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ORIGINAL ARTICLE

Comparison between Bilistick System and transcutaneous bilirubin in assessing total bilirubin serum concentration in jaundiced newborns

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OBJECTIVE: To compare the performance and accuracy of the JM-103 transcutaneous bilirubinometer and Bilistick System in measuring total serum bilirubin for the early identification of neonatal hyperbilirubinemia.
STUDY DESIGN: The study was performed on 126 consecutive term and near-term (⩾36 weeks' gestational age) jaundiced newborns in Cairo University Children Hospital NICU, Egypt. Total serum bilirubin was assayed concurrently by the clinical laboratory and Bilistick System and estimated using the JM-103 transcutaneous bilirubin instrument. Bland–Altman analysis was used to evaluate the agreement between determinations.
RESULT: The limits of agreement of the Bilistick System (−5.8 to 3.3 mg dl^{-1}) and JM-103 system (−5.4 to 6.0 mg dl^{-1}) versus the clinical laboratory results were similar.
CONCLUSION: The Bilistick System is an accurate alternative to transcutaneous (TcB) determination for early diagnosis and proper management of the neonatal jaundice.

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INTRODUCTION

Neonatal jaundice is a physiologic condition characterized by the increase in total bilirubin concentration in the blood, occurring in 60 to 80% of term newborns worldwide.[1] Under normal conditions, the bilirubin concentration should return to normal value within 2 weeks of age. Unfortunately, in some cases severe hyperbilirubinemia occurs and can lead to acute bilirubin encephalopathy and kernicterus/chronic bilirubin encephalopathy (CBE),[2] accounting for long-term morbidity and sometimes mortality in healthy late-preterm and full-term infants.[3] CBE is rare in wealthy first world countries, but severe hyperbilirubinemia and encephalopathy continue to occur in many poorly resourced countries.[4,5] Screening total bilirubin levels in babies before hospital discharge has become routine in most affluent country hospitals.[6] The methods commonly used in clinical practice are laboratory measurement of the total serum bilirubin (TSB) or pre-discharge transcutaneous (TcB) bilirubin determination. Unfortunately, TcB instruments are expensive, and effective laboratory support is often not available in poorly resourced countries, is often inaccurate and reports delayed for hours.[4,7]

TcB bilirubin determination is a non-invasive, painless method frequently used for bilirubin screening in jaundiced infants.[8] Its use as an alternative to laboratory TBS measurement for screening was recommended by the American Academy of Pediatrics (AAP) in 2004.[9] This methodology is based on the estimation of bilirubin concentration using optical spectroscopy and provides instantaneous, non-invasive estimates of TcB bilirubin concentration. A major limitation is the tendency to underestimate bilirubin levels.[10] Furthermore, TcBs have limited measurement scales (up to 15 or 20 mg dl^{-1}, depending on the instrument) and their accuracy is known mostly for Caucasian newborns.[11] In African-American newborns, TcB is often not accurate and significantly overestimates TSB levels[12,13] especially in infants with relatively high TSB value. In addition, the association between TcB and serum bilirubin level becomes increasingly weaker in premature babies less than 30 weeks' gestation and in those who had already received phototherapy.[14,15]

A new method for TSB determination, the Bilistick System (BS, Bilimetrix, Trieste, Italy), was recently developed with the aim of facilitating early diagnosis of hyperbilirubinemia.[16] BS is a Point of Care method used for measuring TSB in newborns' blood samples with values up to 40 mg dl^{-1}. The main advantages are its ease of use, quick results, low cost, portability, sample size of only 25 µl whole blood and no need for sample preparation or reagents.[16] These characteristics make it suitable for screening bilirubin levels of babies in low-resource primary-care facilities[17] and during home-care visits by nurse or midwife.[18,19]

The present study compares the accuracy of the JM-103 TcB device and the BS in determining total bilirubin using the standard laboratory as reference method.

METHODS

The present study was conducted from April to November 2015 at the Neonatal Intensive Care Unit (NICU) of Cairo University Children's Hospital, a tertiary care referral center admitting about 250 severely jaundiced neonates each year.[20,21] The study included a total of 126 newborns with gestational age of >36 weeks' readmitted and investigated for jaundiced as prescribed by the caring physician. Gestational age, sex, weight and age at admission were recorded.

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Blood samples for TSB and BS were collected simultaneously by venous sampling. Standard precautions were used to protect laboratory samples from exposure to light to prevent photodegradation of bilirubin. Laboratory TSB was determined using a Synchron CX PRU 16360 instrument (Beckman-Coulter, Brea, CA, USA).

Blood samples for the BS were collected in 25 µl capillary tubes and loaded on the Bilistick Test Strip cell separation filter. Plasma then diffuses by capillarity from the filter to a nitrocellulose membrane, where TSB is measured by reflectance spectroscopy using the Bilistick Reader. The result is obtained within 2 min from loading. In case of technical problems, such as lack of appropriate saturation of the Test Strip or the presence of hemolysis in the sample, the Bilistick Reader identifies the problem and reports an error message that appears on its display.

TcB bilirubin was measured at the same time or within 5 min from blood collection using the JM-103 device. For those babies undergoing phototherapy, TcB measurements were taken from an unexposed area (beneath the diaper) to avoid the effect of skin bleaching.[22] The device was calibrated before each measurement according to the manufacturer's instructions. Two measurements were taken and the average was employed for analysis.

The study was approved by the Cairo University Hospital Ethics Committee, and consent was obtained from the parents of each patient.

Statistical analysis

Most variables were not Gaussian-distributed and all are reported as percentiles. Bland–Altman plots of the bias versus the average were used to evaluate the presence of a proportional bias.[23,24] Proportional bias was excluded using running plots, and the Bland–Altman limits of agreement (LOAs) were calculated. The bias was Gaussian-distributed as determined by using kernel density plots and is reported as the mean and s.d. Statistical analysis was performed using Stata 14.2 (Stata Corporation, College Station, TX, USA).

RESULTS

Total Bilirubin was measured by JM-103, BS and hospital laboratory assays in 161 enrolled infants. Thirty-five cases were excluded from the analysis because of: (1) technical problems occurring during TSB determination by laboratory assay in four cases and by BS in eleven cases leading to loss of the bilirubin value; or (2) the absence of a value by TcB due to scale limitation (TSB over 20 mg dl^{-1}) in 20 cases.

Data were analyzed for the remaining 126 infants. The demographic characteristics of the neonates in the study are shown in Table 1. The male-to-female ratio was 1.6:1 and the admission weight ranged from 2800 to 4000 with a mean (s.d.) of 3230 g (285). Age at readmission and bilirubin measurement of the infant study population ranged from 16 to 480 h of life, 57% of the samples were within the first week of life and 40 and 3% were in their second and third weeks of life, respectively.

The maximum and minimum differences found between the bilirubin values determined by BS versus Lab were of − 6.7 and 7.9 mg dl^{-1}, whereas those for TcB versus Lab method was of − 11.9 and 7.6 mg dl^{-1}, respectively (Figure 1).

Table 1. Main measurements of the study subjects

	Female (n = *48*)	*Male* (n = *78*)	*Total* (n = *126*)
Age (h)	144 (96–192)	144 (72–240)	144 (96–216)
Gestational age (weeks)	38 (38–39)	38 (38–39)	38 (38–39)
Weight (kg)	3.0 (3.0–3.2)	3.3 (3.1–3.5)	3.2 (3.0–3.5)
Bilirubin by laboratory (mg dl^{-1})	12.8 (9.1–15.0)	11.6 (8.8–15.4)	12.3 (9.0–15.2)
Bilirubin by transcutaneous (mg dl^{-1})	13.4 (10.8–15.0)	12.2 (9.1–15.8)	12.7 (9.8–15.4)
Bilirubin by Bilistick (mg dl^{-1})	11.6 (8.7–13.6)	11.3 (7.8–13.7)	11.4 (7.9–13.7)

All data are presented as 50th percentile (25th-75th percentiles).

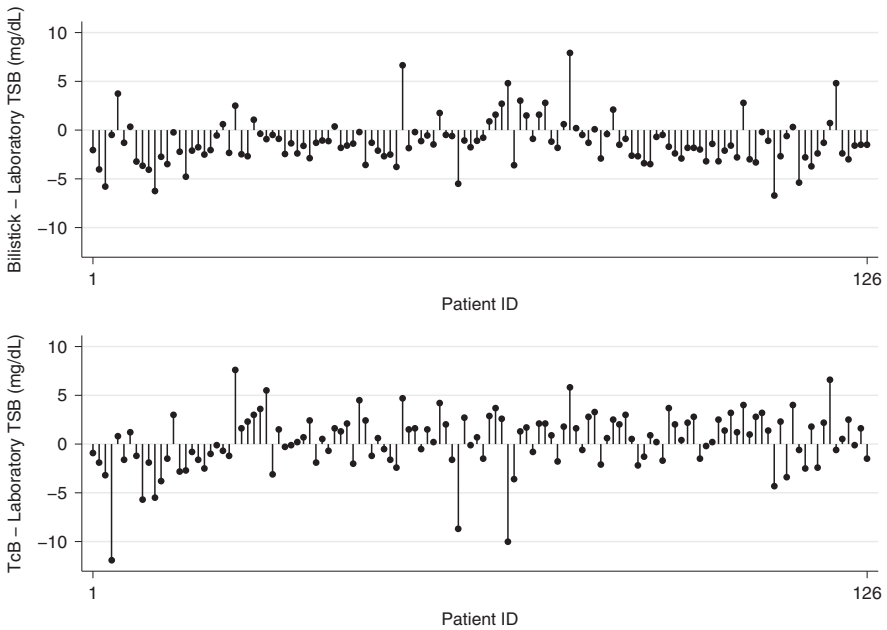

Figure 1. Paired plots of the difference between BS-LAB and TcB-LAB. BS, Bilistick System; TcB, transcutaneous.

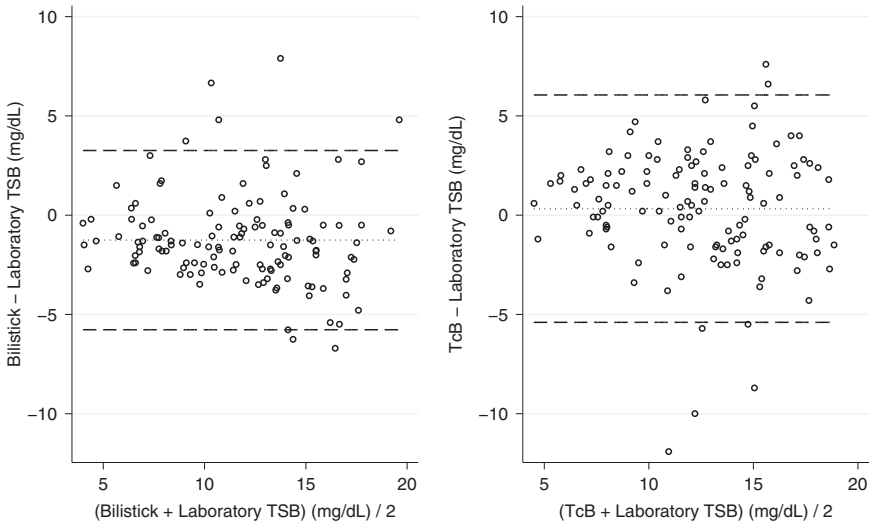

Figure 2. LOA for BS versus LAB and TcB versus LAB. The pointed line is the mean difference and the shaded lines are the LOA. BS, Bilistick System; LOA, limit of agreement; TcB, transcutaneous.

The comparison of methods by Bland–Altman analysis (Figure 2) showed that BS tended to slightly underestimate TSB versus Lab measurement, but the LOA was similar for BS (−5.8 to 3.3 mg dl^{-1}, corresponding to a mean (s.d.) of − 1.3 (2.3) mg dl^{-1}) and TcB (−5.4 to 6.0 mg dl^{-1}, corresponding to a mean (s.d.) of 0.3 (2.9) mg dl^{-1}).

DISCUSSION

Measuring serum bilirubin concentrations in neonates rapidly, accurately and safely has become increasingly important to address the high rate of severe hyperbilirubinemia in low-resource countries.[25] Our study demonstrates that the JM-103 and BS are both reliable methods for the screening of jaundiced newborns. In fact, both methods are interchangeable to the same degree with the reference method.

Several studies reported that TcB provides measurements within 2 to 3 mg dl^{-1} of the TSB.[8,13,26] Accordingly, the AAP practice guidelines proposed that TcB can replace a measurement of serum bilirubin in many circumstances, particularly for TSB levels less than 15 mg dl^{-1}.[9] Unfortunately, TcB measurements in newborns undergoing phototherapy is reported not to be reliable in skin zones reached by phototherapy light since it 'bleaches' the skin.[22] In addition, the ability of TcB to provide accurate measurements in different racial groups is still debated in many studies.[8,27] Furthermore, high bilirubin levels are not read by the TcB device (20 cases were excluded in this study since bilirubin values exceeded TcB scale limits), and TcB tends to underestimate bilirubin concentration by 2 to 3 mg dl^{-1} if the values are over 15 mg dl^{-1},[27] requiring laboratory confirmation before a clinical decision is made. These limitations of the TcB may require laboratory confirmation at high TSB levels and lead to delays in the accurate diagnosis of severe hyperbilirubinemia and implementation of appropriate treatment, especially if laboratory support is not readily available. In this context, the use of the BS for bilirubin assay could provide significant advantages, giving accurate readings up to 30 mg dl^{-1} and reducing turnaround time for results and treatment decisions.[16]

The present study confirms that BS is able to estimate TSB concentration up to 20 mg dl^{-1} with comparable accuracy to TcB instruments. In addition, it is able to assay TSB over a wider range of bilirubin concentrations, up to 30 mg dl^{-1}, and phototherapy does not affect the results. Another advantage of BS when compared with other technologies is the low cost and the ability to conduct rapid assays on whole blood without sample preparation or reagent use. Moreover, the simplicity of the test and the portability of the device allow its use for outpatient follow-up, a critical need for newborns discharged early in low-resource countries.

In many developing countries, such as Egypt, TcB readers are predominantly present in private and tertiary care hospitals. Mothers are discharged very early from public hospitals prior to the onset of peak bilirubin levels,[20] limiting the value of TSB or TcB in projecting the course of post-discharge bilirubinemia. The post-discharge obligatory heel prick used for neonatal screening of several genetic diseases may provide an opportunity to simultaneously screen TSB using the Bilistick.

CONCLUSION

The BS is an accurate cost-effective alternative to the JM-103 TcB device for early diagnosis and management of neonatal jaundice in newborns, especially in low-resource countries and in postnatal home care.

CONFLICT OF INTEREST

Dr Tiribelli is the President and CEO of Bilimetrix s.r.l., and Drs Greco and Coda Zabetta are the employees of Bilimetrix s.r.l. The remaining authors declare no conflicts of interest.

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