Transcutaneous Bilirubin in the Pre-term Infants

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Objective: *1) To evaluate the accuracy of transcutaneous bilirubin (T_CB) measurement compared to total serum bilirubin level (TSB) in the pre-term infants and 2) To establish cut-off values of T_CB that indicated need for TSB.*
Material and Method: *Premature infants whose birth weight was more than 1,000 grams and gestational age less than 36 weeks had paired T_CB-TSB assessment when jaundice was observed. T_CB was done using JM 103 (Minolta AirShields Jaundice Meter) on the forehead. T_CB, which corresponded to TSB level that required phototherapy, was chosen as the cut-off point that indicated blood sampling for TSB.*
Results: *Two hundred and forty-nine paired T_CB-TSB measurements from 196 premature neonates were obtained. Birth weight was 1,887 $\pm$ 344.4 grams. TSB ranged from 4.5-17.6 mg/dL (mean 9.4, SD 2.2mg/dL), T_CB 4.1-17.7 mg/dL (mean 9.7, SD 2.4 mg/dL). The correlation coefficient between T_CB and TSB was significant (r 0.79, $p < 0.0001$). T_CB had a tendency to overestimate TSB with the mean difference of TSB- T_CB = -0.3 $\pm$ 1.5 mg/dL and 95% confidence interval of the mean -0.1 to -0.5 mg/dL. Of all the variables of birth weight, gestational age, and postnatal age, only postnatal age significantly influenced the correlation of T_CB-TSB. In the early postnatal age of 1-4 days, the number of T_CB reading overestimated TSB more than underestimated. However, at $\geq$ 5 days of age, the number of underestimation was more than those of overestimation. The cut-off points of T_CB that indicated the need for blood sampling for TSB were chosen as the same level of TSB of 6, 8, 10, 11, and 12 mg/dL when phototherapy was recommended. Screening with T_CB would eliminate painful procedure of blood taking by 40%.*
Conclusion: *Noninvasive T_CB assessment demonstrated significant accuracy when compared to TSB. T_CB can be adopted as a screening test to identify the need for blood sampling of serum bilirubin in premature infants.*

Keywords: *Transcutaneous bilirubin, jaundice, hyperbilirubinemia, pre-term infants*

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Jaundice in the neonatal period has always been a concern for the pediatricians, more so when it occurs in the premature infants. Although the pathophysiology of developing jaundice is the same in term and pre-term neonates, hyperbilirubinemia in the latter is more severe and more persistent[1]. Pre-term infants have been regarded to be at higher risk to develop hyperbilirubinemia and kernicterus especially if the infants are sick. Kernicterus was reported to occur at low serum bilirubin concentration[2]. Bilirubin encephalopathy is a multifactorial process, and studies have failed to reveal the association between peak total serum bilirubin (TSB) and long-term neurodevelopment outcomes in healthy term and near-term infants[3]. Nevertheless, therapeutic intervention with phototherapy and exchange transfusion was recommended for the pre-term at lower TSB levels than those of the full term[4,5], thus necessitated early and frequent blood sampling.

Transcutaneous bilirubinometry is a non-invasive method in detecting jaundice. Transcutaneous bilirubin (T_CB) was known to correlate well with TSB in full term and near-term infants[6-8]. Clinical implementation of T_CB has been introduced as screening test, monitoring, and follow-up for high risk of developing hyperbilirubinemia[8,9]. However, the accuracy of T_CB

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in the premature neonates varied with some limitation[10-12], although it was endorsed as a screening test used in a selected group of patients[13,14]. The aims of the present study were: 1) To evaluate the accuracy of T_CB compared with TSB in premature infants and 2) To establish a cut-off point of T_CB, which indicated the need for TSB.

Material and Method

The present study was performed in the Neonatal Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University. Measurements were taken from premature infants with birth weight more than 1,000 grams and gestational age less than 36 weeks when jaundice was visually observed. Gestational age was assessed from maternal expected date of confinement and by Ballard scores. All infants were clinically healthy. Infants who were receiving phototherapy, or had exchange transfusion were excluded. T_CB using JM 103 (Minolta AirShields Jaundice Meter) was performed by the investigators on the forehead of the infants within an hour of heel puncture for TSB. Three consecutive scans were obtained for one measurement. The device was calibrated before daily use. Repeated T_CB-TSB was done as clinically dictated at more than 24 hours from the previous one.

Capillary blood from heel prick was used for TSB determination, using Leica Unistat bilirubinometer (Leica Inc. Buffalo, NY, USA). The device was calibrated according to the manufacturer manual. The present study was approved by the Ethical Committee of the Faculty of Medicine.

The Clinical Practice Guideline in the Neonatal Unit for treating pre-term jaundice with phototherapy during the first week of life are arbitrarily chosen as: birth weight 1,000-1,249 grams at TSB level of 5-6 mg/dL, 1,250-1,499 grams at TSB 6-8 mg/dL, 1,500-1,749 gm. at TSB 8-10 mg/dL, 1,750-1,999 gm. at TSB more than 11 mg/dL and birth weight more than 2,000 gm at TSB more than 12 mg/dL. Cutoff points for T_CB levels that could reliably indicate TSB of 5, 6, 8, 10, 11, and 12 mg/dL were determined.

Demographic data were collected and analyzed as percentage, mean, and standard deviation. Pearson Linear Regression analysis was used to detect the correlation coefficient between T_CB and TSB. Error distribution, mean difference, and 95% confidence interval of the difference were evaluated. Correlation coefficients of T_CB -TSB at different periods of postnatal ages were also obtained. The impact of variables: birth weight, gestational age and postnatal age upon T_CB-TSB was analyzed using multiple regression analysis. The cut-off points of T_CB levels that called for blood sampling of TSB were chosen to be those of TSB levels that required phototherpy. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (LR), and accuracy of each cut-off level of T_CB were calculated. A p-value of less than 0.05 was considered significant.

Results

Two hundred and forty nine T_CB-TSB paired specimens from 196 infants were obtained between September 2004 and August 2005. The male to female ratio was 1.23:1. Demographic characteristics by gender, birth weight, gestational age, age at the time of measurement, T_CB and TSB are shown in Table 1.

T_CB was significantly correlated to TSB as demonstrated in Fig. 1 ($r = 0.79$, $p < 0.0001$). The error distribution (Bland, Altmann) in Fig. 2 showed a tendency of T_CB to overestimate TSB with the mean difference of (TSB - T_CB) -0.3 mg/dL $\pm$ 1.5 mg/dL and 95% confidence interval of the mean -0.1 to -0.5 mg/dL. At different postnatal ages (1-2, 3-4, 5-7, and more than 7 days old), the correlations between TSB and T_CB were all significant (Table 2). Using multiple regression

Table 1. Demographic characteristics of the studied population (n = 196)

Characteristics	N	mean $\pm$ SD
Total: Male	108	
Female	88	
Paired samples	249	
Birth weight (grams)	1,050-2,610	1,887$\pm$344.4
Gestational age (weeks)	30-35	33.2$\pm$1.7
Age at the time of measurement (days)	>1-20	4.5$\pm$3.2
T_CB (mg/dL)	4.1-17.7	9.7$\pm$2.4
TSB (mg/dL)	4.5-17.6	9.4$\pm$2.2

Table 2. Correlation between serum bilirubin (TSB) and transcutaneous bilirubin (T_CB) values at different postnatal ages of 1-2, 3-4, 5-7 and > 7 days old (correlation coefficients and significant levels)

Age (d)	n	r	p-value
1-2	67	0.77	<0.0001
3-4	103	0.72	<0.0001
5-7	45	0.81	<0.0001
>7	34	0.81	<0.0001

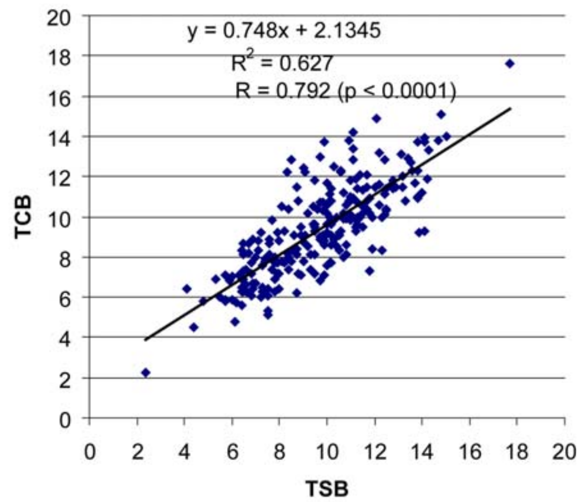

Fig. 1 Correlation between serum bilirubin concentration (TSB) and transcutaneous bilirubin (T_CB) in 196 premature infants

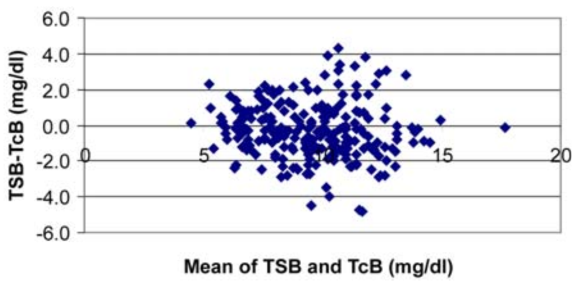

Fig. 2 Error of distribution (Bland-Altman plot) between the difference of TSB-T_CB and the mean of TSB and T_CB

analysis to determine the influence of birth weight, gestational age, and postnatal age on the TSB and T_CB correlation, only postnatal age proved to be significantly important ($p = 0.001$). With T_CB reading within the range of $\pm$ 10% of TSB regarded as acceptable, Table 3 shows acceptable, over and under estimation of TSB at different postnatal ages. About half (47.1-52.4%) of all T_CB were within the acceptable range except those in day 1-2. Noticeably, at an early age of 1-4 days, T_CB overestimated TSB more than underestimation (34-48% VS 14-15%); while at the age of $\geq$ 5 days, the number of underestimation of TSB (29-35%) was more than those of overestimation (18-20%). The cutoff points of T_CB that indicated blood sampling for TSB were set at 6, 8, 10, 11, and 12 mg/dL, the same values as TSB. TSB 5 mg/dL was not analyzed because the number of specimens was too small to obtain a reliable result. Sensitivity, specificity, positive and negative predictive values, relative risk, and accuracy of the chosen cutoff T_CB are shown in Table 4.

Discussion

Studies of T_CB in the premature infants had varied results with correlation coefficients ranged from 0.68 to 0.96[10-13,15]. In the present study, the correlation coefficient between T_CB and TSB was significant (r 0.79, $p < 0.0001$) and was almost equal to that of the full term infant in the authors' previous study (r 0.8, $p < 0.0001$) [8]. The only difference was that in the preterm infants T_CB tended to overestimate TSB, while underestimation was the case for the full term. Correlation at different ages was all significant (Table 2). Gestational age and postnatal age would seem to influence the reading of bilirubin transcutaneously, as they affect the skin maturation. Conflicting results regarding the association of birth weight, gestational age and postnatal age on the accuracy of T_CB in predicting the TSB were presented in several reports[10-13,15,16]. Contrary to several previous studies[11-13,16], ours as well as others[15,17] did not show any influence from gestational age on the T_CB reading or its correlation to TSB, nor was birth weight proved to have any significance[11]. Postnatal age was the only variable that

Table 3. The number of transcutaneous bilirubin (T_CB) reading, with allocation as acceptable (T_CB $\pm$ 10% of TSB), overestimate (T_CB > 10% of TSB) and underestimate (T_CB < 10% of TSB), when correlated to serum bilirubin (TSB), at different postnatal ages

Age (d)	Overestimated (%)	Acceptable (%)	Underestimated (%)	Total
1-2	32 (47.8)	25 (37.3)	10 (14.9)	67
3-4	35 (34.0)	54 (52.4)	14 (13.6)	103
5-7	9 (20.0)	23 (51.1)	13 (28.9)	45
>7	6 (17.6)	16 (47.1)	12 (35.3)	34
Total	82 (32.9)	118 (47.4)	49 (19.7)	249 (100)

Table 4. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), relative risk (RR) and accuracy of the transcutaneous bilirubins (T_CB) chosen to be the cutoff points for blood sampling of serum bilirubin

T_CB	Sensitivity	Specificity	PPV	NPV	RR	Accuracy
6	97.8	40.0	97.5	44.4	1.6	91.5
8	90.4	73.2	89.4	75.4	2.4	85.5
10	81.6	71.5	68.3	81.8	2.8	77.9
11	72.4	83.2	56.8	90.8	4.3	80.7
12	53.1	88.9	41.5	92.8	4.7	84.3

influenced the correlation of TSB and T_CB, and this was in accordance with previous studies(10,16). The duration of postnatal age used in these studies might play some part in this discrepancy(13). A longer period than ours (1-20 days) as well as that of Knudsen and Ebbesen(16) (1-18 days) yielded a positive relationship, while shorter ones (1-7 days) did not(11,13). Most of the authors' T_CB reading was in the acceptable range of $\pm$10% of TSB except those on day 1-2. Skin condition, such as peripheral edema or transparency of the skin during the first couple of days might affect the skin measurement. However, it should be noted that the overestimation of T_CB over TSB was more than the underestimation on the first 4 days (48% overestimation vs. 15% underestimation on day 1-2 and 34% overestimation VS 14% underestimation on day 3-4). For our purpose, T_CB was intended for a screening test, overestimation would suggest that TSB, closed observation, and monitoring would be done earlier, and any TSB that approaches the level of treatment would not be overlooked. As skin thickness and maturation advance in the postnatal days, the correlation of T_CB-TSB seemed to be better (r 0.81) and T_CB tended to underestimate TSB (35 vs. 17%) as in those of the full-term infants in the authors' previous study(8). This should suggest that caution was needed for this group of neonates when applying T_CB in clinical practice, in order not to overlook any in need of treatment.

The TSB levels at which phototherapy were to be initiated in different weight groups of premature infants in our nursery are 5, 6, 8, 10, 11, and 12 mg/dL. Using the cutoff points of T_CBs that correspond to these TSBs (6, 8, 10, 11, and 12) as a screening test to obtain blood sampling, there were higher sensitivity in the lower T_CB (6-10 mg/dL) and higher specificity in the higher T_CB (11-12 mg/dL). It would be a cause of concern to miss some false negative cases, but the relatively low levels of TSB in initiating phototherapy in our unit would counterbalance this. The result in the present study would eliminate the unnecessary painful procedure of blood sampling by at least 40%.

Conclusion

Noninvasive transcutaneous bilirubin measurement in pre-term infants demonstrated significant correlation to total serum bilirubin level. It could be favorably used as a screening test to identify the need for blood sampling of serum bilirubin.

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การวัดค่าบิลิรูบินทางผิวหนังในทารกคลอดก่อนกำหนด

สุวิมล สรรพวัฒน์, อิศรางค์ นุชประยูร

วัตถุประสงค์*: เพื่อประเมินความแม่นยำของการวัดค่าบิลิรูบินทางผิวหนัง (T_cB) ในทารกคลอดก่อนกำหนดเปรียบเทียบกับระดับบิลิรูบินในซีรัม (TSB) และเพื่อหาจุดตัดของ T_cB ที่บ่งชี้ถึงความจำเป็นในการเจาะเลือดหาค่า TSB ที่ระดับต่าง ๆ*

วัสดุและวิธีการ*: วัดค่า T_cB และ TSB เมื่อสังเกตว่ามีภาวะตัวเหลืองในทารกคลอดก่อนกำหนดที่มีสุขภาพดี มีน้ำหนักตัวแรกคลอดมากกว่า 1,000 กรัม และอายุครรภ์น้อยกว่า 36 สัปดาห์ การวัด T_cB ใช้ JM 103 (Minolta AirShields Jaundice Meter) วัดบริเวณหน้าผาก จุดตัดของ T_cB ที่บ่งชี้ถึงความจำเป็นในการเจาะเลือดหาค่า TSB ใช้ค่าที่สอดคล้องกับระดับ TSB ที่ต้องเริ่มให้การรักษาภาวะตัวเหลืองด้วยการส่องไฟ*

ผลการศึกษา*: ใช้ตัวอย่าง T_cB-TSB จำนวน 249 คู่ จากทารกคลอดก่อนกำหนด 196 ราย ที่มีน้ำหนักตัวแรกคลอด 1,887 $\pm$ 344.4 กรัม ระดับ TSB เท่ากับ 4.5-17.6 มก./ดล. (9.4 $\pm$ 2.2 มก./ดล.) T_cB เท่ากับ 4.1-17.7 มก./ดล. (9.7 $\pm$ 2.4) Correlation coefficient ระหว่าง T_cB-TSB มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติ (r 0.79, $p < 0.0001$) ค่า T_cB ที่วัดได้มักจะสูงกว่า TSB โดยมีความแตกต่างเฉลี่ยของ TSB-T_cB เท่ากับ -0.3 $\pm$ 1.5 มก./ดล. และ 95% confidence interval of the mean -0.1 ถึง -0.5 มก./ดล. ในจำนวนตัวแปร เช่น น้ำหนักตัวแรกคลอด อายุครรภ์ และอายุหลังคลอดเป็นวัน มีเพียงอายุหลังคลอดเท่านั้นที่มีผลต่อ Correlation ของ T_cB-TSB ทารกอายุ 1-4 วัน T_cB ที่วัดได้สูงกว่า TSB มีจำนวนมากกว่า T_cB ที่วัดได้ต่ำกว่า TSB ในทางตรงกันข้าม ทารกที่มีอายุมากกว่าหรือเท่ากับ 5 วัน T_cB ที่วัดได้ต่ำกว่า TSB มีจำนวนมากกว่า T_cB ที่วัดได้สูงกว่า TSB จุดตัดของ T_cB ที่บ่งชี้ความจำเป็นในการเจาะเลือดหาค่า TSB ใช้ระดับเดียวกับระดับของ TSB ที่ต้องเริ่มให้การรักษาด้วยการส่องไฟ คือ ระดับ 6, 8, 10, 11 และ 12 มก./ดล.*

สรุป*: การเปรียบเทียบค่าบิลิรูบินที่วัดทางผิวหนังกับค่าบิลิรูบินในซีรัมในทารกคลอดก่อนกำหนดมีความแม่นยำอย่างมีนัยสำคัญทางสถิติ และสามารถใช้การวัดทางผิวหนังเป็นวิธีคัดกรองที่บ่งชี้ถึงความจำเป็นในการเจาะเลือดเพื่อหาค่าซีรั่มบิลิรูบินได้*