimate TsB, with mean difference of 0.7 mg/dL, SD 1.6 mg/dL, and 95% confidence interval 0.85 and 0.55 mg/dL. TcB values of 8, 9, 10, 12 mg/dL were chosen as cut-off points that indicated the need for blood sampling for TsB (corresponded to hour-specific levels of 10, 12, 13 and 15 mg/dL, respectively when phototherapy should be initiated). In conclusion, noninvasive TcB assessment demonstrates significant accuracy, compared to TsB. It can be used as a screening test to identify the need for blood sampling for serum bilirubin level.

Keywords : *Transcutaneous bilirubin, Hyperbilirubinemia, Jaundice, Newborn infants*

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Jaundice is a common clinical problem in the neonatal period. Many neonates develop hyperbilirubinemia that requires intervention. In healthy term infants, it can progress to severe hyperbilirubinemia, resulting in kernicterus[1-4]. Regimens to identify infants at risk and/or practice parameters to prevent kernicterus have been proposed[5-7]. Most of them rely on the serum bilirubin level. Noninvasive methods of estimating the intensity of jaundice have been described since 1925. Various transcutaneous devices have been developed and evaluated and it has been concluded that transcutaneous bilirubin (TcB) correlated well with total serum bilirubin (TsB) and could be used as a screening test[8-10] or even a replacement for blood sampling [11-13]. Yasuda et al[14], reported a new transcutaneous jaundice device with two optical paths (Minolta AirShields Jaundice Meter, JM 103) that provided a good correlation between TcB and TsB in term and preterm infants. It measured the spectral reflectance of bilirubin by determining the difference between optical densities for light in the blue (450 nm.) and green (550 nm.) wavelength regions. Transcutaneous bilirubin determination was more objective than visual assessment which decided whether blood sampling for serum bilirubin was needed. The objectives of the present study were: 1) To evaluate the accuracy of TcB measured by JM 103 compared with TsB used clinically in the hospital setting and 2) To establish a cut-off point of TcB level which indicated the need for TsB.

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Patients and Method

The study was performed in the full-term nursery at King Chulalongkorn Hospital, Bangkok. Term and near-term neonates were recruited in the study when visual observation of jaundice by health-care personnel raised concern for risk of hyperbilirubinemia and necessitated serum bilirubin determination. TcB was performed within 10-15 minutes of blood sampling by heel puncture for TsB. Some infants had repeated TcB-TsB measures as clinically dictated and this was done $\geq$ 24 hours from the previous one. Specific age in hours at the time of study were recorded, along with birth weight and gender. All infants had a gestational age $\geq$ 36 weeks, and were clinically healthy except for jaundice. Infants who were receiving phototherapy and had exchange transfusion were excluded.

All TcB were performed by one investigator using JM 103. The fiber optic probe was placed against the forehead of the infant in supine position. Gentle pressure was applied during measurement to ensure an even contact of the probe and skin. Three consecutive scans were performed and a computerized mean value was displayed as TcB in mg/dL. The intradevice error was determined by obtaining 3 values of TcB measurements at an interval of a few minutes in each of the 33 infants.

TsB was done by clinical laboratory method using Leica Unistat Bilirubinometer (Leica Inc. Buffalo, NY, USA) in the unit.

Both devices were calibrated before daily use in accordance with the manufacturer's instructions. Verbal consent was obtained from the parents and the study was approved by the Ethical Committee of the Faculty of Medicine.

Demographic data, TcB and TsB values were analyzed using SPSS. The correlation coefficient between TcB and TsB was performed using Pearson Linear Regression Analysis. Error distribution, mean difference, and 95% confidence interval of the difference were evaluated. Sensitivity and specificity of TcB values in 1 mg/dL increment were analyzed in relation to various TsB levels. P value of < 0.05 was considered statistically significant.

The cut off point of TcB value was determined to match each threshold of hour-specific TsB which required phototherapy according to the Clinical Practice Guideline, developed by the present staff and is currently in routine use in neonatal unit[15].

Results

From August to November 2003, 388 new born infants were tested from which 460 paired TcB and TsB samples were obtained. The mean $\pm$ SD birth weight was 3117.57 $\pm$ 424.82 gm. Demographic characteristics by gender, number of infants at different postnatal age when assessed and distribution of TsB are shown in Table 1. The cases of male babies with jaundice out numbered the females by a ratio of 1.35: 1. Postnatal age ranged from 11 to 216 hours ($\bar{x}$ = 64.05, SD = 2.46). TsB ranged from 4 to 19.6 mg/dL ($\bar{x}$ = 10.5, SD = 2.46).

The correlation between TcB and TsB value was significant ($r = 0.8$, $p < 0.001$) as shown in Fig. 1. The error distribution (Bland, Altman)[16] in Fig. 2 shows a tendency of TcB to underestimate TsB with the mean difference 0.7 mg/dL, SD 1.6 mg/dL, and 95% confidence interval of the mean 0.85 and 0.55 mg/dL. The sensitivity and specificity of TcB at an increment of 1 mg/dL when compared to TsB levels of 10,12,13 and 15mg/dL which were the hour-specific thresholds that indicated the need for phototherapy are shown in Table 2 and 3. Cut off levels of TcB of 8, 9, 10 and 12mg/dL that suggested TsB should be done was determined from the Receiver Operator Characteristics (ROC) curve (Fig.3 and Table 4). The sensitivity was between 92-96% and specificity between 50-83%. The intradevice coefficient of variance was 4.6%.

Discussion

Kernicterus is a major concern in neonatal hyperbilirubinemia. Awareness of infants at risk and intervention based on significant serum bilirubin level can prevent this problem. Visual determined jaundice

Table 1. Demographic characteristics

Characteristics	n	%
Total (388) : male	223	57.5
female	165	42.5
Samples	460	-
Age at the time of measurement (hr)		
< 24	16	3.48
24-48	108	23.48
49-72	212	46.08
73-96	89	19.35
> 96	35	7.61
TsB (mg/dL)		
$\leq$ 10	197	42.82
10.1-11	71	15.44
11.1-12	74	16.09
12.1-13	43	9.35
13.1-14	42	9.13
14.1-15	20	4.35
> 15	13	2.82

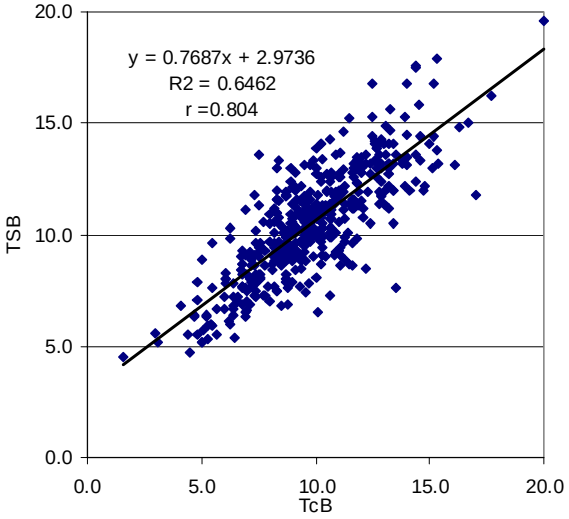

Fig. 1 Correlation between TcB and TsB

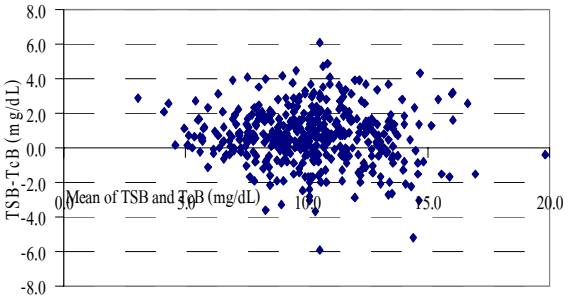

Fig. 2 Error distribution (Bland-Altman plot) between the difference of TsB-TcB and the mean of TsB and TcB

leads to blood sampling for serum bilirubin level. However, visual inspection, being subjective, usually inaccurate and unreliable results in a number of unnecessary blood letting. Transcutaneous bilirubin device provides an answer for an objective, noninvasive measurement. Several studies have identified the accuracy and clinical usefulness of Bilicheck (SpectRx Inc, Norcross, GA, USA)[8-13,17]. The Minolta AirShields Jaundice Meter, JM 102, measured transcutaneously in jaundice index[10,14,18-20], has limited accuracy due to interference from skin pigmentation, age and weight[21-23]. A new device, JM 103, introduced in 2003[14], provides the measurement result in a clinical unit and was reported to have less influence of skin maturation level and melanin than the previous JM 102. In the present study, the correlation coefficient between TcB (JM 103) and TsB is significant ($r = 0.8$, $p < 0.05$) but less so than that of Yasuda et al[14] ($r = 0.93$). One factor which may account for the difference

Table 2. Sensitivity and specificity of TcB to predict specific TsB levels

Value level (mg/dl)		n	Sensitivity (%)	n	Specificity (%)
TsB>15	Total	14		446	
	TcB>13	11	78.6	406	91.0
	TcB>12	13	92.9	373	83.6
	TcB>11	14	100.0	327	73.3
	TcB>10	14	100.0	263	59.0
TsB>13	Total	75		385	
	TcB>13	36	48.0	370	96.1
	TcB>12	54	72.0	353	91.7
	TcB>11	64	85.3	316	82.1
	TcB>10	69	92.0	257	66.8
	TcB>9	73	97.3	176	45.7
	TcB>8	74	98.7	103	26.8
TsB>12	Total	118		342	
	TcB>12	67	56.8	323	94.4
	TcB>11	89	75.4	298	87.1
	TcB>10	102	86.4	247	72.2
	TcB>9	112	94.9	172	50.3
	TcB>8	117	99.2	103	30.1
TsB>10	Total	263		197	
	TcB>10	170	64.6	170	86.3
	TcB>9	223	84.8	138	70.1
	TcB>8	254	96.6	95	48.2
	TcB>7	261	99.2	60	30.5

Table 3. Clinical Practice Guideline*: Management of hyperbilirubinemia in healthy fullterm infant. Neonatal unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University 2001[15]

Age (hr)	Phototherapy	Double Phototherapy	Exchange transfusion if double phototherapy fails	Exchange transfusion plus intensive phototherapy
≤ 24*				
25-48	10-12	≥ 15	≥ 20	≥ 25
49-72	≥ 13	≥ 16	≥ 20	≥ 25
>72	≥ 15	≥ 17	≥ 25	≥ 25

* abnormal: investigation, phototherapy and repeat TsB within 4-6 hr

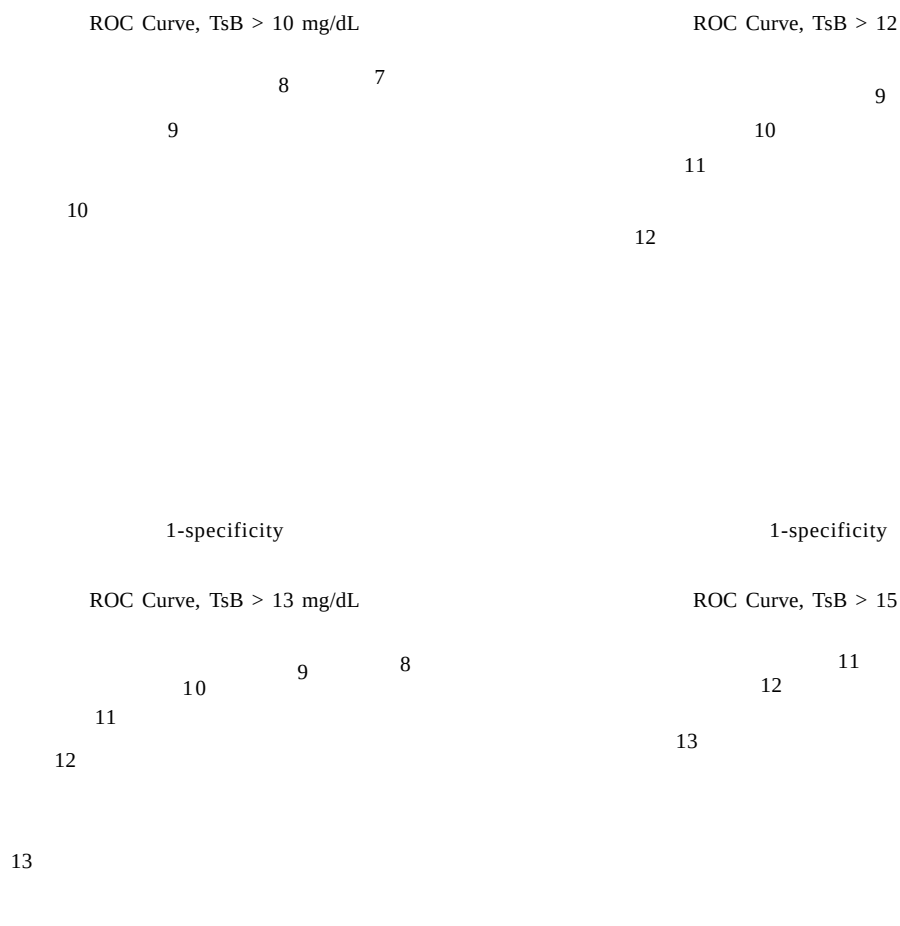

Fig. 3 ROC curves of TcB compared with different levels of TsB

is different laboratory measurement of TsB. Inter-laboratory variability with a wide range of uncertainty is well documented[24,25]. It should be noted that TcB tends to underestimate TsB (Fig. 2).

Table 4. Cut-off levels of TcB at which TsB should be done

Age (hr)	TsB level	TcB level
≤ 24[a]	-	-
25-36	10	> 8
37-48	12	> 9
49-72	13	> 10
> 72	15	> 12

Practice parameters have been developed for the evaluation and treatment of healthy term and near-term neonates with hyperbilirubinemia[5,7,27]. These recommendations need to be adapted to suit one's unique population. In view of ethnicity with a high prevalence of G6PD deficiency[28], different environment, social life style and health care system, Clinical Practice Guideline for management of hyperbilirubinemia has been developed[15] and implemented in routine practice in the unit since 2001 (Table 3). Up to the time of the present study, infants who needed phototherapy were 5-8 % and less than 0.5 % of these jaundiced babies required exchange transfusion. However, a lower level of TsB upon which treatment begins can

cause frequent monitoring of blood sampling, a painful procedure with possible complications and parental anguish. TcB can be used as a screening test to determine the need for TsB measurement[9]. To consider the cut-off point of TcB which requires TsB, sensitivity of 100 % is an ideal choice. On the other hand, a number of infants will be assessed unnecessarily as specificity decreases while sensitivity increases. Taking this into consideration, the cut-off points of TcB are chosen to be more than 8, 9, 10, and 12 mg/dL for the corresponding TsB levels of 10, 12, 13 and 15 mg/dL (Table 4). It would be a cause of concern to miss some false negative cases, but the relatively low level of TsB in initiating phototherapy in our clinical practice leaves a safety margin to TsB level that kernicterus is considered a threat. In addition, follow-up TcB can be done easily. JM 103 has been adopted for daily use in identifying infants who need blood sampling in our unit since January 2004, with reference to the result from the present study. Preliminary data suggests that about 50% of cases that have raised doubt about jaundice visually avoided blood sampling. There has been no unusual hyperbilirubinemia that required exchange transfusion.

Although the accuracy of TsB is not clarified by comparison with high performance liquid chromatography, considered to be the gold standard for bilirubin assay, the TsB, performed by clinical laboratory method, is the test a physician routinely relies upon to make decision in management of hyperbilirubinemia. It was only pragmatic to use TsB in the present study to apply for clinical usefulness.

Conclusion

Noninvasive transcutaneous bilirubin assessment by JM 103 has demonstrated significant accuracy when compared to total serum bilirubin measured by clinical laboratory method. It can be favorably used as a screening test to identify the need for serum bilirubin measurement when TcB are more than 8, 9, 10 and 12 mg/dL at specific age in hours.

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การใช้ค่าบิลิรูบินที่วัดทางผิวหนังเป็นวิธีคัดกรองที่บ่งบอกความจำเป็นในการหาค่าบิลิรูบินในเลือด

สุวิมล สรรพวัฒน์, อิศรางค์ นุชประยูร

ภาวะบิลิรูบินสูงเป็นปัญหาที่พบบ่อยในทารกแรกเกิด ถ้าระดับสูงมากอาจทำให้เกิด kernicterus ได้ โดยทั่วไปมักจะใช้ค่าบิลิรูบินในซีรั่มที่ได้จากการเจาะเลือดเป็นตัวตัดสินความรุนแรงของโรคและความจำเป็นในการรักษา การวัดค่าบิลิรูบินทางผิวหนังเป็นวิธีที่ไม่เจ็บ ค่าที่ได้มีความแม่นยำเมื่อเทียบกับค่าบิลิรูบินในซีรั่ม วัตถุประสงค์ของการศึกษานี้ เพื่อหาความแม่นยำของการวัดค่าบิลิรูบินทางผิวหนัง โดยใช้เครื่องมือ JM 103 (Minolta AirShields Jaundice Meter) เปรียบเทียบกับค่าบิลิรูบินในซีรั่ม (Leica Unistat Bilirubinometer) และเพื่อหาจุดตัดของค่าบิลิรูบินทางผิวหนัง ซึ่งบ่งบอกความจำเป็นในการเจาะเลือดเพื่อหาค่าบิลิรูบินในซีรั่มที่ระดับต่าง ๆ

การศึกษาทำในทารกคลอดครบกำหนดและใกล้ครบกำหนด จำนวน 388 คน ได้ตัวอย่าง ค่าบิลิรูบินทางผิวหนัง (TcB) และบิลิรูบินในซีรั่ม (TsB) จำนวน 460 คู่ น้ำหนักแรกเกิดเฉลี่ย 3117.57 $\pm$ 424.82 กรัม ค่าบิลิรูบินในซีรั่มระหว่าง 4.0 -19.6 มก/ดล (x 10.5, SD 2.46) Correlation coefficient ระหว่าง TcB และ TsB มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติ ($r = 0.8$, $p < 0.001$) TcB ที่วัดได้มักจะต่ำกว่า TsB โดยมีความแตกต่างเฉลี่ย 0.7, SD 1.6 และ 95% confidence interval 0.85 และ 0.55 มก/ดล ระดับ TcB ที่ควรเจาะเลือดตรวจบิลิรูบินคือ 8, 9, 10, 12 มก/ดล เทียบกับ TsB ที่ 10, 12, 13 และ 15 มก/ดล ซึ่งเป็นระดับที่ควรให้การรักษาด้วย phototherapy ตามอายุที่คิดเป็นชั่วโมง โดยสรุปการเปรียบเทียบค่าบิลิรูบินที่วัดทางผิวหนังกับค่าที่วัดในซีรั่มมีความแม่นยำอย่างมีนัยสำคัญทางสถิติ และสามารถที่จะใช้การวัดทาง ผิวหนังเป็นวิธีคัดกรองที่บ่งบอกความจำเป็นในการเจาะเลือดเพื่อหาค่าบิลิรูบินในซีรั่มได้