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Comparison of diagnostic accuracy of transcutaneous bilirubin at different sites with serum total bilirubin measurement in preterm neonate

Abdullatif Mohammed Amneenah
Associate Professor and Head of Pediatrics Departments-Faculty of Medicine-University of Derna, Consultant Pediatrician, Head of Pediatrics Departments- Al Wahda Teaching Hospital (Derna), Libya
*Corresponding author email: aemnaina@gmail.com

Raga A. Elzahaf
Associate Professor Department of Public Health College of Medical Technology – Derna-Libya MENA Research Group -Libya

Fayiza Ibrahim Shahat
Lecturer at Faculty of medicine –University of Derna, Consultant Pediatrician at Al Wahda Teaching Hospital (Derna), Libya

***Abstract*---**Background: Transcutaneous bilirubin measurement (TcB) is widely used in term babies, but its effectiveness as well as the suitable site for (TcB) measurement in preterm babies still debated. Aim and Objective: To compare the diagnostic accuracy of different transcutaneous bilirubin sites with serum total bilirubin measurement in preterm neonate. Methods: This prospective comparative study was carried out in special care baby unit at Alwahda teaching hospital-Derna-Libya. (102) preterm infants (gestational age less than 37 weeks) in whom clinical jaundice was significant mandating TSB measurement were included in the study. Study subjects who met the inclusion criteria were chosen consecutively. All the measurements were carried out within first postnatal week. Transcutaneous bilirubin was measured from four sites: forehead, sternum, abdomen and interscapular region and within 30 min of TSB measurement. Results: Correlation coefficients of transcutaneous bilirubin measured from forehead, sternum, abdomen and interscapular sites were 0.69, 0.70, 0.67 and 0.69 respectively. TcB measured from all the four sites correlated significantly with serum bilirubin ($p < 0.001$), but the correlation was best at abdominal site. Conclusions: Transcutaneous bilirubin

measurement is an acceptable method for identification of hyperbilirubinemia requiring treatment in preterm newborns. We recommend abdominal region as a reliable site in infants of gestational age ≤34 wk for measuring transcutaneous bilirubin.

***Keywords*---**diagnostic accuracy, transcutaneous bilirubin, serum, preterm neonate.

Introduction

One of the most prevalent disorders requiring medical attention in newborn infants is jaundice. In the first week of life, around 60% of term babies and 80% of preterm babies develop jaundice. It is estimated that up to 10% of neonates have severe neonatal hyperbilirubinemia. Hyperbilirubinemia is usually a harmless condition, but high levels of serum bilirubin for an extended period of time can permanently damage the globus pallidus, subthalamic nuclei, hippocampus, and oculomotor nucleus, as well as other central nervous system structures, causing kernicterus in the infant (1). Preterm neonates are more likely than term neonates to develop bilirubin encephalopathy and kernicterus due to higher neonatal red cell, hepatic, and gastrointestinal immaturity. Premature infants may also have a poorer postnatal development of hepatic bilirubin absorption and conjugation. Furthermore, the delay in initiating enteral feedings, which is typical in the clinical management of ill premature babies, may decrease intestinal flow and bacterial colonization, resulting in increased bilirubin enterohepatic circulation. These developmental and clinical factors contribute to premature infants having a higher degree and duration of neonatal jaundice (2).

To avoid these consequences and to begin appropriate management, such as phototherapy or blood exchange, as soon as feasible, all sensitive infants with jaundice have their serum bilirubin levels tested. Serum bilirubin estimation is an invasive method that requires drawing blood and is also inconvenient due to technical difficulties in venous puncture, discomfort, pain, delay in results, and parental stress; therefore, it is critical to limit the number of draws and minimize the amount of blood the newborn loses due to blood draws (3). Transcutaneous bilirubinometry (TcB) was initially developed as an alternative to invasive blood sample. Earlier investigations found a high association between TcB measurements obtained from the forehead and sternum as the most prevalent sites in term and late preterm newborns. If these results correlate well with serum bilirubin readings, the use of point-of-care TcB monitoring in early preterm infants may improve early diagnosis of hyperbilirubinemia in this vulnerable population. The interscapular location was also included in this study since unconjugated bilirubin is lipophilic and the interscapular region is one of the early sites for fat accumulation in the fetus (4).

Aim and Objective

To compare the diagnostic accuracy of different transcutaneous bilirubin sites with serum total bilirubin measurement in preterm neonate.

Patients and Methods

A prospective comparative study that was carried out on 102 patients admitted special care baby unit at Al-wahda teaching hospital-Derna-Libya. Ethical clearance was obtained from institutional ethics committee before undertaking the study. Preterm neonates of less than 37 weeks gestational age, neonates whose phototherapy hadn't started yet with good perfusion (Capillary refill < 3 seconds) were included in the study. Study subjects who met the inclusion criteria were chosen consecutively. Neonates in whom phototherapy was already initiated and those with poor perfusion (capillary refill time > 3 s) were excluded from the study. This study base on study carried out by Agrawal et al., 2019 (5). Epi Info STATCALC was used to calculate the sample size by considering the following assumptions: - 95% two-sided confidence level, with a power of 80% & an error of 5% odds ratio calculated = 1.115. The final maximum sample size taken from the Epi- Info output was 102.

The parents provided informed consent. All measurements were taken during the first postnatal week. The gestational age of the newborns was established using either the Ballard score or prenatal USG. Transcutaneous bilirubin was measured using a bilirubinometer at three different locations: the forehead (TcBF), the sternum (TcBS), the abdomen (TcBA), and the interscapular (TcBI). For evaluation, an average of three consecutive readings from these sites were taken. Within 30 minutes of measuring TcB, 0.5 ml of blood was obtained through a peripheral vein using aseptic procedure and immediately delivered to the laboratory. The diazo technique was used to determine the total serum bilirubin level. Gender, gestational age, weight, and age at bilirubin measurement (in hours) were all recorded, and the mean, median, and standard deviation were computed.

Statistical analysis

The data were entered and analyzed using the Statistical Package for Social Science 25.0 (SPSS 21.0, Inc., Chicago, IL) and R packages for all statistical analyses. Descriptive statistics were obtained and means, standard deviation, and frequency distribution were calculated. Pearson's correlation was used to compare the measurement of Transcutaneous Bilirubin (in the forehead and sternum) with TSB. A linear scatter plot was also calculated to determine the correlation curve trend. In practice studies, using the Pearson coefficients alone can be a poor indicator of the agreement between any two diagnostic tests, so other technique called a Bland-Altman can be also used to assess (TcBF, TcBS, TcBA,TcBI) and TSB variability. In this analysis, the difference between each (TcBF, TcBS, TcBA,TcBI) and TSB was plotted against the average of each (TcBF, TcBS, TcBA,TcBI) and TSB, and displayed with 95% confidence limits in order to compare the variability across a range of bilirubin results. In other words, the mean difference is expressed as mean SD, while the limit of agreement is calculated based on the mean 1.96. In statistical analysis, when there are two sets of data have the same units of measurements, the variance and standard deviation for each can be easily compared. But, to compare standard deviations of data when their units are different there is other measure called the coefficient of variation is used to compare the data. The coefficient of variation (CV) is defined

as the ratio of the standard deviation to the mean. The higher the coefficient of variation the greater the dispersion.

Results

One hundred and two preterm infants (gestational age < 37 wks) with clinical jaundice were included in the present study. Fifty-four preterm neonate (52.9%) were male, with a mean weight of 2120.59± 609.19 kg, mean age at measurement (hours) 90.36± 62.86 hours and mean gestational age of 33.75±2.23 weeks. Of the total number of newborns, 23 (22.5%) showed an adequate birth weight. Their demographic characteristics are summarized in Table 1.

Table 1
Patients characteristics

Characteristic	Mean ± SD
Gender	
Male	48 (52.9%)
Female	54 (52.9%)
Gestational Age (Weeks)	33.75±2.23
Birth Weight (Grams)	2120.59±609.19
Age at Measurement (Hours)	90.36±62.86

The mean Total Serum Bilirubin in the preterm neonate patients was 8.27±2.76 ranged from 1.90 mg/dL to 13.50 mg/dL and median was 8.25 mg/dL. The mean Transcutaneous Bilirubin in the Forehead (TcBF) was 8.84±3.48 ranged from 1.5 mg/dL to 17.8 mg/dL and median was 8.3 mg/dL, the mean Transcutaneous Bilirubin in the Sternum (TcBS) was 9.11±3.39 ranged from 0.6 mg/dL to 18.0 mg/dL and median was 9.25mg/dL, the mean Transcutaneous Bilirubin in the abdomen (TcBA) was 7.65±3.11 ranged from 0.7 mg/dL to 14.6 mg/dL and median was 8.0 mg/dL and the mean Transcutaneous Bilirubin in the interscapular (TcBI) was 7.72±2.88 ranged from 0.5 mg/dL to 15.6 mg/dL and median was 7.5 mg/dL as summarized in Table 2.

Table 2
Bilirubin measurements

Characteristic	Mean	Median	SD	Minimum	Maximum
Total Serum Bilirubin (TSB)	8.27	8.26	2.76	1.9	13.50
Transcutaneous Bilirubin in the forehead (TcBF)	8.84	8.3	3.48	1.5	17.8
Transcutaneous Bilirubin in the Sternum (TcBS)	9.11	9.25	3.39	0.8	18
Transcutaneous Bilirubin in the abdomen (TcBA)	7.65	8.00	3.11	0.7	14.6
Transcutaneous Bilirubin in the interscapular (TcBI)	7.72	7.5	2.89	0.5	15.6

Pearson's correlation between Total Serum Bilirubin (TSB) versus Transcutaneous Bilirubin in the Forehead (TcBF) was 0.687(P=0.001). Total Serum Bilirubin (TSB) versus Transcutaneous Bilirubin in the Sternum (TcBS) was 0.704(P=0.001). Total Serum Bilirubin (TSB) versus Transcutaneous Bilirubin at abdomen (TcBA) was 0.670 (P=0.001). Total Serum Bilirubin (TSB) versus Transcutaneous Bilirubin at interscapular (TcBI) was 0.690 (P=0.001). Transcutaneous bilirubin measured from all the four sites correlated significantly with serum bilirubin ($p < 0.001$), but the correlation was best at the sternum site as summarized in Table (3).

Table 3
Correlation between serum bilirubin and different bilirubin measurements

	Pearson's Correlation	P-Value
TSB - TcBF	0.687	P=0.001
TSB – TcBS	0.704	P=0.001
TSB – TcBA	0.670	P=0.001
TSB – TcBI	0.690	P=0.001

The mean difference between TSB and (TcBF, TcBS,TcBA,TcBI) and their CI 95% for particular measurements sites are shown in Table (4). The mean deviation and variability ± 1.96 SD between (TcBF,TcBA and TcBI) and TSB values were + 0.56 ± 2.56, 0.62 ± 2.41 and 0.57 ± 2.23, respectively. While the mean difference between the TcBS values and Total Serum Bilirubin was − 0.83 ± 2.44. Thus, the Bland-Altman plot showed a greater degree of underestimation (negative mean bias) of the TSB level by the TcBS than by the others (TcBF, TcBA and TcBI). In addition, the Bland Altman of the agreement between TcBI and TSB measurement shows that only (9/102) 8.82% of the points lie outside the limits of agreement as summarized in table (4).

Table 4
Bland Altman of the agreement between serum bilirubin and other bilirubin measurements

Difference	Mean	SD	95% (mean ±1.96 SD)	P-Value
TSB - TcBF	0.56	2.56	(- 4.44841,5.574488)	P=0.028
TSB – TcBS	- 0.83	2.44	(- 5.60954,3.944249)	P=0.001
TSB – TcBA	0.62	2.41	(- 4.09741,5.341918)	P=0.010
TSB – TcBI	0.57	2.23	(- 3.80633,4.919468)	P=0.013

Likewise, in the present study, we also attempted to find out whether the correlation between TSB versus transcutaneous bilirubin measured using TcBF, TcBS, TcBA and TcBI is affected by birth weight. For this, when we divided neonates into two groups based on birth weight ≤ 2500 g and birth weight > 2500 g and coefficient correlations of TSB and all four sits were calculated, significant correlation was found from all four sites in both groups ($p < 0.001$). It is clear that, correlation of TSB obtained from forehead TcBF and sternum TcBS were better in > 2500 g birth weight group as compared to ≤ 2500 g birth weight group. At abdomen TcBA and interscapular sites TcBI, however, correlation was better in ≤

2500 g birth weight group. At forehead site TcBF, correlation was highest and better in birth weight > 2500 g (0.751 vs 0.689) compared to the other sites and in the interscapular site TcBI, correlation was highest compared to the other sites and better in birth weight ≤ 2500 g (0.714 vs 0.641) as summarized in table (5).

Table 5
Birth weight and gestational age affection on measured bilirubin

Characteristic	n(%)	TcBF	TcBS	TcBA	TcBI
Gestational age (GA Weeks):					
$GA \leq 34$	48 (47.1)	0.707 (p=0.000)	0.696 (p=0.000)	0.706 (p=0.000)	0.713 (p=0.000)
$GA > 34$	54 (52.9)	0.680 (p=0.000)	0.729 (p=0.000)	0.631 (p=0.000)	0.670 (p=0.000)
Weight (WT)					
$WT \leq 2500$	84 (82.4)	0.689 (p=0.000)	0.708 (p=0.000)	0.687 (p=0.000)	0.714 (p=0.000)
$WT > 2500$	18 (17.6)	0.752 (p=0.000)	0.714 (p=0.001)	0.623 (p=0.006)	0.641 (p=0.004)

ROC curve was generated (Fig. 1) and area under the curve was calculated. Area under the curve for TcBF, TcBS, TcBA and TcBl were 7.95, 8.2, 4.45 and 6.05 respectively with sensitivity of 92.9%, 92.9%, 93% and 93% and specificity of 69%, 74.7%, 82% and 64% respectively.

Table 6
Cut off value of each site and sensitivity and specificity

	Cut off value	Area under curve	Asymptotic 95% Confidence Interval		Sensitivity	Specificity	P. Value
			Lower Bound	Upper Bound			
TcBF	7.95	.847	0.760	0.935	92.9%	69%	< 0.001
TcBS	8.2	.868	0.777	0.959	92.9%	74.7%	< 0.001
TcBA	4.45	.832	0.716	0.949	93%	82%	< 0.001
TcBl	6.05	.835	0.735	0.934	93%	64%	< 0.001

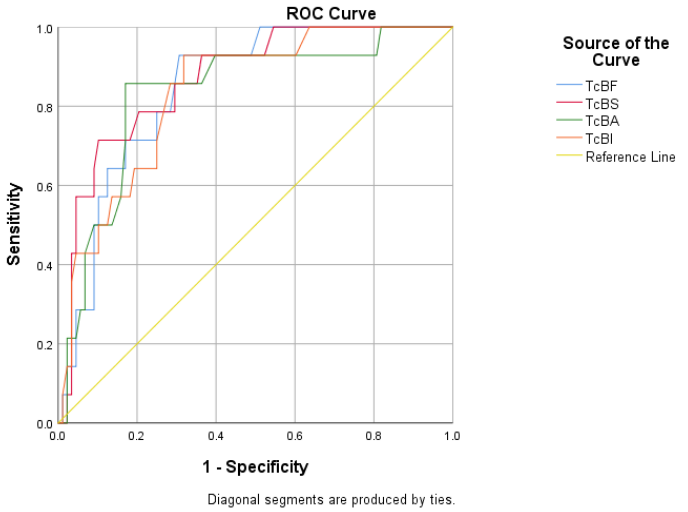

Figure 1. Roc curve. TcBF: transcutaneous bilirubin forehead, TcBS: transcutaneous bilirubin sternal, TcBA : transcutaneous bilirubin abdominal, TcBI : transcutaneous bilirubin interscapular

Discussion

Early diagnosis and management of neonatal jaundice in preterm infants is a challenge for physicians because of its potential to cause permanent encephalopathy. Immediate, accurate and painless evaluation of neonatal jaundice is highly desirable. Transcutaneous bilirubin measurement is a potentially useful method to achieve this goal. The results of present study demonstrated a statistically significant correlation between the TcB values and TSB levels. The correlation coefficient of forehead TcB of 0.687 ($p = 0.001$) found in index study was higher than that described by other studies (Sajjadian et al. (6): 0.56) but was lower as compared to findings of (Knüpfer et al. (7): 0.73; De Luca et al. (8): 0.79; Yaser et al. (9): 0.90). The discrepancy in correlation of forehead and total serum bilirubin found in different studies may be due to the fact that the forehead is continuously exposed to ambient light and has excessive hair; hence results vary from infant to infant.

Measuring TcB over sternum seems to be also suitable for hyperbilirubinemia screening. The correlation coefficient of sternum TcB of 0.704 ($p = 0.001$) in present study was comparable to findings of study by Schmidt et al. (10) (0.79). The correlation coefficient of interscapular TcB was 0.690 ($p < 0.001$). Previously, only one study by Yaser et al. (9) has evaluated this site for preterm neonates. The correlation between TSB and TcB obtained from interscapular site in their study was different from the present study ($r = 0.86$). The correlation coefficient of Abdomen TcB of 0.670 ($p = 0.001$) found in our study was lower than that described by other studies De Luca et al. (8): 0.79; and Sajjadian et al. (6): 0.56. In our study, we attempted to find out whether the correlation between TcB and TSB is affected by birth weight. For this, when they divided patients into two groups based on birth weight ≤ 2500 g and > 2500 g and correlation of TcB and TSB was calculated, significant correlation was found from all four sites ($p <$

0.05). Also, correlation of TcB obtained from forehead was better in >2500 g birth weight group as compared to ≤ 2500g birth weight group. At Sternum site, correlation was almost similar in both groups, at abdominal site, correlation was better in in birth weight of > 2500 and in interpleural site, correlation was better in birth weight of < 2500. Karolyi et al. (11) studied correlation of TcB from sternum and TSB among neonates with birthweight < 2500 g and they found this correlation to be 0.68 ($p < 0.001$). Kurokawa et al. (12) assessed the accuracy of transcutaneous bilirubin (TcB) measurements at 5 different body sites in Japanese very low birthweight (VLBW) infants and they found that TcB significantly correlated with TSB, but they did not compare it with neonates more than 2500 g. Badiee et al. (13) found that the TSB – TcB correlation coefficient increased with increasing gestational age and birth weight, which is in contrast to our study as correlation was higher in cases with GA of < 34.

The sensitivity of forehead transcutaneous bilirubin in identifying study participants in need of phototherapy in present study was 79.2% which is lesser than Knüpfer et al. (7) who found a sensitivity of 86.8% but similar to Yaser et al. (9), who found a sensitivity of 80.3%. Yaser et al. (9), looked at sensitivity of the sternum transcutaneous bilirubin in determining need to initiate phototherapy and found this value to be 69.7%. In the present study, we found sensitivity at sternum of (92.9%). In the present study, the abdominal TcB had a sensitivity of 93% with the highest specificity of 82%. As compared to findings of Yaser et al. (9), who obtained 93.9% sensitivity at this site, the present values were lower, though comparable. The difference might be because of ethnic and racial variation.

Conclusion

This study reveals the validity of transcutaneous bilirubin (using four sites: forehead TcBF, sternum TcBS, abdomen TcBA and interscapular TcBI sites) as a screening tool for neonatal jaundice in preterm neonates, as it demonstrated a significantly and strong correlation and predictive accuracy in preterm neonates between TSB and TcBF, TcBS, TcBA and TcBI levels. Transcutaneous bilirubinometry in neonates (gestational age less than or equal 34 weeks) is large accurate using TcBA than in neonates with age greater than 34 weeks. In addition, when the weight of neonates was greater than 2500 g high correlation between TSB and TcBF, TcBS, TcBA and TcBI levels. This study also shows that, TcBA is the most sensitive parameter.

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