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Transcutaneous Bilirubin Measurement: Evaluation of Bilitest™

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Key Words
Newborn jaundice · Transcutaneous bilirubin measurement · Hyperbilirubinemia

Abstract
Objective: The early discharge of neonates from hospitals makes transcutaneous measurement of total serum bilirubin concentration a useful tool to monitor neonatal jaundice. The objective of this study was to evaluate the Bilitest BB 77™ (Bertocchi SRL Elettromedicali, Cremona, Italy), a new device for noninvasive transcutaneous total bilirubin measurement. ***Methods:*** We studied 241 newborn infants ≥32 weeks of gestation admitted to the Neonatal Nursery of Careggi University Hospital, Florence. These infants had total serum bilirubin (TSB) levels measured by a standard laboratory test (group B = 198) as part of their normal care, and transcutaneous bilirubin (TcB) levels were obtained within 10 min after heel pricking. ***Results:*** There was a good correlation between TSB and TcB values. The linear regression plot showed a general underestimation of Bilitest BB 77 measurement compared to standard laboratory test; the negative difference between Bilitest BB 77 values and TSB increased at higher bilirubin levels, as confirmed by the Bland-Altman error plot. To visualize the accuracy of the Bilitest BB 77 measurements, ROC curves plot sensitivity versus specificity and the maximum range of difference between Bilitest BB 77 and TSB were considered. Pearson correlation analysis demonstrated that Bilitest BB 77 accuracy was independent of gestational and postnatal age of newborns. ***Conclusion:*** We conclude that the Bilitest BB 77, a new device for bilirubin transcutaneous measurement, shows a good correlation with standard laboratory method and has the merit to be quite inexpensive and does not need calibration with consumable or disposable parts. However, because TcB measurements with Bilitest BB 77 underestimated STB levels particularly at STB ≥12 mg/dl, serum bilirubin measurements are still required when treatment with phototherapy or exchange transfusion is being considered.

Early discharge of newborns from hospitals makes measurement of total serum bilirubin concentration before discharge an important tool to monitor infants with jaundice [1, 2].

Transcutaneous measurement of total bilirubin (TcB) is also ideal for outpatient use and seem very useful in ensuring appropriate surveillance of infants after their discharge from the hospital [3]. In addition, nomograms of transcutaneous bilirubin percentiles of healthy full-term infants have been recently published [4]. However, one of the new devices (Chromatics Colormate III™, Chromatics Color Science International Inc., New York,

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N.Y., USA) needs an early determination of skin color measurement within the first 30 h of life [5]. BiliCheck™. (Respironics Inc., Murrysville, Pa., USA), which shows a satisfactory inter-operator and inter-device coefficient of variation [4] with an accuracy and precision of the TcB measurement comparable with the standard of care laboratory test [1, 6, 7], needs to be calibrated before each measurement with a calibration standard (called BiliCal) with an additional cost. On the contrary, the TcB measurements using the new JM-103 jaundice Meter™ (Minolta/Hill-Rom Air-Shields) correlate closely with TSB levels and, since the measurement technique is so simple, repeated measurements can be performed over time: this should significantly reduce the likelihood of error [8]. In the same way, Bilitest BB 77™. (Bertocchi SRl Elettromedicali, Cremona, Italy) is a new device for noninvasive TcB measurement which does not need a consumable or disposable part nor calibration before use. Our aim was to determine whether TcB measurement, performed with BB 77, correlates with TSB levels, measured with standard laboratory methods.

Methods

Patients

This study was performed on 241 healthy newborn infants admitted to the Neonatal Nursery of Careggi University Hospital, Florence. Total serum bilirubin was determined according to the judgment of the physician in charge and not for research purposes. However, the Ethical Committee of the Department of Neonatology approved the study protocol. All of 241 newborns had a measurement of both transcutaneous and serum bilirubin. No infants received phototherapy. Gestational age, birth weight, and postnatal age were recorded.

Total Serum Bilirubin (TSB) Measurement

Capillary blood samples from heel pricks were used to measure TSB levels by means of ABL 735 blood gas analyzer (Radiometer, Denmark) or by GB 13/A Bilirubinometer (Bertocchi SRL Elettromedicali, Italy).

The ABL 735 analyzer is a computer-controlled blood gas analyzer equipped with a spectrophotometric unit for detection of hemoglobin and bilirubin. Absorption spectrum from blood samples are recorded by a 128 single-wavelength photodiode array (wavelengths from 478 to 672 nm are separated by a concave interference grating) and contributions of single absorption spectra from bilirubin and different forms of hemoglobins to the overall absorption spectrum are best fitted by the computer software.

Transcutaneous Bilirubin Measurement

The yellowness of the skin was measured, on the forehead, by means of the new Bilitest GB 77. This is a fully automated noninvasive device consisting of a photometer for the noninvasive bilirubin concentration measurements in the skin and under-skin layers of neonates. Operating method is the following: the pulse of light, emitted by the light source, passes to the baby's skin through an optical channel; the reflected light from the skin is then directed to the optical analyzer, which consists of two channels, each one with an high precision optical filter and photodiode. The evaluation of the concentration of bilirubin C_B is based upon the well-known formula of light absorption:

$$L(x) = L_0 \exp(-K * x),$$

where L_0 = initial intensity of light, x = optical path, L(x) = intensity at the distance x, K = coefficient, which depends upon the concentration of absorbing substance and wave length.

The light in the tissues of a patient is absorbed also by hemoglobin and melanin in the same wave band as bilirubin. The bilirubinometer must eliminate this absorption, which causes the errors of bilirubin evaluation. The spectral absorption characteristics of bilirubin and hemoglobin are different, so if the absorption of two different waves λ_1 and λ_2 are measured, the two registered intensities L (λ_1) and L (λ_2) give the possibility to calculate only the bilirubin concentration:

$$C_B = K_p [K_1 * (\text{In } L (\lambda_1)) - K_2 * (\log L (\lambda_2))],$$

where K_p = adjustment coefficient, K_1, K_2 = weight coefficients, which must be evaluated empirically.

The wavelengths are chosen as a compromise between the necessity of measurement in the bands of maximum absorption of hemoglobin and bilirubin, and the necessity of the same diffusion of beams in the tissues. For the Bilitest GB 77 the following wavelength are accepted: λ_1 = 520 nm, λ_2 = 598 nm. In order to eliminate the influence of melanin, the two-sources method is used. The electrical output of the photodiodes is converted into the data of the optical property of the skin at the wavelength of the bilirubin absorption and the display shows the concentration of bilirubin in the blood, in mg/dl or in μmol/l. The calibration of the instrument was made by the company on the basis of multiple bilirubin determinations, and never needs to be repeated.

Measurements took place in a quiet environment with controlled artificial light, and the newborns were not crying at the time of measurement. Meter readings were obtained every time an evaluation of serum bilirubin concentration was required to evaluate clinical jaundice and sometimes in the course of routine blood examinations. Within a period of 10 min after heel pricking, three measurements of TcB were obtained for each infant and the average value was used for correlation with serum blood value. TcB readings were always performed by the same person, without prior knowledge of the total serum bilirubin value.

Statistical Analysis

Data obtained were analyzed utilizing (1) the correlation coefficients (Pearson product moment) calculated with the use of linear regression techniques between Bilitest and laboratory TSB and ABL 735, (2) the sensitivity and specificity of Bilitest to predict accurately serum bilirubin estimated at a range of values and plotted on receiver operating characteristics (ROC) curves, (3) Bland-Altman scatterplots [9], and (4) Pearson correlation of differences Bilitest versus laboratory TSB to analyze the influence of gestational age and postnatal age on the Bilitest readings.

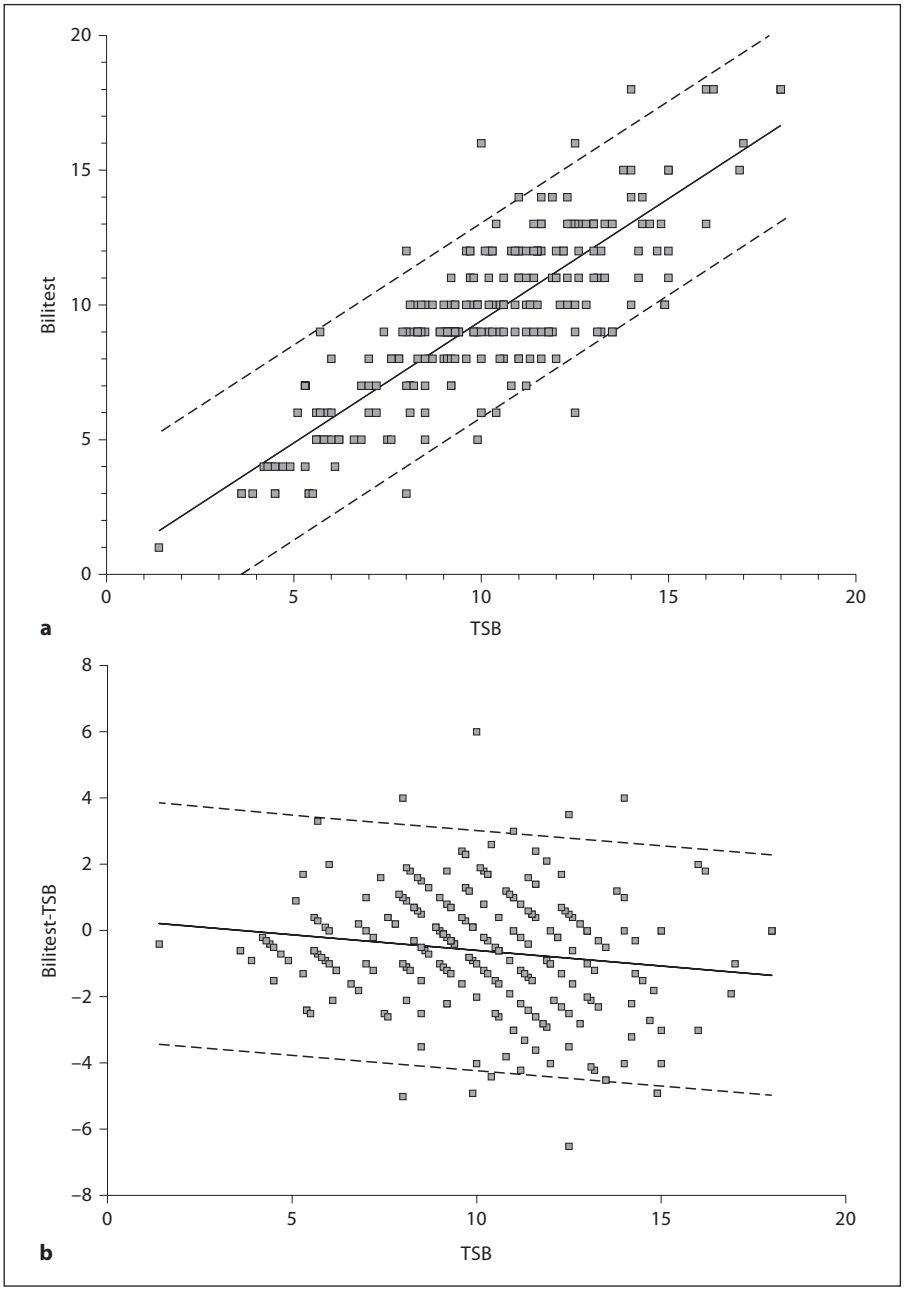

Fig. 1. Regression chart (**a**) and error plot (**b**) of Bilitest vs. TSB measurements with a standard laboratory test.

Results

The demographic characteristics of the 241 newborns studied were birth weight 2,955 ± 746 g (mean ± SD), gestational age 38 ± 2 weeks (mean ± SD) and postnatal age 4 ± 3 days (mean ± SD). Only 5.8% of infants had TSB levels >15 mg/dl. The correlation coefficients (r) of TcB to total serum bilirubin, the intercept and slope coefficients are reported in table 1. Regression plots of Bilitest and standard laboratory test are shown in figure 1a. Error

Table 1. Relationship between TcB measured with Bilitest™ and TSB measured with standard laboratory methods

Patients	r	Slope	Offset
All	0.83 (0.74–0.88)	0.90 (0.82–1.05)	0.35 (–0.8–1.7)

Values in parentheses are 95% confidence limits. r = correlation coefficient; slope = slope of the regression line: y = mx + b; offset = the y intercept in the regression equation: y = mx + b (mg/dl).

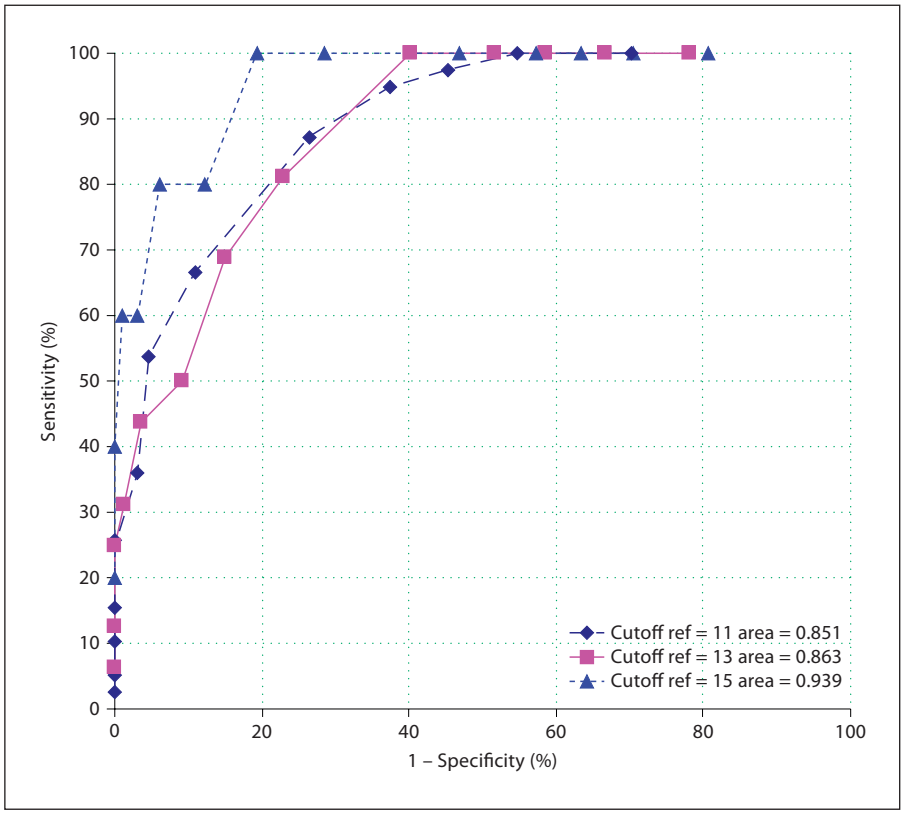

Fig. 2. ROC curve for Bilitest and TSB measurements with a standard laboratory test.

plots (according to Bland and Altman) are shown in figure 1b. The linear regression plot (fig. 1a) showed a general underestimation of bilitest measurement as compared to standard laboratory test; the negative difference between Bilitest values and TSB increased at higher bilirubin levels, as confirmed by the Bland-Altman error plot (fig. 1b). To visualize the accuracy of the Bilitest measurements ROC curves plot sensitivity vs. specificity and the maximum range of difference between Bilitest and TSB were considered. The ROC curves for Bilitest TcB compared with TSB at 2 levels of TSB are reported in figure 2. Using a Pearson correlation analysis we found no significant influences of gestational and postnatal age differences between readings performed by Bilitest or other instruments.

Discussion

Jaundice is the most frequent problem observed in newborns, but only about 5% of full-term neonates develop TSB concentrations of more than 12.9 mg/dl (222 μmol/l) [10]. However, heel punctures to measure TSB levels are performed on many newborns although this procedure is painful and time consuming. A noninvasive device for predicting serum bilirubin levels in newborns diminishes the need of skin punctures. Now, several different devices are present in hospitals. The BiliCheck (Respironics, Marietta, Ga., USA) uses multiple wavelengths, and it seems to work finely in a multiracial neonatal population [6]. The new JM-103 Jaundice Meter from Minolta/Hill-Rom Air-Shields uses 2 wavelengths and a dual optical path system [8]. The correlation in black infants was not as close as in other groups, but because the tendency in blacks is for the JM-103 to overestimate serum bilirubin levels, dangerous clinical errors were unlikely to occur [8].

In our study, we evaluated a new device for TcB, which has the merit to be low-priced and does not need calibration with consumable or disposable parts. We compared this measurement with the laboratory TSB determination in Caucasian healthy neonatal population. The Bilitest GB 77 showed a good correlation with the standard laboratory test (r = 0.89). The skin pigmentation represents an important limitation of this device, because the absorption at two wavelengths eliminates the effect of the hemoglobin but does not eliminate the effect of melanin and dermal thickness. However, the error plots in figure

1b indicate that TcB measurements with Bilitest underestimated STB levels in comparison with standard laboratory methods, particularly at STB levels ≥ 12 mg/dl. Our study has some limitations. First, we had few infants with TSB levels >15 mg/dl (257 μmol/l). Only 5.8% of our infants had TSB levels >15 mg/dl, but if we assess the clinical utility of the TcB compared with the laboratory methods, according to the ROC curves, we can identify accurately the patients with TSB levels of interest.

When the standard Laboratory methods is set at 15 mg/dl, using a cutoff point of 13 mg/dl for Bilitest, TcB produced a sensitivity of 85% and specificity of 98%. Setting the standard laboratory test at a level of 13 mg/dl, it can be seen that a cutoff of 9 mg/dl on the Bilitest has a sensitivity of 85% and specificity of 70%. As TSB levels <12.9 mg/dl account for a high percentage of the serum bilirubin analyses [6, 10–12], the vast majority of infants can be monitorized without the heelstick technique, lancet puncture incision, and collection of blood by the drip method. TSB levels were measured with two different laboratory methods. It is well known that bilirubin determination is subjected to a large interlaboratory variability [13, 14]. However, the accuracy of TSB measurement in our unit by reflectance spectrophotometry (GB 13/A™ Bilirubinometer, Bertocchi SRL Elettromedicali, Italy) was recently tested, and the correlation between our laboratory method and the HPLC method was high (r = 0.927; 95% CI = 0.906–0.944) [6]. Moreover, some reports have shown that the new multi-wavelength spectrophotometric method developed by Radiometer measures TSB concentrations accurately and precisely in conjunction with blood gas analysis/co-oximetry (ABL 735™) [15, 16].

In our study, all of the TcB measurements were obtained by the same technician. In clinical setting, where measurements are performed by a large number of nursing staff, accuracy and precision are likely to be poorer. The main applications of bilirubin measurements are to identify by nomogram the infants at risk of severe hyperbilirubinemia and to identify TSB levels that indicates intervention with phototherapy or exchange transfusion: this strategy needs repeated bilirubin measurements. Because Bilitest technique is rapid and convenient, the noninvasive TcB measurements with the Bilitest can be an important addition in the monitoring and management of the Caucasian jaundiced newborn infants. We believe that using TcB measurement with Bilitest in Caucasian neonatal population, we could eliminate 90% heel pricks. However, when TcB is higher than 13 mg/dl, especially in the first 24–48 h of life, a serum bilirubin determination must be carried out.

In conclusion, the Bilitest appears to be a very useful screening device which matches easy utilization and inexpensive use.

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Erratum

In the Methods section of the Abstract of the paper 'Transcutaneous Bilirubin Measurement: Evaluation of Bilitest™' by G. Bertini et al. [Neonatology 2008;93:101–105] the words '(group B = 198)' should be deleted. The correct sentence reads:

These infants had total serum bilirubin (TSB) levels measured by a standard laboratory test as part of their normal care, and transcutaneous bilirubin (TcB) levels were obtained within 10 min after heel pricking.