Transcutaneous Bilirubin Measurement in Preterm Neonates

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Abstract- Hyperbilirubinemia is a common problem during neonatal period especially in preterm neonates. Transcutaneous bilirubin measurement (TcB) by special devices had been documented as an effective tool for predicting neonatal jaundice in full term neonate, but for preterm infants the present evidences are controversial. We carried out a prospective study in Shariati Hospital NICU. 126 paired TcB/total serum bilirubin (TSB) measurements were obtained. TcB (on forehead and sternum) were measured using JH2-1A device for every admitted preterm infant who clinically showed jaundice and TSB measurements was obtained within 30 min of TcB. 58 (46%) were male and 68 (54%) were female. The mean gestational age was 31 week and mean birth weight was 1728 ± 60 g. 30 percent of neonates were ill. The mean value obtained by TBS was 8.8 mg/dl and for frontal TcB was 8.2mg/dl and for sternal TcB was 7.4mg/dl. There were good correlation between TBS and TcB and the maximum correlation were seen in 33-37 weeks of gestation and birth weight more than 2500 g with forehead TcB measurement. Healthy preterm infants had significant correlation of TSB and TcB (r=0.56, $P<0.001$) and ill preterm neonate had r =0.82, $P<0.001$. The correlation between TBS and TcB with and without phototherapy was r=0.66, $P=0.000$ and r=0.69, $P=0.000$ respectively. Although TcB measurement may underestimate TBS but there is significant correlation between TcB and TBS in preterm cases even in ill neonate or who receiving phototherapy. This method can be used for determination of bilirbin level in preterm neonate and reduces the number of blood sampling.

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Introduction

Neonatal jaundice is one of the most common symptoms appeared in neonatal period. Hyperbilirubinemia in preterm is more sever and more persistent. Jaundice is potentially more problematic in preterm neonates and these neonates have risk factors that predispose to neurotoxicity at lower bilirubin levels.

Visual inspection is the most commonly used means of detection of hyperbilirubinemia but total serum bilirubin level assessment in clinical laboratory is an objective and expensive method with significant interlaboratory and intralaboratory variability (9).

Although blood may be sampled routinely from ill preterm neonates, it is associated with risk of local infection and is a painful process. An accurate and precise noninvasive method of monitoring of jaundice in such neonates would be desirable if easily carried out between blood sampling times. In addition, some preterm neonates are relatively stable, and blood sampling may occur less frequently in this group.

Transcutaneous bilirubinometry is a method using reflectance photometry or transcutaneous colorimetry is a noninvasive and immediate estimate of total serum bilirubin (TSB) levels and is cost effective that reduce the number of invasive blood sampling (9). The use of point-of-care transcutaneous bilirubin (TcB) monitoring in preterm neonates might enhance early detection of hyperbilirubinemia in this vulnerable population. Transcutaneous bilirubinometry has been shown to correlate with TSB, and evidence indicates that TcB can be used as a reliable alternative to direct measurement of TSB. Furthermore, the use of TcB values is more convenient and is less invasive than determination of TSB (14). The majority of earlier studies have examined the use of TcB in term and near-term neonates

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(2,6,11,15,18,23) whereas studies that have been carried out in preterm neonates have yielded varying results (1,3-5,10,12,13,16,21,22).

Yasuda *et al.* reported that the correlation between TcB and TSB was similar in both preterm and term neonates (24). However, Namba and Kitajima reported that accuracy and reliability of TcB versus TSB were diminished in neonates with birth weights <1000 g or gestational ages <28 weeks, compared with results in larger, more mature preterm neonates (16).

A number of studies have shown that these instruments provide fairly accurate estimates of TSB in term and near term newborn infants although additional studies are warranted to establish a strong and reliable correlation between TcB and TSB in preterm and during phototherapy usage and in sick neonates so we did study to evaluate the accuracy of TcB versus TSB in preterm neonate and assess the correlation of them in different situation (health state, during phototherapy treatment) and ability of this technique for prediction of Phototherapy need.

Material and Methods

This cross sectional study was carried out from January to July 2009, in Shariati Hospital NICU (Tehran, Iran). All preterm neonates who their jaundice was visually observed were entered the study consecutively. Gestational age was assessed from maternal expected date of confinement and by Ballard scores. The study population included of healthy and ill neonate and who had exchange transfusion and more than 2 weeks of age were excluded.

TcB using JH 20-1A (NINGBO David medical Device co LTD china) was performed by the trained investigators on the forehead and sternum of infants within an hour of blood sampling from peripheral vein for TSB measurements. At the start of phototherapy we covered the forehead and a small area over sternum to prevent the effect of phototherapy on these measurement sites. The device was calibrated before usage and was used according to the manufacturer's recommendations, and daily quality control measures were performed.

Average of three consecutive reading over each measurement sites multiply in 0.7 was recorded in mg/dl. TSB levels were measured in our hospitals clinical chemistry using the method of Diazo. Repeated TcB-TBS was done as clinically indicated. Normality of distribution was checked as needed. Pearson's Correlation analysis was performed to assess correlation coefficient (r) between TcB and TSB, and graphically presented using linear regression model.

In order to assess the accuracy of noninvasive bilirubin concentration measurement, difference (Δ) between TSB and TcB and their 95% confidence intervals (CI 95%) were evaluated. Receiver operating characteristics (ROC) curve analysis were used to find the cut-off points of TcB levels that called for blood sampling of TSB were chosen to be those of TSB levels that required phototherapy (9). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of each cut off level of TcB were calculated. *P*-value of less the 0.05 was considered to be statistically significant.

The ethic committee of Tehran University of Medical Sciences has approved the project in accordance with the tenets of the Helsinki declaration and the national ethical guideline for medical research.

Results

From a total of 64 infants (35 female and 29 male), 126 TcB -TSB paired simples were obtained. Their clinical and demographic characteristics are shown in table 1.

A significant correlation between TcB (Forehead or Sternum) and TSB was found. (r=0.66 and r=0.63 respectively; $P<0.001$) (Figures 1 and 2). The maximum correlation coefficients for TSB and TcB (F or S) measurement were seen for neonate with birth weight over than 2500 g (r=0.83 and r=0.81 $P<0.001$), for gestational age 33-37 (r=0.64 and r=0.57, $P<0.001$) and post natal age of 3-4 day old (r=0.71 and r=0.70, $P<0.001$). The neonates with gestational age 25-28 weeks had no significant correlation of TSB versus TcB measured over forehead (r=0.34, $P=0.415$) but this correlation was significant over sternum (r=0.80, $P=0.018$) for this age groups. The ill neonates also had significant correlation of TSB and TcB (F or S) (r=0.82 and r=0.73, $P<0.001$) and healthy one (r=0.56 and r=0.57, $P<0.001$).There were significant correlation coefficients of TSB versus TcB (F or S) for patients under phototherapy (r=0.67 and r=0.69, $P<0.001$) and in neonates without phototherapy(r=0.69 and r=0.64, $P<0.001$).

Using partial correlation analysis, controlling for gestational age, birth weight and postnatal age, correlation coefficient was same. The mean difference (Δ) between TSB and TcB and their CI 95% for particular measurements sites are shown in table 2.

Transcutaneous bilirubin measurements over sternum and forehead showed significant difference and TcB over these sites had tendency to underestimate

Table 1. Demographic characteristics of the studied patients.

Characteristics	N	Means ± SD
Male	29	
Female	35	
Paired sample	126	
Birth weight (gram)	730-3550 g	1728±676 g
Gestational age (weeks)	25-37	31.1±2.7
Age at the time of measurement (days)	1-14	4.53±4.00
TcB(frontal) (mg/dl)	4.6-13.3	8.22±1.70
TcB (sternum) (mg/dl)	2-14.6	7.42±1.91
TSB (mg/dl)	1.5-19.7	8.86±3.18
Healthy/ill	88/38	
Phototherapy Yes/No	85/41	

Table 2. The mean difference (Δ) between TSB and TcB and their 95% confidence interval for particular measurements sites.

Difference	Mean (SD)	95%CI	*P* value
TSB–TcB forehead	0.64 (2.4)	0.21-1.06	0.004
TSB-TcB sternum	1.44 (2.5)	1.01-1.88	<0.001

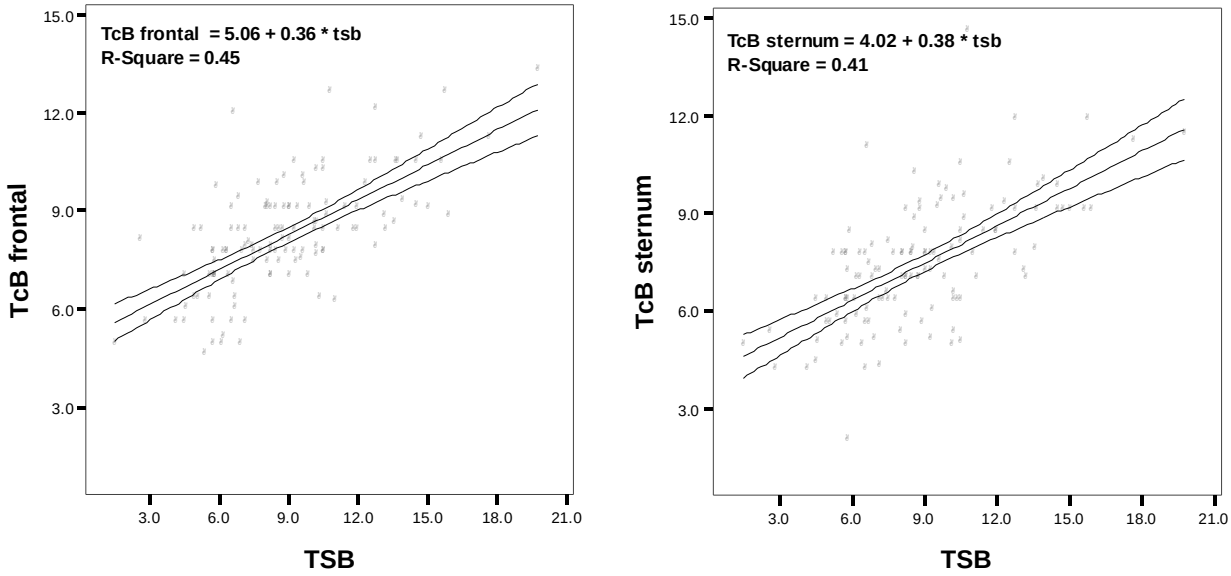

Figure 1. Linear regression scatter plot of TSB versus TcB (forehead and sternum).

serum bilirubin level significantly (P<0.05) and TcB over sternum underestimate TSB more than over forehead.

The cutoff points of TcB value was determined to match each threshold of birth weight based TSB which required phototherapy according to text. Sensitivity, specificity, and accuracy of the chosen cut off TcB are shown in table 3. Due to small sample size of extremely low birth weight (ELBW) neonate (only 6 neonates who 5 of them had TSB more than 5 mg/dl), we could not able to establish an accurate cut off points for starting phototherapy.

Sensitivity and specificity and accuracy of TcB to predict specific TSB level for initiation of phototherapy

Table 3. Sensitivity, specificity, and accuracy of the chosen cut off TcB forehead.

Value level		Sensitivity (%)	Specificity (%)	Accuracy (%)	B. S. *reduction (%)
TSB≥6:					
	TcB≥5.7	38/38 (100)	6/16 (37.5)	44/54 (81.5)	6/54 (11)
	TcB≥6.4	36/38 (95)	7/16 (44)	43/54 (80)	9/54 (17)
TSB≥8:					
	TcB≥5.7	17/17 (100)	4/24 (17)	21/41 (51)	4/41 (10)
	TcB≥6.4	16/17 (94)	6/24 (25)	22/41 (54)	7/41 (17)
TSB≥10:					
	TcB≥10	1/1 (100)	6/7(86)	7/8 (87.5)	6/8 (75)
TSB≥12:					
	TcB≥9	5/5 (100)	7/12(58)	12/17 (71)	7/17 (41)
	TcB≥9.7	4/5 (80)	10/12(83)	14/17 (82)	11/17 (65)

*blood sampling

and percent of decrease of blood sampling are shown in table 3.

Discussion

Hyperbilirubinemia is a common problem during neonatal period especially for preterm neonate. Transcutaneous bilirubin measurement by special devices had been documented as an effective tool for predicting neonatal jaundice in full term neonate. For preterm infant the present evidences are controversial.

Several previous studies were done with various results and correlation coefficients ranged from 0.68 to 0.96 (10,20). In Schmit *et al*. study correlations between TcB and TSB ranged from 0.79 to 0.92 (20). Most of the differences between TcB and TSB were ± mg per 100 ml, and there was no trend for the difference to increase with increasing bilirubin values. Sensitivity, specificity and negative predictive values ranged from 0.67 to 1.0, 0.29 to 0.81 and 0.60 to 1.0, respectively (20). They mentioned that TcB correlates significantly with TSB in preterm neonates. Routine measurement of TcB in preterm neonates may provide enhanced clinical monitoring for hyperbilirubinemia (20).

In present study overall correlation coefficient between TcB and TSB were significant (r forehead= 0.66, r sternum=0.63) with some variation in subgroups according to birth weight, gestational age, time of measurement, status of health and phototherapy state. Neonates with birth weight of more than 2500 gram had the highest correlation (r=0.83) that is comparable to Schmit *et al*. study (20) and Stillova *et al.* study (21) which was conducted to evaluate the accuracy of transcutaneous bilirubinometry in preterm newborns less than 32 weeks of gestation (r forehead=0.85, r sternum=0.81, r abdomen=0.73). 32 jaundiced infants of less than 32 weeks of gestation without phototherapy, including 10 ELBW neonates, were enrolled. Close correlation (R=0.933) existed between total serum bilirubin and transcutaneous bilirubin values measured over sternum (21).

Measuring TcB over sternum seems to be also suitable for hyperbilirubinemia screening although it underestimate TSB more than TcB measurement over forehead. For neonates under 28 weeks of age, TcB over sternum had better correlation than TcB over forehead. It may be due to excessive hair on forehead of this premature group that makes measurement on sternum to be become more reliable.

It seems that correlation coefficient in our population is lower than other mentioned studies. This may be due to different character of population because we included the sick and healthy neonate and also considered the patients who receive phototherapy in our study. Various sensitivity and accuracy of devices and different methods of TSB measurement may explain these differences between studies but like other mentioned study the correlations were significant.

Variable like birth weight, gestational age, and post natal age and other mentioned variable did not show any effect on correlation of TSB versus TcB which is similar to Donzelli and Pratesi study (4). Sanpavat and Nuchprayoon showed that variable like gestational age, and birth weight had no effect on correlation except post -natal age. TcB-TSB measurements coefficient between TcB and TSB was significant (r=0.79, P<0.0001). TcB had a tendency to overestimate TSB with the mean difference of TSB-TcB=-0.3±1.5 mg/dl and 95%

confidence interval of the mean -0.1 to -0.5 mg/dl. Of all the variables of birth weight, gestational age, and postnatal age, only postnatal age significantly influenced the correlation of TcB-TSB. In the early postnatal age of 1-4 days, the number of TcB reading overestimated TSB more than underestimated. However, at > or =5 days of age, the number of underestimation was more than those of overestimation (19). TcB had a tendency to overestimate TSB with the mean difference of TSB-TcB =0.64±2.4 mg/dl and 95% confidence interval of the mean 0.21-1.06 mg/dl for forehead measurement and mean difference of TSB- TcB=1.44±2.5 mg/dl and 95% confidence interval of the mean 1.01-1.88 mg/dl for sternal measurement this show that measurement over sternum underestimate TSB more than over forehead.

Noninvasive TcB assessment demonstrated significant accuracy when compared to TSB. TcB can be adopted as a screening test to identify the need for blood sampling of serum bilirubin in premature infants

Donzelli and Pratesi mentioned that post natal age had no significant influence on correlation coefficient of TSB and TcB. The mean difference in bilirubin concentrations measured with HPLC and the BiliCheck device was identical (-3.4 μM) in both groups. He found no significant effect of postnatal age on BiliCheck accuracy (r=0.16; t-test for non-zero slope, t=1.53; *P*>0.05) (4). We showed that TcB measurement can be used for sick neonates reliably. In Ghafari and Vahid Shahi study the correlation of TSB and TcB were also significant in ill patients (7).

Neonates who are receiving phototherapy had significant correlation because the tested areas were covered by opaque patch. This may significantly reduce the number of blood sampling in agreement to Nanjundaswamy *et al*. study (17).

Jangaard *et al*. studied the effect of phototherapy on TcB correlation. Transcutaneous bilirubin measurements obtained with the BiliCheck instrument were accurate for measuring bilirubin levels in term jaundiced infants not receiving phototherapy and in those receiving phototherapy if an area of skin was patched (8).

According to presented results, the measurements of TcB had a tendency to underestimate TSB level and there is trend for the difference to increase with increasing billirubin values. We had higher sensitivity in lower TcB level and higher specifity in higher level which is in agreement with the study of Sanpavat *et al.* (19). For neonatal hyperbilirubinemia, a screening procedure should have a high sensitivity and low rate of false negative observation so that few neonates with cut off level are missed by the procedure even if few cases are falsely picked up. So if the sensitivity of test is not 100%, it is likely to miss some false negative cases, but due to selection of low level of TSB for initiation of phototherapy in our study, it is not dangerous for our neonates to underestimate TSB level at lower level of serum bilirbin.

Our results indicate that this technique has potential to reduce blood sampling and therefore painful procedure and so we can obtain frequent and early assessment of TcB and an earlier TSB level for starting treatment with phototherapy and in neonate with birth weight over 1500 g, the TcB can decrease at least 40% of blood sampling for monitoring of TSB.

Measuring TcB over sternum seems to be also suitable for hyperbilirubinemia screening although it underestimate TSB more than TcB measurement on forehead. There is higher sensitivity in lower TcB level and higher specificity in higher level. It seems that TcB measurement can be used for sick neonates and in whom receiving phototherapy.

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