

## Relationship between Transcutaneous and Serum Bilirubin in Preterm and Term Neonates before and during Phototherapy

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### Abstract

#### Background

Neonatal jaundice is a common condition. Total serum bilirubin (TSB) measuring is standard for bilirubin testing, while transcutaneous bilirubin (TcB) is an alternative method. We aimed to evaluate the correlation between TSB and TcB in term and preterm neonates.

#### Materials and Methods

This prospective cross-sectional study was conducted to on 93 term and preterm neonates in Fatemeh Hospital in 2018, Hamadan, Iran. The samples were categorized into two groups, including term and preterm icteric neonates. Neonates were evaluated to determine the necessity of bilirubin estimation with TSB measurement. After the confirmation of jaundice, the blood samples obtained were sent to the laboratory for bilirubin estimation, and at the same time, the TcB measurement was performed by the bilirubinometer. Selectra X-L was utilized by which the blood samples were analyzed through the dichloroanilin method. The Pearson correlation coefficient was used to evaluate the relationship and stringency of the correlation between the approaches.

#### Results

In general, 61% and 38% of neonates were boys and girls, respectively. Before phototherapy, the TSB values were lower than TcB estimations in term and preterm neonates. The estimated Pearson correlation coefficients were obtained at  $r=0.729$  ( $P<0.001$ ), and  $r=0.802$  ( $P<0.001$ ) in term and preterm neonates, respectively. After phototherapy, contrary to the obtained results before phototherapy, the TSB concentration was higher than TcB concentrations. The difference between the measured values of the two approaches was more significant in term neonates. The Pearson correlation coefficient estimations were  $r=0.804$  ( $P<0.001$ ), and  $r=0.901$  ( $P<0.001$ ) in term and preterm neonates, respectively.

#### Conclusion

Based on the results, there was a significant correlation between the values of TSB and TcB in term and preterm neonates.

**Key Words:** Hyperbilirubinemia, Neonatal jaundice, Phototherapy, Transcutaneous bilirubin.

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## 1- INTRODUCTION

Neonatal jaundice is a very prevalent disorder, which is characterized by yellowish discoloration of skin, sclera, and mucous membranes. About 50-60% of term and 80% of preterm newborns are affected by jaundice during the first week of life (1, 2). Commonly, neonatal hyperbilirubinemia occurs 24-72 h after birth(3). The incidence of neonatal jaundice differs based on several factors, such as race, geographical region, altitude from the sea level, maternal factors, birth weight, gestational age, and breastfeeding (4). The main reason for neonatal hyperbilirubinemia is the imbalanced production of bilirubin (resulted from hemoglobin breakdown), and its clearance by the immature liver (5-8).

The high concentration of bilirubin is linked to brain damage and finally can result in encephalopathy, kernicterus, mental retardation, and death. The sensitivity of the brain is related to the immaturity of the brain; in addition, cerebral ischemia would increase the risk of neonatal jaundice complications (9). In 1994 the American Academy of Pediatrics developed a guideline to manage jaundice in healthy term newborns (10), the updated version of which in the following years provided a framework for the prevention and management of hyperbilirubinemia(11).

To prevent the complication risk of this disorder, immediate management is necessary (9, 12). Phototherapy(13), pharmacological intervention (14), and exchange transfusion(15) are recommended for neonates with hyperbilirubinemia symptoms. Visual assessment, transcutaneous bilirubin (TcB), and total serum bilirubin (TSB) estimations are approaches that make detection of the neonatal hyperbilirubinemia feasible (16). The visual assessment involves the inspection of the skin, sclera, and mucous

membranes, as well as the observation of the cephalocaudal progression of jaundice. Gradually tools and techniques, such as bilirubinometer, appeared to estimate the amount of bilirubin through the skin. Clinical assessments were applied to treat the neonatal hyperbilirubinemia by two main approaches for detecting the amount of bilirubin in neonates. TSB and TcB are considered invasive and noninvasive methods, respectively (17). Over the last two decades, TcB estimation has been suggested as an alternative approach to overcome the invasive method. Although there are concerns in relation to TcB accuracy, it has been developed as a noninvasive, safe, painless, and convenient technique (18, 19). A negotiable factor in the management of neonatal jaundice was the variability in the laboratory measurements of bilirubin via TSB.

Commonly, TcB bilirubin is used to reduce the frequency of blood sampling and its complications. The fluctuations in TSB values and stressful condition of invasive sampling were the reasons for the detection of alternative procedures. Although, TSB is more accurate in comparison to TcB bilirubin (20), according to the evidence, it has been shown that the studies performed to assess the accuracy of the introduced noninvasive method (i.e., TcB), have been increased over time. Therefore, the correlation of these two methods has been evaluated in numerous trials to investigate whether TcB estimation is a perfect alternative or not (19, 21). This study aimed to evaluate the relationship between TSB and TcB measured values in term and preterm neonates to provide the knowledge of whether TcB is accurate and efficient enough or not.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

This prospective cross-sectional study was conducted to evaluate the relationship

of TcB with TSB measured values in term and preterm neonates. This study was performed in the neonatal intensive care unit (NICU) of Fatemeh Hospital in 2018, Hamadan, Iran. A total of 93 term and preterm neonates with jaundice during the hospitalization were enrolled in this study. Sample size was determined based on previous study (22), with expected power of 20% ( $\beta=20\%$ ). In order to increase the power of test R-value was considered 0.50. The samples size was calculated based on follow formula:

( $\alpha=0.05$ ,  $\beta=20\%$ ,  $z_{1-\alpha/2}=1.96$ ,  $z_{1-\beta}=81\%$ ,  $r=0.5$ ,  $n=28$ ).

$$n = \left( \frac{z_{1-\frac{\alpha}{2}} + z_{1-\beta}}{0.5 \ln\left(\frac{1+r}{1-r}\right)} \right)^2 + 3$$

## 2-2. Methods

The samples were categorized into two groups, including term and preterm icteric neonates. According to the objectives and variables of the study, all the relevant data (such as age and gender) were collected using a predesigned questionnaire to record the patients' demographics. In this study, each neonate's bilirubin concentration was assessed based on the TSB; at the same time, the subjects' bilirubin concentrations were evaluated by the application of the alternative technique (i.e., TcB). At the first step, the neonates were examined by a neonatologist in order to evaluate the necessity of bilirubin estimation with TSB measurement. After the confirmation of jaundice, the blood samples obtained were sent to the laboratory for bilirubin estimation, and at the same time, the TcB measurement was performed by the bilirubinometer. The detector of the tool was applied on the forehead. Following the measurements, the results of total serum bilirubin and

transcutaneous bilirubin were recorded on a checklist.

## 2-3. Measuring tools

The bilirubinometer model used in this study was MBJ20 (M&B Electronic Instrument Co. Ltd. China), and Selectra X-L was utilized by which the blood samples were analyzed through the dichloroanilin method.

## 2-4. Laboratory measurements

The TcB and TSB were measured at the same time with the clinical indications.

## 2-5. Ethical consideration

This study was performed after obtaining the approval of Hamadan University of Medical Sciences, Hamadan, Iran; since the TSB measurement was an obligatory process, the TcB, and TSB were measured at the same time with the clinical indications; therefore, parental consent was not required.

## 2-6. Inclusion and exclusion criteria

The inclusion criteria were term and preterm neonates with jaundice symptoms or those hospitalized for other reasons while showing icteric signs. The patients with conjugated hyperbilirubinemia were excluded from this study.

## 2-7. Data Analyses

Data analysis was performed using SPSS software (version 16.0). Data normality was measured by Kolmogorov–Smirnov test. The quantifications were calculated, including frequency, percentage, mean, and standard deviation. Tables and diagrams were used to report the information and results systematically. The Chi-square test was used to compare the collected data. The Pearson correlation coefficient quantified the strength of the relationship between TcB, and TSB. P-value less than 0.05 was considered statistically significant.

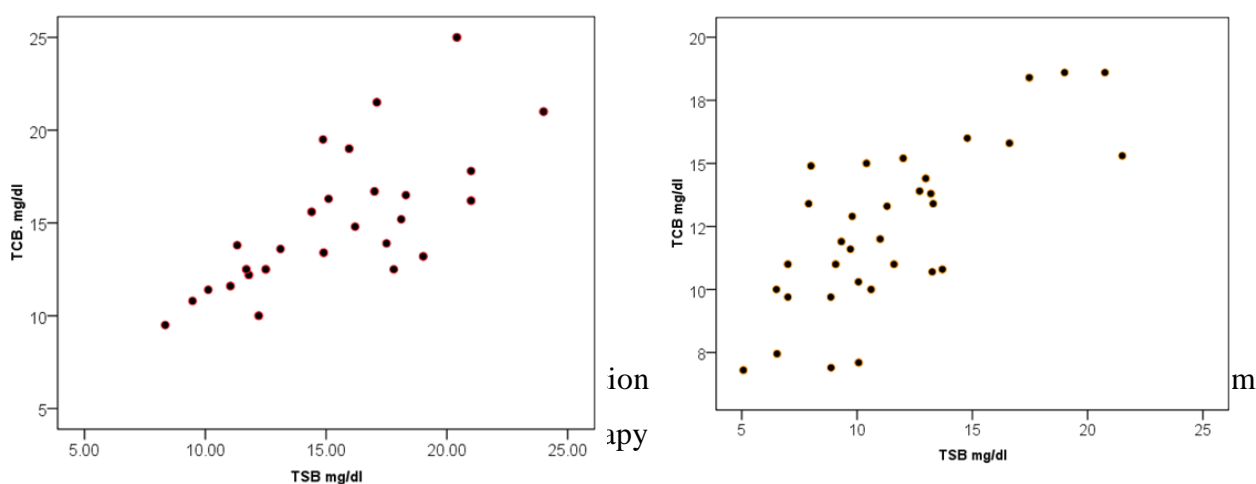
### 3- RESULTS

A total of 93 term and preterm neonates with jaundice during the hospitalization were enrolled in this study, 57 (61%) and 36 (38%) neonates were boys and girls, respectively. The birthweight of the neonates ranged from 1190 to 4280 g. The mean scores of newborns' weight were reported as  $2569.25 \pm 649.85$  g. There were 43 (45%), and 51 (54%) neonates in term and preterm groups, respectively. Before phototherapy, the mean TcB value estimated by the bilirubinometer was reported as  $13.80 \pm 3.98$  mg/dL. The minimum and maximum values of the

recorded data ranged from 6.8 to 25 mg/dl, and the results obtained through serum detection varied from 5.07 to 24 mg/dl. Moreover, the mean value was calculated at  $13.67 \pm 4.29$  mg/dl. According to the findings shown in **Table.1**, the mean serum values were 0.15 and 0.44 mg/dl in term and preterm neonates, respectively, lower than the values obtained by the bilirubinometer through the skin. Normality was confirmed by Kolmogorov–Smirnov test. Before phototherapy, a positive correlation was observed between TcB, and TSB in term ( $r=0.729$ ;  $P<0.001$ ), and preterm ( $r=0.802$ ;  $P<0.001$ ) neonates (**Figure.1**).

**Table-1:** Estimated values by transcutaneous bilirubin and total serum bilirubin techniques in term and preterm neonates before phototherapy.

Gestational age	Total serum bilirubin (Mean±Standard deviation)	Transcutaneous bilirubin (Mean±Standard deviation)	P-value
Preterm	(12.01±3.34)	(12.45±3.45)	0.404
Term	(15.66±3.96)	(15.51±4.18)	0.819



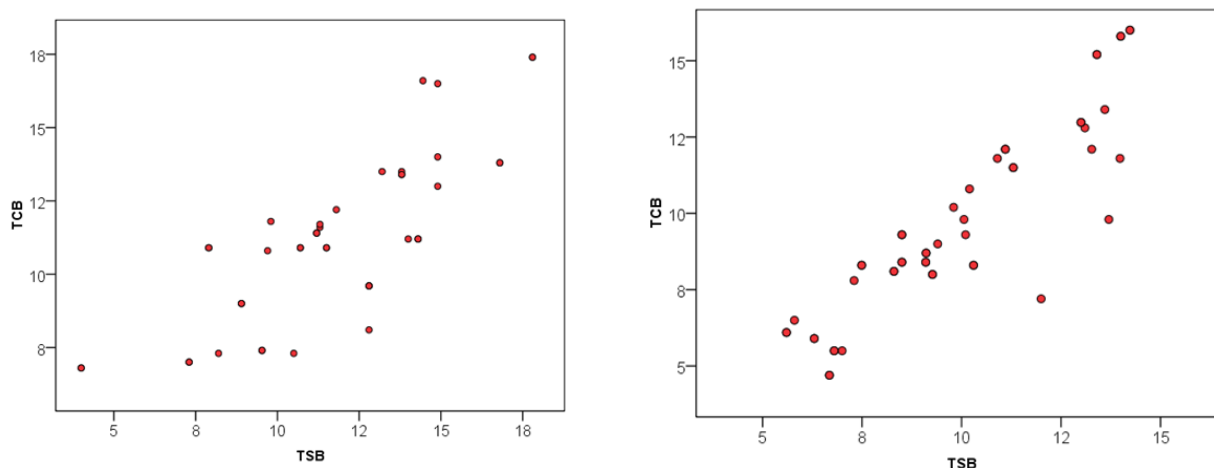
**Fig.1:** Estimated frequency distribution of transcutaneous bilirubin and total serum bilirubin in term neonates before phototherapy.

The values recorded through TcB were higher than those obtained from the laboratory results in both term and preterm groups. The values recorded by TSB estimation in term and preterm neonates were 0.56 and 0.23 mg/dl, respectively. Normality was confirmed. The difference between the results of the two approaches was higher in term neonates (**Table.2**). The correlation between the approaches after photography was positive in term

neonates ( $r=0.804$ ;  $P<0.001$ ). Furthermore, the preterm neonates showed a significant correlation between the results of TcB and TSB estimations ( $r=0.901$ ;  $P<0.001$ ). The estimated values before phototherapy demonstrated that there was no correlation between the results of the TcB, and TSB estimations in patients with bilirubin concentration higher than 15 mg/dl (**Figure.2**).

**Table-2:** Estimated values by transcutaneous bilirubin and total serum bilirubin techniques in term and preterm neonates during phototherapy.

Gestational age	Total serum bilirubin (Mean±Standard deviation)	Transcutaneous bilirubin (Mean±Standard deviation)	P-value
Preterm	(9.92±2.67)	(9.69±3.16)	0.162
Term	(11.70±3.27)	(11.14±2.89)	0.105



**Fig.2:** Estimated frequency distribution of transcutaneous bilirubin and total serum bilirubin in preterm neonates during phototherapy.

#### 4- DISCUSSION

In this study, the bilirubin concentrations were evaluated in both groups of term and preterm neonates before and during phototherapy to detect whether there was a meaningful correlation between the measured values. The TcB, and TSB estimations were performed to assess the difference between the measured bilirubin through the serum

and skin before and during phototherapy. The term neonates showed a higher concentration of TSB, compared to TcB (0.15 mg/dl). However, the preterm neonates' bilirubin concentration by the serum was lower than the estimated TcB (0.44 mg/dl). The mean concentration of serum bilirubin was recorded after phototherapy in both term and preterm neonates and the findings of this study showed that the TSB values were higher

than TcB estimations. Numerous studies have been conducted focusing on different gestational ages, sites (23), and different conditions, such as before, during, and after phototherapy (21). In a study conducted on 72 preterm neonates undergoing phototherapy, a strong correlation was observed between obtained serum bilirubin values and TcB values through the covered skin on the forehead. The correlation between the sternum and serum bilirubin was less strong but more meaningful (22). Despite the lower sample size of the present study and uncovered skin measurements, the outcomes of both studies were similar. To provide more evidence, in a study performed by Babaei et al. on 212 icteric babies, there was no meaningful difference between the TcB, and TSB concentrations (23). In the present study, both term and preterm neonates were examined, but with lower sample size. The same results were obtained despite the difference between the numbers of patients. Regarding the correlation coefficients of TcB and TSB values, term neonates in this study demonstrated a higher value, compared to that in the aforementioned study.

A potentially significant issue related to the accuracy of TcB estimations is the neonatal age that is the reason for most of the discordance of TcB measurements. Kitsommart et al. who aimed to assess the accuracy of TcB in screening icteric term and post-term neonates, reported that the difference between TSB and TcB levels was equal to 1.87 mg/dl (24). However, in the present study, the difference between TSB and TcB levels in both term and preterm neonates was 0.56 (maximum), and 0.15 (minimum) mg/dl before and after phototherapy, respectively. On the other hand, in very preterm infants aged 24-28 weeks, a strong correlation between TcB and TSB has been reported (25). Moreover in infants aged  $\leq 34$  weeks, measurement of bilirubin through

TcB in different sites of the body was done (26, 27). The results of a study carried out by Mandel et al. in India about the neonates hospitalized in NICU, demonstrated that the mean values of TSB and TcB in term newborns were 14.58 and 13.34 mg/dl ( $r=0.94$ ), and in preterm neonates were 12.43 and 11.18 mg/dl, respectively ( $r=0.92$ ). The correlation coefficient between TcB and TSB was equal to 0.94 (28). In the present study, the mean of TcB in term neonates was lower than that of TSB. Moreover, the mean of TcB in preterm newborns was higher than that of TSB. In this regard, the results of the present study are in line with the findings of Mandal et al. (28), and there was a significant correlation between TcB, and TSB estimations. Cucuy et al. independently examined preterm neonates in a study, and correlation coefficient was obtained ( $r=0.8$ ). The authors reported the correlation coefficient in different conditions, including before phototherapy ( $r=0.77$ ), during phototherapy ( $r=0.82$ ), and after phototherapy ( $r=0.88$ ) (29).

Furthermore, the correlation measured by De Luca et al. in a total of 340 preterm neonates within the age range of 30-36 weeks was similar to our results (30). The results of a study performed on term neonates in Turkey showed a higher level of TSB than that of TcB; however, there was a correlation between TSB and TcB levels (31). The evaluation of TcB accuracy in low-birth-weight neonates is another investigated issue. Kurokawa et al. calculated the TcB on the forehead, sternum, lower abdomen, upper back, and waist. There was a significant correlation between the serum and skin levels of bilirubin, and this correlation in the sternum and upper back was higher than that of other parts (32). In a study carried out by Chawla et al. also on preterm low-weight neonates, there was a strong correlation between TSB and TcB values (33). However, the results obtained from

extremely low birth weight neonates do not correlate with the TSB values and cannot be used as a surrogate for TSB measurement (34). Generally, the results of this study are in line with the findings of other studies. Due to observed discrepancies in the results, more studies should be carried out to answer possible open questions in this field, for instance, with larger sample sizes.

#### 4-1. Study Limitations

Small sample size, affecting outcome by uncontrolled intervention variables, and the impossibility of long-term follow-up are the main limitation of the study. Therefore, we cannot generalize our findings. Future studies with large sample size and long-term follow up is recommended to check the results obtained from our study.

#### 5- CONCLUSION

In both groups of term and preterm neonates, before and during phototherapy, a significant and strong relationship was observed between the measurement results of the two applied techniques. Based on the results, there was a significant correlation between the values of TSB and TcB in term and preterm neonates. Bilirubin measurement by a bilirubinometer through the forehead can be a safe and high-throughput measurement method to anticipate the serum bilirubin level in term and preterm newborns. Therefore, it is recommended to estimate the bilirubin level using a bilirubinometer, as an alternative procedure, to reduce frequency and complication of blood sampling in icteric neonates. In addition, performing this study on a larger sample size would be more helpful to obtain more reliable results.

**6- CONFLICT OF INTEREST:** None.

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