

Clinical Investigation

Clinical Evaluation of a New Device for Transcutaneous Bilirubin Measurement in Japanese Infants

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Abstract

Background: The advantages of using noninvasive techniques of bilirubin measurement are the avoidance of pain and of local infection as well as real-time results. Recently the accurate measurement of total serum bilirubin by transcutaneous bilirubin using a reflectance spectrophotometer, the BiliCheck™, has been introduced in a heterogeneous newborn population. But there is limited data on the use of BiliCheck™ on Oriental babies including Japanese newborn infants.

Methods: A total of 240 transcutaneous bilirubin measurements were taken from the three body sites (forehead, chest, and left or right upper arm) of 52 Japanese neonates and compared with simultaneous total serum bilirubin measurements determined by the direct spectrophotometric method. Of 240 occasions, 206 measurements were taken before starting phototherapy and 34 were during phototherapy. A phototherapy eye-patch was placed over the measurement site on the forehead prior to the start of phototherapy.

Results: As a preliminary study, total serum bilirubin concentrations measured by the direct spectrophotometric method and by the bilirubin oxidase method were compared. There was a good correlation between the values obtained by these 2 methods ($r=0.980$, $y=1.05x+0.176$, $p<0.0001$). The precision of the device was expressed as a mean coefficient of variation of less than 5 % and operator difference was small as coefficient of variation below 5 %.

Before phototherapy, the correlations between the transcutaneous bilirubin measurements by the BiliCheck™ and total serum bilirubin by the direct spectrophotometric method were high; $r=0.925$ on forehead, 0.848 on chest and 0.822 on upper arm, respectively. However, the correlation became less during phototherapy (on forehead $r=0.803$, $p<0.001$).

Conclusion: These data indicate that accurate measurements of total serum bilirubin by transcutaneous bilirubinometry with BiliCheck™ are applicable in Japanese infants. But the use of the device for infants who receive phototherapy needs further study.

Keywords: transcutaneous bilirubinometer, total serum bilirubin concentration, phototherapy, Japanese infants

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More than 80 % of Japanese newborn infants develop visible physiologic jaundice in the first week after birth. The incidence of hyperbilirubinemia is reported to be especially higher in Japanese infants¹⁾. It has been a routine procedure in every nursery to screen the degree of individual jaundice by noninvasive transcutaneous bilirubin measurements with Minolta transcutaneous bilirubin meter and to measure the serum concentration with blood sampled from the heel of each infant when the reading is high²⁾. However,

the device available at present only shows the reading values of the device, and the values do not correspond directly to the values of serum bilirubin concentration³⁾. Therefore, many infants, especially sick neonates and smaller infants, still require unnecessary invasive serum bilirubin measurements.

The BiliCheck™ is a new transcutaneous bilirubin measurement device that uses spectral reflectance analysis algorithms based on recent studies of the dermal light scattering and light absorption characteristics

of neonatal skin and corrects for the interfering pigments⁴). In contrast to the Minolta transcutaneous bilirubin meter, the BiliCheckTM provides absolute values of the total serum bilirubin. Recently in a mixed population, the applicability of the BiliCheckTM has been examined⁵). But the number of Asian infants was too small in comparison to white and black subjects. The aim of this study is to determine the accuracy and reliability of the BiliCheckTM device in the measurement of transcutaneous bilirubin in Japanese infants.

Subjects & Methods

We measured transcutaneous bilirubin using the BiliCheckTM on 52 Japanese infants who were born in Saitama Medical Center, Saitama Medical School during the period of 6 months, from June to November 1998. Infants were sequentially enrolled as many as possible in the study from both the well-baby nursery and the neonatal intensive care unit. The gestational age was between 33.4 and 41.7 weeks (average: 35.5 weeks). The newborns weighed between 1064 g and 3410 g (average: 2138 g). Preterm infants were <37 weeks of gestational age. No infant had clinical manifestations of sepsis, heart or circulatory disease, respiratory distress, or clinical evidence of hemoglobinopathy. The same physician took BiliCheckTM measurements on each patient after obtaining parental informed consent.

The measurements were made on three of the following sites ; forehead, chest, and right or left upper arm within 30 minutes of the blood withdrawal via heel stick for conventional laboratory measurement. During phototherapy, the BiliCheckTM measurement was taken only on the forehead that had been completely protected by the round patch (approximately 3 cm in diameter) made from photo-opaque material.

Total serum bilirubin level was measured using bedside bilirubinometer (Nakamura Medical, Tokyo, Japan) that uses the direct spectrophotometric method. In order to confirm the accuracy of bedside bilirubinometer, 50 stocked serum samples from neonates were simultaneously checked for serum bilirubin concentration by 2 different methods; bilirubin oxidase method using automatic analyser (Hitachi 717) and direct spectrophotometric method using bedside bilirubinometer, as a preliminary experiment.

The precision of BiliCheckTM was tested on five different newborn infants with total serum bilirubin concentrations ranging from 1.2 to 17.3 mg/dL. In each

instance, the same test was performed on the same infant, on the same body site, by the same physician.

For the survey on operator difference in transcutaneous bilirubin measurement, all of the four authors performed the measurements on the other 5 infants and observed for the difference.

Regression analysis according to Pearson was used to test the correlation between two variables. A p value of <0.05 was considered to be significant.

Results

Preliminary study on 50 stocked serum samples revealed an excellent correlation between the values of total serum bilirubin obtained by the direct spectrophotometric method and the bilirubin oxidase method as shown in Fig. 1 ($r=0.980$, $y=1.05x+0.576$, $p<0.0001$). Thus the accuracy and reliability of the BiliCheckTM was tested by comparison with measurements on withdrawn blood samples using the bedside bilirubinometer.

The precision of the device was shown in Table 1. The 20-test sampling for precision produced coefficients of variation ranging from 2.11 to 4.80 %.

Table 2 summarizes the operator difference in transcutaneous bilirubin measurement. The coefficients of variation ranged from 1.14 to 4.33 %.

A total of 240 measurements (37 preterm infants and

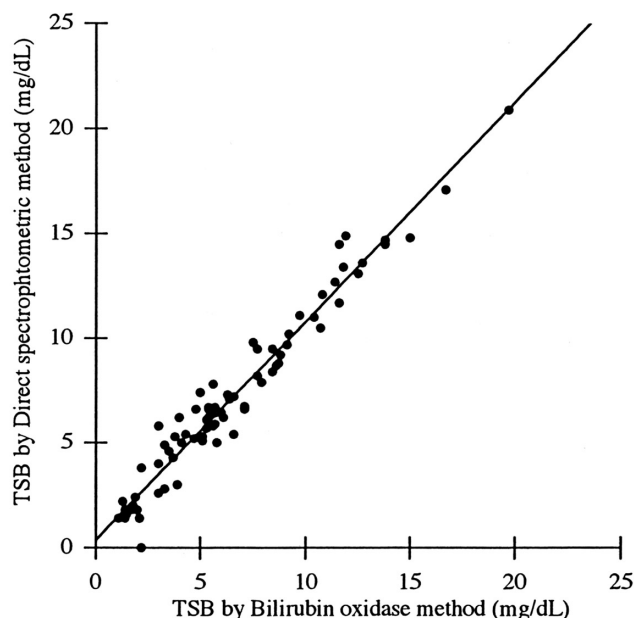


Fig. 1. Correlation between total serum bilirubin concentrations by bedside bilirubinometer (direct spectrophotometric method) and by automatic analyzer (bilirubin oxidase method). Coefficient of correlation; $r=0.980$ and regression line; $y=1.05x+0.176$ ($n=50$, $p<0.0001$).

Table 1. Precision of transcutaneous bilirubinometry

TSB (mg/dl)	transcutaneous measurement sequence of reading				mean	CV (%)
	1st	2nd	3rd	4th		
1.2	1.7	1.7	1.8	1.6	1.7	4.8
5.5	6.0	5.8	6.1	6.0	6.0	2.11
7.4	7.2	7.3	7.6	7.5	7.4	2.47
13.8	15.1	16.6	15.1	15.4	15.8	4.29
17.3	17.1	17.8	17.4	16.8	17.3	2.47

TSB ;the total serum bilirubin concentration by direct spectrophotometric method, CV ;coefficient of variation

Table 2. Operator difference in transcutaneous bilirubinometry

TSB (mg/dl)	operator				mean	CV (%)
	A	B	C	D		
4.7	6.0	6.2	6.3	5.9	6.1	2.99
7.9	10.9	10.1	10.1	9.9	10.25	4.33
8.0	8.6	8.8	8.8	8.8	8.75	1.14
11.4	12.3	13.4	12.7	12.5	12.7	3.76
15.6	15.6	15.7	15.4	15.0	15.42	2.01

TSB ;the total serum bilirubin concentration by direct spectrophotometric method, CV ;coefficient of variation

15 term infants) were taken between 0 and 10 days after birth and 206 measurements were taken before phototherapy and 34 were during phototherapy.

The correlation between the transcutaneous bilirubin measurements by the BiliCheckTM on the forehead and total serum bilirubin by the direct spectrophotometric method before phototherapy was excellent as shown in Fig. 2. The transcutaneous bilirubin levels ranged from 1.4 to 19.9 mg/dL, while the total serum bilirubin levels ranged from 0.0 to 20.9 mg/dL. The coefficient of correlation was 0.925, with regression line; $y = 0.932x + 1.757$ ($N = 204$, $p < 0.0001$). There were no differences in correlation among the gestational maturity. Table 3 shows the correlation of the values between the total serum bilirubin and the transcutaneous bilirubin measured on 3 different body sites. Measurement on the forehead revealed the best correlation, and those on the upper arm and chest were less accurate. When the transcutaneous bilirubin measurement was performed on the forehead, the 95 % confidence limits against bedside bilirubinometer was ± 1.758 mg/dL.

There were no apparent differences in correlation among the birth weight groups or gender.

The correlation between the transcutaneous bilirubin measurements by the BiliCheckTM and the total serum bilirubin by bedside bilirubinometer during

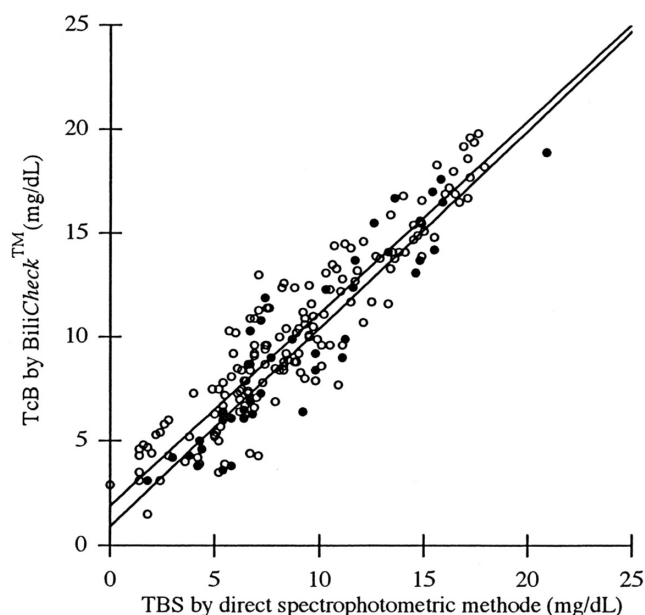


Fig. 2. Correlation between total serum bilirubin concentrations by bedside bilirubinometer and transcutaneous bilirubin measurements on the forehead by the BiliCheckTM before phototherapy. (○), preterm infants (n=166); (●), term infants (n=40). Coefficient of correlation; $r = 0.925$, 0.965 , and 0.962 (total, preterm, and term infants, respectively). Regression line; $y = 0.932x + 1.757$ ($p < 0.0001$), $y = 0.926x + 1.898$ ($p < 0.0001$), and $y = 0.951x + 0.912$ ($p < 0.0001$) (total, preterm, and term infants, respectively).

Table 3. Results of linear correlation analysis before phototherapy

Correlation	n	RMSE	r	SE-y	Equation: y=
TcB vs TSB					
forehead	206	1.625	0.925	0.879	$0.932x + 1.757$
chest	206	2.152	0.848	1.673	$0.808x + 3.346$
upper arm	206	2.204	0.822	1.192	$0.746x + 2.384$

TcB ;the transcutaneous bilirubin measurement by the Bili CheckTM, TSB ;the total serum bilirubin concentration by direct spectrophotometric method, RMSE ; Root Mean Square Error, SE-y ;Standard Error of the Estimate.

phototherapy was also good, but less than that of before phototherapy ($r = 0.803$, $y = 0.79x + 3.937$, $p < 0.001$) (Fig. 3). The transcutaneous bilirubin level tended to be higher than the total serum bilirubin level in the lower range during phototherapy, and lower in the higher range. The 95 % confidence limits against bedside bilirubinometer was ± 1.158 mg/dl.

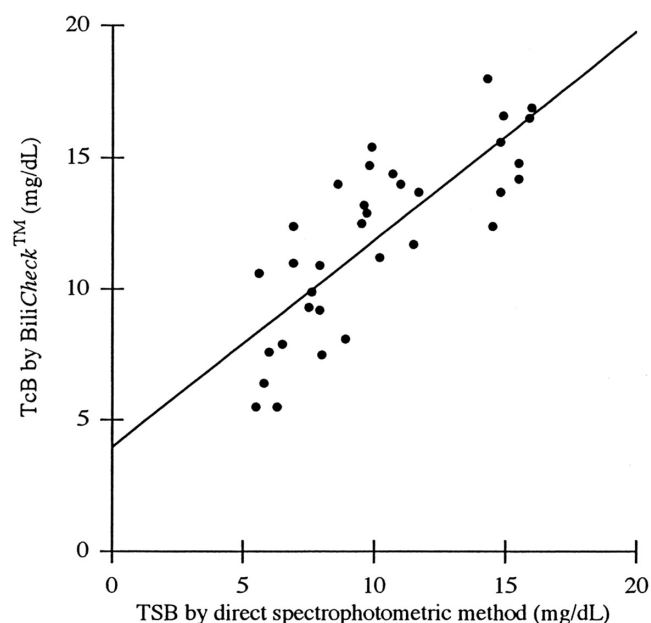


Fig. 3. Correlation between total serum bilirubin concentrations by bedside bilirubinometer and transcutaneous bilirubin measurements on the forehead by the BiliCheck™ during phototherapy. Coefficient of correlation; $r=0.803$ and regression line; $y=0.79x+3.937$ ($n=36$, $p<0.001$).

Discussion

The transcutaneous bilirubinometer has been evaluated in a number of studies^{2,3,6-8)} and has been proposed as a valuable screening device that might aid in decreasing length of stay at hospital after birth. These products also provide rapid, point-of-care bilirubin measurement as a replacement for traditional clinical chemistry methods. These results are achieved with no trauma to the patient, no risk of infection, and potentially reduced cost of monitoring serum bilirubin by minimizing the use of hospital personnel and supplies. In addition, as Knudsen et al⁹⁾ has suggested, transcutaneous bilirubin measurement could be a somewhat better predictor of kernicterus than total serum bilirubin measurement. But concerns exist regarding linearity of transcutaneous measurement⁹⁻¹²⁾.

The BiliCheck™ works by directing white light into the skin of the newborn and measuring the intensity of the specific wavelengths, which are returned. The major skin components, which impact the spectral reflectance in newborns, are dermal maturity, melanin, hemoglobin, and bilirubin¹³⁾. Each of these four components has been considered in the development of the algorithm used to compute the bilirubin measurement. Measuring the intensity of the relaxant light at 137 individual wavelengths performs a spectral analysis. By subtracting the special contribution of the

known components, the bilirubin absorbance can be quantified and is then correlated to the laboratory gold standard high performance liquid chromatography. So the measurement can indicate the result in clinical units of mg/dL or $\mu\text{mol/L}$.

Previous report shows there was no significant difference in accuracy of transcutaneous bilirubin assays in black and white babies⁵⁾. In their report, however, there are a few Asian people, which are enrolled in subjects. So to determine the clinical accuracy of the device for measuring transcutaneous bilirubin in Asians, additional data with sufficient number of infants are indispensable. Our data indicate that accurate measurement of total serum bilirubin by transcutaneous bilirubin assay with this device is possible in a heterogeneous newborn population including Japanese infants.

There are limited data on use of the BiliCheck™ on infants under the phototherapy^{11,14)}. Our results demonstrate that transcutaneous bilirubin measurement using the BiliCheck™ correlates less with total serum bilirubin level during phototherapy. The use of phototherapy to decrease the serum bilirubin level has been rapidly reduce the concentration of bilirubin in the skin through photo-conversion of the bilirubin molecule and subsequent washout into the blood¹⁵⁾. This intentional alteration in the blood-skin relationship decreases the skin bilirubin concentration and introduces an error in transcutaneous measurement without protection of the measurement site by a photo-opaque material¹⁶⁾. It is suspected that in our study the measurement site, forehead, was not protected completely because of head position, which was changed every three hours. So accurate measurements of transcutaneous bilirubin techniques in babies receiving phototherapy require continued study.

In conclusion, our data indicate that accurate measurements of total serum bilirubin by transcutaneous bilirubin assay with the BiliCheck™ are possible also in Japanese infants. Accurate measurements of total serum bilirubin by transcutaneous technique in babies receiving phototherapy require continued study.

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日本人新生児における新型経皮的ビリルビン測定装置の臨床的検討 中村 利彦, 山田 大悟, 板倉 敬乃, 小川 雄之亮

目的：非侵襲的ビリルビン測定は児の疼痛、局所感染の回避と言う意味で迅速に結果が得られることと同様に有利である。ビリチェック™という経皮的ビリルビン測定装置によって血清中総ビリルビン値を多民族における新生児で正確に測れる事が報告された。しかし、日本を含んだ東洋人に関しては十分なデータがなかったため、今回日本人を対象にビリチェック™の有用性を検討した。

対象および方法：52人の日本人新生児を対象に240回、前額部、胸部、上腕部3ヶ所でビリチェック™による経皮的ビリルビン測定と同時に血清総ビリルビン値を測定した。光線療法中の34回はアイパッチで前額部が遮蔽された箇所ではビリチェック™を使用した。

結果：ビリルビノメーターとビリルビンオキシ

ダーゼ法を比較すると、 $r=0.980$, $y=1.05x+0.176$, $p<0.0001$ と極めて良い相関を確認し、以後の検討をビリルビノメーターとビリチェック™の値を比較した。ビリチェック™における各ビリルビン濃度の変動係数は5%以下と再現性は良好であり、測定者間での変動係数も5%未満と測定者の影響は問題なかった。光線療法前の児では、ビリルビノメーターと前額部($r=0.925$)、胸部($r=0.848$)、上腕部($r=0.822$)の順では良い相関が得られた。しかし、光線療法中では前額部でも $r=0.803$ とやや相関が悪くなった。

結論：今回の結果より、日本人においてもビリチェック™による経皮的ビリルビン測定は血清総ビリルビン値を正確に反影することが確認された。しかし、光線療法中に関してはさらなる検討を要する。