Sudarshan Publication

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THE PHARMA RESEARCH

An International Journal of Pharmacy Research

Comparison of the Accuracy of Noninvasive Bilirubin Measurements by optical imaging (ToB) using BiliCapture and Transcutaneous Bilirubinometer (TcB) using BiliChek with laboratory serum bilirubin level (TSB)

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ARTICLE INFO

Published on: 15 Dec 2016

ISSN: 0975-8216

Keywords:

Hyperbilirubinemia; jaundice; neonates; transcutaneous; bilirubin

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ABSTRACT

Background and Aims: Hyperbilirubinemia is very common in preterm infants and can potentially harm the central nervous system. The bilirubin test involves currently being followed is either 'heel pricking' or sometimes 'application of cannula for subsequent extraction of blood samples which is indeed very painful. Therefore, this gives an urge to researchers to develop a device, which could detect the bilirubin levels in the body of newborns and interpret the severity of jaundice in them. Methods: In this descriptive cross-sectional study, 100 neonates were enrolled. Total bilirubin was measured using a transcutaneous bilirubinometer (TcB) on the forehead and optical imaging using scanning of conjunctiva of eyes (ToB). Then, during the subsequent 30 minutes' blood samples were obtained and sent to the laboratory for determining the Total Serum Bilirubin (TSB) levels. Results: The mean±SD values of serum, transcutaneous and optical imaging bilirubin levels were 10.73±2.02 and 11.68±2.72 and 13.1±2.34 g/dl, respectively. A high correlation of r=0.88 was observed between TSB and TcB and r=0.73 between TSB and ToB. Bland-Altman plots demonstrated good agreement with the comparison values for both BiliCheck and BiliCapture devices. The sensitivity and specificity of transcutaneous bilirubinometer using BiliChek were 88% and 76% and that of optical imaging using BiliCapture for bilirubin measurement were 92% and 75.6%, respectively. Conclusions: The optical imaging of conjunctive for bilirubin assay is a safe alternative to laboratory bilirubin assay and transcutaneous bilirubinometer (BiliChek).

INTRODUCTION

Neonatal jaundice, commonly found in 60% of normal newborns, is normally a self-resolving episode ending 72 to 96 h after birth (American Academy of Pediatrics, 2001). Jaundice is a yellowish 2 pigmentation of the skin, the conjunctiva, and other mucous membranes caused by increased levels of bilirubin in blood beyond normal levels (hyperbilirubinemia). There is little bilirubin concentration in blood plasma (30 µmol/L) if a person suffers from jaundice, also called hyperbilirubinemia (increased bilirubin concentration in blood plasma) (Silbernagl S, 2010). Newborns can suffer from increased levels of bilirubin just after birth due to a high hemoglobin turnover and their bodies not being able to get rid of all the bilirubin as quickly as needed. This occurs in approximately 60% of term infants and 80% of preterm infants (Odell GB, 2010). If untreated, serious brain damage and even death can occur, thus early diagnostics is crucial. Treatment is usually light therapy, but in severe cases even blood transfusion (Kumar P, 2011; Stokowski LA, 2006).

The ordering of serum bilirubin in neonates is based on visual evaluation by either physicians or nursing staff. However, estimation of serum bilirubin by visual inspection of the skin or sclera is rapid and cost free but not sufficiently accurate, especially when applied to newborns of mixed ethnicity or diverse racial backgrounds. (American Academy of Pediatrics, 2004; Bhutani VK, Maisels MJ, 1998). Another technique for estimating serum bilirubin that is noninvasive, fast, and relatively in expensive is the use of transcutaneous spectrophotometric measurement or TcB (Kaplan M, 2004; Ip S, 2004). TcB testing has become more popular than visual assessment because of the known limitations of visual identification of hyperbilirubinemia, especially in nonwhite babies.

The gold standard to assess hyperbilirubinemia in neonates remains the total serum bilirubin (TSB) measurement. It requires a blood sample from the patient and hence a needle prick, which is painful and when repeated can lead to anemia. Because blood collected from newborns is often hemolyzed, this could affect the accuracy of the clinical laboratory methods. Frequent measurement of TSB in babies with bilirubin concentrations below the treatment threshold is inappropriate because it requires unnecessary blood sampling. Furthermore, waiting for results may delay the discharge of both the mother and baby from the hospital.

Optical methods offer a non-subjective assessment compared to visual assessment by a clinician. Transcutaneous Bilirubinometry (TcB) measurement is a viable option in screening neonates to determine if they are at risk for clinically significant hyperbilirubinemia. Various methods have therefore been developed to aid non-invasive diagnosis of hyperbilirubinemia and approximation of TSB levels. They include cephalocaudal staging of jaundice and transcutaneous bilirubin (TcB) reference devices.

The objective of this study was to check the agreement between two different methods of measuring bilirubin - transcutaneous bilirubin using BiliChek (TcB) and Optical Imaging (ToB) using BiliCapture in neonates with or without phototherapy in order to determine whether ToB measurements would alter clinical practice.

MATERIALS AND METHODS

PATIENTS

The patient's samples were collected from the King Khaled University Hospital from Al-Majma'ah and Riyadh (Eastern Province) Saudi Arabia. Written information leaflets were given to parents of all noenates before including them in this study. Subsequently, written consent was obtained from those willing to participate. Both ethics and Research & Development committee's approvals were obtained before starting this study.

The exclusion criteria were as follows: 1) GA < 35 weeks, 2) BW < 2 kg, 3) major illness followed by NICU or hospital admission, and 4) discharge before 18 h after birth. GA was extracted from the medical records of mothers and the first-trimester ultrasound examinations. If the recorded data in the medical records were unreliable, GA was estimated by the Ballard Scale.

In this cross study, 50 healthy newborns were selected. Hyperbilirubinemia was defined as a serum bilirubin value of greater than 12.9 mg/dL. Immediately after delivery, about 5 cc

blood samples were obtained from the maternal side of the umbilical cord and transferred to the laboratory. The serum was separated within two hours of sample collection and refrigerated at 2-8°C until the serum bilirubin measurement was completed.

Total serum bilirubin (TSB) level was determined using Diazo method with dichloroaniline (DCA). Within 30 minutes of obtaining the blood sample and without prior knowledge of the serum value, both devices, BiliChek and BiliCapture were tested on each infant. Under existing controlled artificial light, bilirubin measurement was done first using the BiliChek on forehead and BiliCapture taking the conjunctival images.

Where a clinical decision was made to undertake TSB measurement, a simultaneous TcB measurement using BiliChek was also obtained. The decision to commence phototherapy was made by the clinicians based on the TSB result. The threshold used depends on gestational age [threshold = (Gestation x 10)- 100]; thus, for example the threshold for a 35-week gestation infant would be250 mmol/L. If the baby did not require phototherapy, he/she was monitoredclinically and any further decision to repeat TSB was made on clinical grounds by the medical and/or nursing staff. If, however, the baby required phototherapy, the TSB was repeated in 6–8 h (to ensure a downward trend and improvement in bilirubin levels) and then12–24 h, till a decision was made to stop phototherapy. TSB was repeated 8–12 h after stopping phototherapy to ensure that the bilirubin levels were still below the treatment level (and there was no significant rebound increase in its level). To assess precision, BiliChek TcB measurement was assessed 5x in succession in 10 infants.

TSB MEASUREMENT

Universal predischarge screening for TSB was performed on capillary blood samples; these samples were obtained by puncturing the newborn's heel. TSB measurements were performed, using UNISTAT Bilirubinometer (USA) and direct spectrophotometric assay with an accuracy (bias) of ±5%. All measurements were performed by the skilled personnel of the clinical chemistry laboratory of the hospital.

TcB MEASUREMENT

When samples for TSB measurement were collected, a contemporaneous TcB measurement was also carried out within 15–30 min by applying BiliChek (Respironics Inc.,Chichester, UK; http://www.respironics.co.uk/) to the infant's forehead with the infant lying supine. Disposable probe tips were calibrated as per the manufacturer's instructions before each TcB measurement. The tip was then applied with light pressure to the skin and the BiliChek device was automatically triggered for five consecutive spectral analyses, which are used to display a calculated averaged reading in either mmol/L or mg/dL.

Simultaneous multiple measurements were taken if the neonate required repeated TSB measurements, e.g. during/after phototherapy. The area of forehead used for TcB was not exposed to direct sunlight and/or phototherapy. If an infant required phototherapy, BilEclipse TM (phototherapy protective patch) was positioned over the measurement site prior to starting phototherapy. All phototherapy lights were turned off while a BiliChek measurement was taken. The BilEclipse protective patch was opened and after taking the BiliChek measurement, the flap was closed before recommencing phototherapy. Once phototherapy was discontinued, the BilEclipse flap was removed but subsequent BiliChek measurements were taken from the site on the forehead that had not been exposed to the phototherapy lights. Care was taken to avoid skin areas with bruising, birthmarks, haematomas or excessive hairiness. Gestation, birth weight, postnatal age and ethnicity were recorded.

STATISTICAL ANALYSIS

Excel (Microsoft Office Professional 2010) and SPSS (Version 18.0 for Windows) will be used for statistical calculations and graphs. Data are expressed as mean ± SD or median and its 25–75 interquartile interval for nonnormally distributed variables, or number and percentages. The agreement

between two methods was evaluated by linear regression (correlation coefficients) and Bland and Altman analysis, which determined bias, precision, and agreement of optical measurement and transcutaneous bilirubinmoetry, taking the automated analysis in the laboratory as the reference (Bland JM, 1986). All P values were two tailed, and a P value <0.05 was considered significant.

RESULTS

A total of 50 samples were obtained from 50 term or near-term infants (28 male and 22 female infants). All infants were with a mean gestational age of 39 weeks (range: 35–42 weeks). The mean birth weight was 3.3 kg (range: 2.16 – 4.35 kg), and the mean age at the time of blood sampling was 3 days (range: 0– 5 days). None of the infants had any medical conditions like sepsis, respiratory distress, or cardiac or circulatory disease.

The mean serum bilirubin concentration for all infants (n = 50) was 10.73±2.02 (SD) mg/dL; the range was 8.1 to 16.8 mg/dL. The mean bilirubin concentration obtained by transcutaneous bilirubinometer (TcB) of neonates (n = 50) using BiliChek was 11.68±2.72 (SD) mg/dL; the range was 8.3 to 17.4 mg/dL. The mean bilirubin concentration measured through optical imaging using BiliCapture was 13.1±2.34 and the range was 8.6 to 18.1 mg/dL.

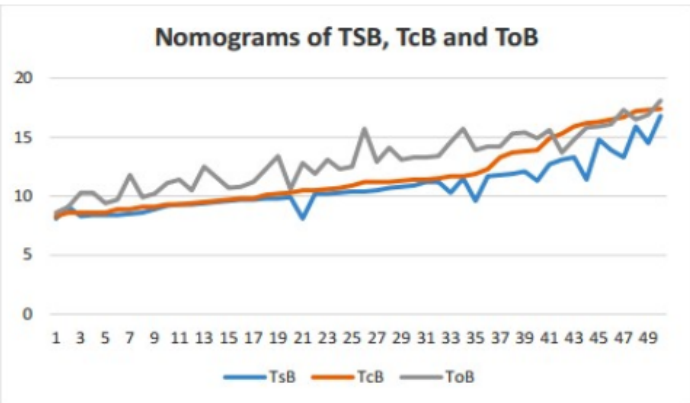

Figure 1: Distribution of total serum bilirubin, transcutaneous bilirubin and optical imaging bilirubin for the study population.

There was linear correlation between serum bilirubin and the transcutaneous bilirubinometer value, (y = 1.28 x – 1.92, r = 0.88, standard error of the estimate (sy.x) = 0.74). The specificity and sensitivity of the transcutaneous bilirubinometer was calculated using a value of more than 25 as a cutpoint. This cutpoint was determined by evaluating the data in accordance with guidelines given in the transcutaneous bilirubinometer manual. 5 This same cutpoint is also obtained by calculating that cutpoint which will give approximately 25 false-positive results for every one false-negative result given the prevalence of hyperbilirubinemia in this study. 6 The device classified hyperbilirubinemia with a sensitivity of 92% and a specificity of 75.6%. This represented one false-negative value and 20-false-postivie values. The predictive value of a positive test was 47%. The predictive value of a negative test was 99%.

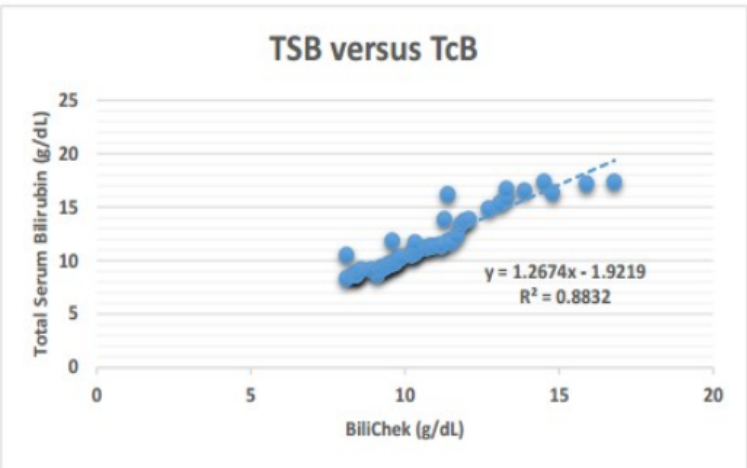

Figure 2: Representation of linear regression between neonatal serum and transcutaneous biliuribinometer (BiliChek) bilirubin concentrations. The correlation between them is found to follow a second order polynomial equation with an R^2 value of 0.88.

A linear relationship also existed between serum bilirubin and the bilirubin values obtained by optical imaging using BiliCapture y = 0.99x+2.42, r = 0.73, sy.x = 0.47. The mean and standard deviation bilirubin value for each serum bilirubin, BiliChek and BiliCapture are presented in Table 1. Using an BiliCapture value of more than 4 as a cutpoint, the device classified hyperbilirubinemia with a sensitivity of 88% and specificity of 76%. Four of Five false-negative results occurred in the first few measurements the remaining measurements with the BiliCapture produced a sensitivity of 95% and specificity of 81%. Predictive values of positive and negative tests were 41% and 94%, respectively (n = 100)

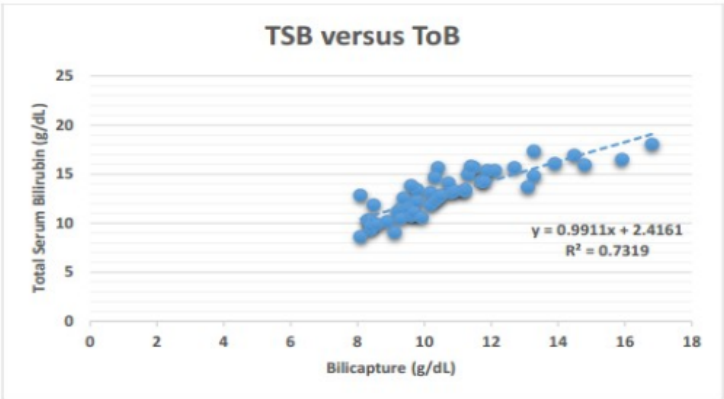

Figure 3: Comparison of neonatal serum and optical imaging (BiliCapture) bilirubin concentrations. The correlation between them is found to follow a second order polynomial equation with an R^2 value of 0.73.

Table 1 Correlation Analysis (R, P) and Bland and Altman Comparison for Evaluation of the Accuracy of bilirubin measurement by transcutaneous bilirubin using BiliChek (TcB) and Optical Imaging (ToB) using BiliCapture vs. Automated Laboratory Bilirubin Measurement (TSB)

-	Bilirubin measurement (g/dL)	Linear correlation		Bland and Altman Analysis			
		Correlation coefficient R	P value	Bias (g/dL)	Precision (g/dL)	Agreement limits (g/dL)	Outliers n (%)
TSB	10.73±2.02 (8.1; 16.8)	-	-	-	-	-	-
TcB	11.68±2.72 (8.3; 17.4)	0.94	<0.001	0.99±1.06	1.26±0.73*	[-1.09; 3.07]	31 (42%)*
ToB	13.1±2.34 (8.6; 18.1)	0.86	<0.001	2.32±1.21	0.91±0.56	[-0.05; 4.69]	16 (18%)

Data are mean ± SD [range] or number (percentage). Reference for comparisons is total serum bilirubin. (n =100bilirubin measurements). Outliers are defined as difference values with the reference method out of the interval ± 1 (g/dL)
* P < 0.05 vs. TcB

In order to find the statistical significance of the optical imaging device, BiliCapture for determination of the bilirubin level, correlation and regression analyses were used (Bland JM, 1994; Bland JM, 1995; Bland JM,1995). The Bland-Altman method was used for assessing the agreement between the conventional laboratory serum detection, transcutaneous bilirubinometer (BiliChek) and our optical imaging device, BiliCapture. Two crucial factors decide whether a new method can be used interchangeably with an already established method: the amount of agreement between the methods and its clinical evaluation. We compared our proposed noninvasive bilirubin detection method to an established biochemical method using the approach described by Bland and Altman (Bland JM, 1986; Bland JM, 2003) in order to assess the statistical agreement. Bland-Altman plots demonstrated good agreement with the comparison values for the two noninvasive instruments (Figure 4). Slopes of the regression lines were close to 1.0 for all methods tested. Details are given in Table 1.

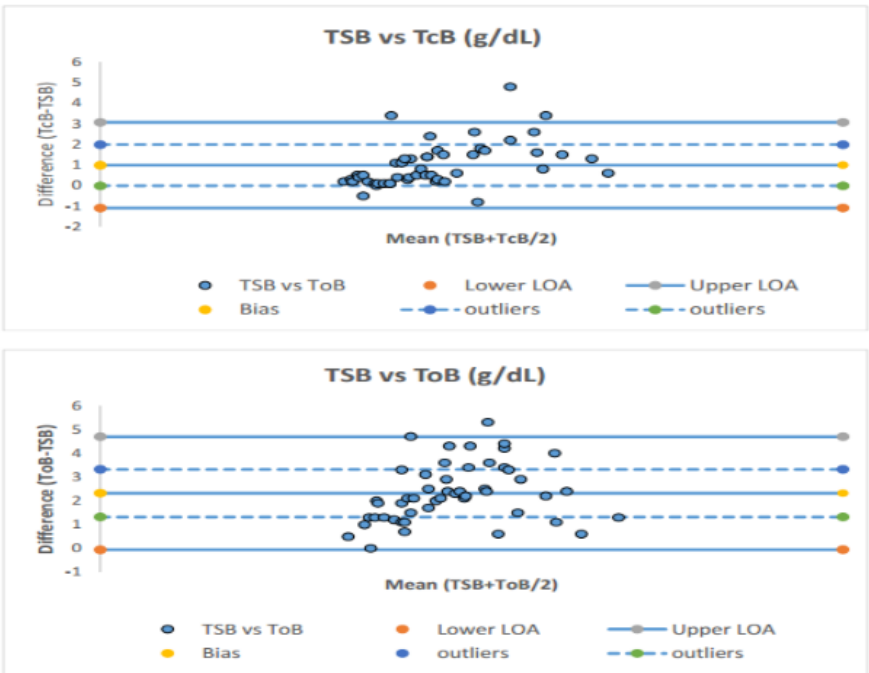

Figure 4: Bland and Altman representation of comparison analysis between (A) neonatal serum and transcutaneous biliuribinometer (BiliChek) bilirubin concentrations and (B) neonatal serum and optical imaging (BiliCapture) bilirubin concentrations.

Bias (dashed line), limits of agreement (bias±1.96*SD, continuous lines) and outlier limits (bias±1g/dL, dotted lines) are represented on the graphs (n = 50). The mean difference between the two methods is depicted as a horizontal line and is rated as bias. The other two horizontal lines (Mean±2SD) represent limits of agreement which explains that 95% of the differences were assumed to lie within these limits.

DISCUSSION

Non-invasive transcutaneous bilirubin measurements are potentially attractive modality because it is a quick, noninvasive technique to screen for hyperbilirubinemia (Maisels MJ, 2009). According to the 2004 American Academy of Pediatrics (AAP) practice guidelines, (American Academy of Pediatrics, 2004) transcutaneous bilirubin(TcB) was recommended as an alternative to total serum bilirubin(TSB) for screening jaundiced neonates1; and because transcutaneous bilirubinometry minimizes invasive blood sampling and allows for a tim eeffective and reasonably accurate estimation of bilirubin levels, the method has become particularly popular among health care professionals involved in neonatal care (American Academy of Pediatrics, 2004). There is a paucity of evidence based data on the use of transcutaneous bilirubin (TcB) measurements in preterm infants, especially when receiving phototherapy.

Transcutaneous bilirubinometry for noninvasive determination of skin bilirubin in neonates was first introduced in 1980 by using a bilirubinometer, developed by Minolta which used a two-filter design to measure “the yellow color of skin” (Yamanouchi I, 1980). Since then other commercial devices have become available, e.g. ColorMate TLc BiliTest System (Manufacturer specifications of Colormate) which requires an initial measurement shortly after birth, BiliChek (by SpectRx) (Jacques SL, 1997) which requires five replicate measurements at one site and is based on reflectance analysis at multiple wavelengths, and Jaundice Meter (by Minolta/Hill-Rom Air-Shields) which is based on two wavelength analysis.

In BiliChek, the use of multiple wavelength (400 to 760 nm) readings allows correction for

differences in skin pigmentation and hemoglobin, eliminating the need for a patient-specific baseline reading. A study done to compare BiliChek and Jaundice Meter JM-102 concluded that the variability of the BiliChek system is less than that of the Jaundice Meter, and that BiliChek system is not affected by skin color which means that a multi-wavelength analysis gives significantly better results for skin bilirubin estimation (Robertson A, 2002). Compared to HPLC, the BiliChek device was shown to be more accurate than clinical laboratory bilirubin measurements (Rubaltelli FF, 2001). Although BiliChek was recognized as a significant improvement over the older transcutaneous devices (Ip S, 2004), a clean, disposable tip is required for each measurement, substantially increasing the cost of the test.

Recently, Leite et al. (Leite M, 2007) found that TcB measurements using BiliChek gave the same information as a capillary plasma bilirubin if the TcB concentration was< 240 mmol/L (<14mg/dL). Above this concentration, they believed that the BiliChek device should be considered only as a screen and samples should be sent to a central laboratory for confirmation. Conversely, Boo and Ishak (Boo N, 2007) stated that BiliChek should not be considered a substitute for TSB, although they found that TcB was useful in the identification of infants with a TSB ≥300 mol/L (17.5mg/dL). These infants require additional bilirubin monitoring and frequently receive phototherapy. In the present study, we have demonstrated that the conjunctiva could be a targeted organ to diagnose jaundice independent of race, age, and sex by using a simple diffused reflection measurement technique. Based on the aforementioned principle, we have also developed a noninvasive, easy, expeditious, Reliable, and practical device for routine measurement of bilirubin levels.

Results from all 2 methods used in our study had extremely strong correlations with laboratory bilirubin level. Therefore, the mean of both transcutaneous bilirubinometer (BiliChek) and Optical imaging bilirubin (BiliCapture) was considered to be close to the "true" bilirubin concentration and served as a comparison value, because a true standard test for bilirubin determination has not been established. Only a proposed reference method has been published; it is neither used frequently nor accepted widely, because of its requirement for a manual procedure.

CONCLUSION

Statistical analysis revealed that our proposed method is in agreement with the TcB method. The practical application of these findings is that considering the high sensitivity of ToB compared to TcB, we can predict neonatal hyperbilirubinemia using a noninvasive method without spending much time and money. ToB is an ideal method for outpatient followup and aid the quick diagnosis of hyperbilirubinemia in order to prevent its consequent side effects.

CONFLICTS OF INTEREST

No conflicts of interest were declared by the authors.

ACKNOWLEDGEMENTS

The authors would like to thanks Basic and Health Science Research Center (BHSRC), Majmaah University, Majmaah, KSA for the financial support as wells as the routine supervision of entire research project.

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