

# Effect of Phototherapy on Transcutaneous vs Total Serum Bilirubin Level in Preterm Neonates- A Prospective Cohort Study

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## ABSTRACT

**Introduction:** Neonatal jaundice is one of the most common problems encountered in the first week after birth. Neonates who develop significant hyperbilirubinemia require phototherapy. Delay in the diagnosis and management of jaundice may lead to neonatal morbidity and mortality. Total Serum Bilirubin (TSB) estimation is considered the gold standard method. However, this invasive procedure causes pain, anxiety, and may lead to infection and iatrogenic anaemia, especially in preterm neonates. Transcutaneous Bilirubin (TcB) estimation, which measures bilirubin through the skin, has been proposed as an alternative screening method for hyperbilirubinemia in term and near-term neonates.

**Aim:** To compare TcB to TSB in preterm neonates of 30-34 6/7 weeks gestational age before, during, and after phototherapy.

**Materials and Methods:** This hospital-based prospective cohort study was conducted at SDMCMS&H, Dharwad, Karnataka, India, between December 2019 and November 2020. A total of 100 preterm neonates between 30 to 34 6/7 weeks of gestation with clinically suspected jaundice were enrolled in the study. TSB was measured in the laboratory using the Diazo Method, while TcB was measured using the Drager jaundice meter JM 103. TcB and TSB were measured and compared in preterm

neonates with clinically suspected jaundice before phototherapy, during phototherapy (8 to 12 hours after initiation), and after 12-18 hours of discontinuation of phototherapy. The collected data was analysed statistically using the mean, standard deviation, dependent t-test, Karl Pearson's correlation coefficient, and scatter plots.

**Results:** This study enrolled 100 neonates diagnosed with neonatal jaundice, of which 57 were males and 43 were females, resulting in a male-to-female ratio of 1:1.3. Phototherapy was administered to neonates with TSB values, with 79% of the babies between 30-32 weeks and 21% between 32-34 weeks. In the present study, TcB and TSB were compared before, during, and after phototherapy, and the results were analysed, showing statistical significance. The mean TcB levels were 12.05, 9.66, and 7.23 before, during, and after phototherapy, respectively. The mean TSB levels were 11.28, 10.16, and 7.65 before, during, and after phototherapy, respectively. Based on Karl Pearson's correlation coefficient, a positive correlation was found between TcB and TSB before ( $r=0.8319$ ,  $p$ -value  $<0.001$ ), during ( $r=0.6069$ ,  $p<0.001$ ), and after phototherapy ( $r=0.8154$ ,  $p<0.001$ ).

**Conclusion:** TcB values are comparable to TSB values and can be adopted as the standard method to measure bilirubin levels in preterm babies in a clinical setting.

**Keywords:** Bilirubinometer, Hyperbilirubinemia, Liver, Newborn, Subcutaneous tissue

## INTRODUCTION

Neonatal jaundice is the clinical manifestation of hyperbilirubinemia and is due to the deposition of bilirubin on the skin, subcutaneous tissue, and the sclera [1]. Neonatal jaundice is clinically evident at a serum level above 5 mg/dL. Neonatal hyperbilirubinemia is frequently seen, but only a few affected individuals require intervention. Whatever the causes, TSB levels above the defined thresholds warrant phototherapy to prevent the development of bilirubin-induced brain damage. Hyperbilirubinemia is noticed in the first week of life in approximately 60% and 80% of term and preterm infants [2]. The peak levels upto 10 to 12 mg/dL may be seen in preterm neonates on the fifth day after birth and can increase further in the absence of treatment without any specific abnormality of bilirubin metabolism [3].

Preterm babies are more prone to hyperbilirubinemia compared to term babies. This may be due to decreased Uridinediphosphateglucuronosyltransferase1A1 (UGT1A1) enzyme activity, which is responsible for conjugating bilirubin and making it water-soluble for excretion. Additionally, preterm babies exhibit a similar degree of erythrocyte turnover and heme degradation compared to their term counterparts. Preterm babies also have

immature sucking and swallowing coordination, which leads to a failure in achieving effective breastfeeding, contributing to exaggerated hyperbilirubinemia [4].

Jaundice in newborns is typically harmless and a self-limiting condition. However, a condition called Kernicterus, which is permanent brain damage, can be caused by extremely high levels of bilirubin [5]. Neurological signs have a grave prognosis, with more than 75% mortality and 80% of affected survivors experiencing morbidities such as choreoathetosis with involuntary muscle spasms, mental retardation, deafness, and spastic quadriplegia [6]. To prevent these complications and initiate appropriate management early, all susceptible neonates with jaundice are checked for serum levels of bilirubin. Clinical evaluation of hyperbilirubinemia is done using Kramer's rule, which includes demonstrating jaundice in the skin, sclera, and mucous membranes [7].

Mortality and morbidity in hyperbilirubinemia can be decreased by early detection of at-risk neonates, investigating the cause of pathological hyperbilirubinemia, determining the threshold for treatment, and ensuring follow-up. The measurement of Total Serum Bilirubin (TSB) remains the standard for bilirubin estimation. However, most diagnostic tests for total bilirubin estimation in

premature neonates involve invasive drawing of serum. This requires repeated blood sampling for TSB measurement, which is resource-intensive and painful, leading to unnecessary delays in hospital discharge and parental anxiety [8]. Different methods for assessing hyperbilirubinemia include clinical assessment, serum bilirubin estimation, and Transcutaneous Bilirubin (TcB) estimation.

Many studies have shown that screening tools such as Kramer's rule may fail to detect significant neonatal hyperbilirubinemia before discharge and may result in inadequate follow-up [9,10]. Serum bilirubin estimation is an invasive procedure, and some parents may not consent to it. Therefore, TcB estimation could be a better screening method [11].

The American Academy of Paediatrics (2016) position statement recognises the need for purposeful methods to minimise painful stimuli among neonates [12]. TcB has been approved as a surrogate method for detecting neonatal jaundice. Its additional advantages include being painless, non-invasive, reducing the risk of injury and infection, being less time-consuming, providing instantaneous results, and avoiding repeated blood sampling [13], thus preventing iatrogenic anaemia.

Several studies have reported good accuracy of TcB measurements in both term and preterm neonates, but these studies are largely limited to the Western population and focus on measurements before starting phototherapy [14-16]. However, limited research has been conducted on the use of TcB measurements in preterm neonates after the initiation of phototherapy [13,17,18]. Therefore, this study was conducted to compare TcB levels with TSB levels in preterm neonates between 30-34 6/7 weeks of gestational age before, during, and after phototherapy.

## MATERIALS AND METHODS

The hospital-based prospective cohort study was conducted at the Neonatal Intensive Care Unit, Shri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Dharwad, Karnataka, India. The study was conducted from December 2019 to November 2020, lasting one year. Institutional Ethical Committee permission was obtained to conduct the study (IEC LETTER NUMBER: SDMIEC:199:2019).

**Inclusion criteria:** All preterm neonates born between 30 to 34 6/7 weeks of gestation with clinically suspected jaundice [19], regardless of the mode of delivery, and whose parents provided consent, were included in the study.

**Exclusion criteria:** Preterm neonates with evidence of haemolytic diseases (DCT positive, increased reticulocyte count, fall in Hb, or peripheral smear showing evidence of haemolysis), major congenital anomalies, hydrops foetalis of any cause, birth asphyxia, and direct hyperbilirubinemia were excluded from the study.

**Sample size:** The sample size was calculated using the formula  $N = Z^2 PQ/d^2$ , where P=Prevalence (79.8), d=error (8%), and Q=100-P [19]. The calculated sample size was 100.

**Data collection:** Data was collected using a pre-designed proforma. Modified Ballard Scores [20] were used for gestational age assessment. Preterm neonates were assessed for clinical jaundice using Kramer's staging [7]. TSB and TcB measurements were paired by study personnel before phototherapy, during phototherapy (at 8-12 hours after initiating phototherapy), and 12-18 hours after discontinuation of phototherapy. The TSB measurement was done in the laboratory using the Diazo Method [21] after drawing 2 mL of blood under aseptic precautions. The Drager jaundice meter JM 103 REF (MU 19526) NO 3204014 was used for TcB measurement

over the sternum. TcB was measured for three readings, and an average was obtained. A 2.5 cm diameter photo-opaque patch was placed over a portion of the sternum before the initiation of phototherapy. This photo-occlusive patch covered the area of the skin on the sternum and was used for TcB sampling before and after phototherapy. Treatment decisions for initiating, continuing, or discontinuing phototherapy were based on Threshold Serum Bilirubin levels as per standard normograms for preterm newborns [22]. Paired TcB and TSB samples were obtained within 45 minutes of each other.

## STATISTICAL ANALYSIS

A database was created in MS Excel after appropriate cleaning and analysis using SPSS version IBM, New York, USA. Descriptive statistics such as mean and standard deviation were used to describe the findings. The paired t-test was used to determine statistical significance, with a p-value of <0.05. Scatter plots and the Karl Pearson correlation coefficient were used to assess statistical significance. The Bland-Altman plot was used to assess agreement between two different assays.

## RESULTS

In the present study, a total of 100 cases of preterm neonates with gestational age between 30-34 weeks and 6/7 days were included, meeting the inclusion criteria. There was a male preponderance in the study population, with 57 males and 43 females. Out of the 100 neonates, 79 were born between 30 to 31 weeks and 6 days, and 21 were born between 32 weeks and 33 weeks and 6 days. Among the participants, 58 newborns were born via lower segment caesarean section and 42 via preterm vaginal delivery [Table/Fig-1]. Kramers staging includes 5 zones (zones 1-5). In the present study, out of the 100 preterm newborns, 16% were in Zone 2 (bilirubin level 6-8 mg/dL), 57% were in Zone 3 (bilirubin level 8-12 mg/dL), and 27% were in Zone 4 (bilirubin level 12-14 mg/dL).

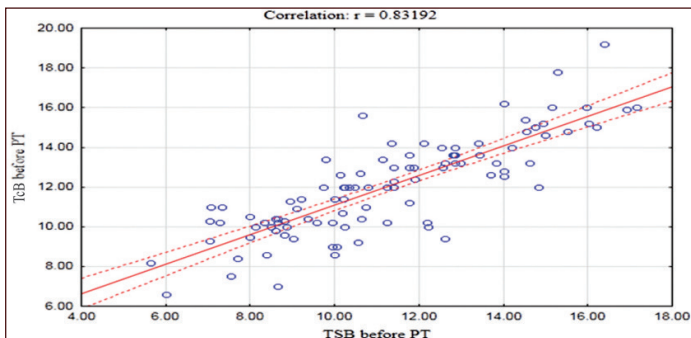
Demographic profile	Percentages (Total N=100)
<b>Sex</b>	
Male	57%
Female	43%
<b>Gestational age (in weeks)</b>	
30 to 31 weeks 6/7 days	79%
32 to 34 weeks +6/7 days	21%
<b>Mode of delivery</b>	
Vaginal delivery	42%
Lower segment caesarean section	58%
<b>Phototherapy</b>	
Single surface phototherapy	78%
Double surface phototherapy	22%

**[Table/Fig-1]:** Shows the demographic details of the neonates.

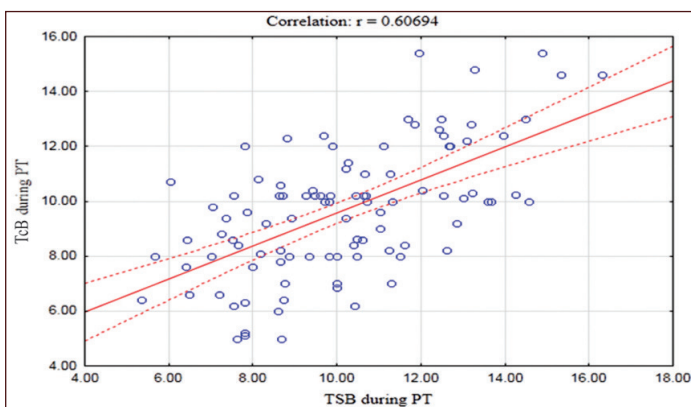
On comparison of TcB and TSB before phototherapy, during phototherapy, and after discontinuation of phototherapy, the mean differences were statistically significant with p-values of 0.0001, 0.0187, and 0.0117, respectively [Table/Fig-2]. The statistical analysis in the study showed that the correlation coefficient (r value) and p-values were found to be 0.8319 (p<0.001), 0.6069 (p<0.001), and 0.8153 (p<0.001), suggesting a linear relationship between TSB and TcB measured at the sternum before initiation of phototherapy, during phototherapy, and after discontinuation of phototherapy, respectively, and having significant statistical value [Table/Fig-3-5].

Variables	Mean value±Standard deviation		Mean/SD difference	t-value	p-value
	TcB	TSB			
Before PT	12.05±2.41	11.28±2.69	0.77/1.50	5.1440	0.0001*
During PT	9.66±2.34	10.16±2.36	-0.50/2.08	-2.3908	0.0187*
After PT	7.23±2.41	7.65±2.78	-0.42/1.62	-2.5685	0.0117*

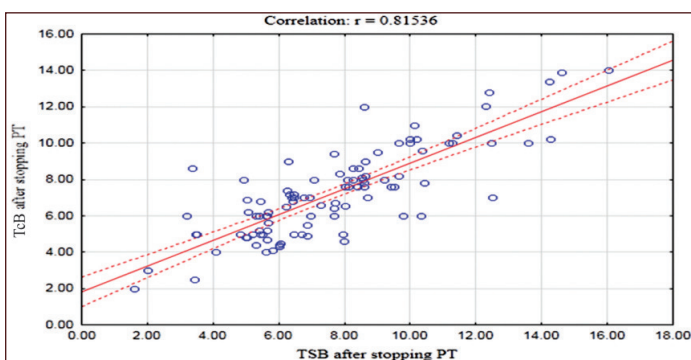
**[Table/Fig-2]:** Comparison of TcB and TSB by dependent t-test before PT, during PT and after PT. Dependent t-test and paired t-test were applied to obtain the results



**[Table/Fig-3]:** Scatter diagram showing the correlation between TcB and TSB before PT.



**[Table/Fig-4]:** Scatter diagram showing the correlation between TcB and TSB during PT.

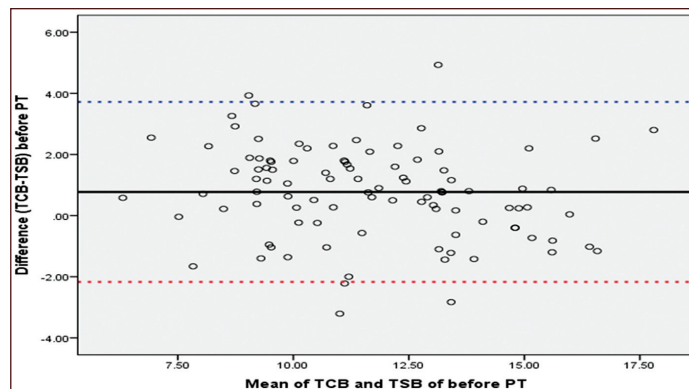


**[Table/Fig-5]:** Scatter diagram showing the correlation between TcB and TSB after stopping PT.

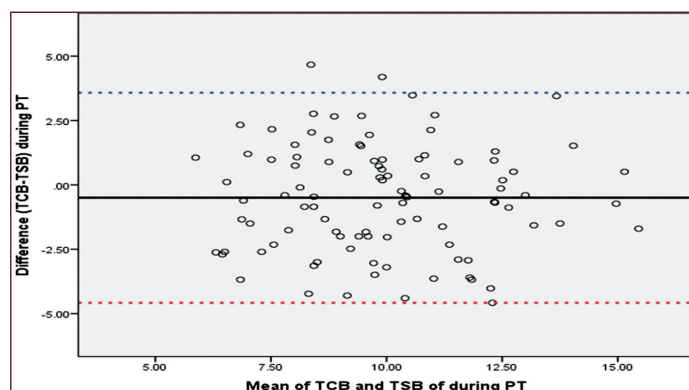
The Bland-Altman plot demonstrates the agreement between TcB and TSB measurements before initiating phototherapy, during phototherapy, and after discontinuation of phototherapy. The mean difference between TcB and total serum bilirubin value, with a standard deviation of +1.96, is 3.9, and with a standard deviation of -1.96, is -2.2. Only four fall outside the standard deviation line of difference, indicating that the differences are normally distributed before initiating phototherapy [Table/Fig-6].

For the phase of phototherapy, the +1.96 standard deviation was 3.4, and the -1.96 standard deviation was -4.6. Only two fall outside the standard deviation line of difference, indicating that the

differences are normally distributed during the phototherapy phase [Table/Fig-7].

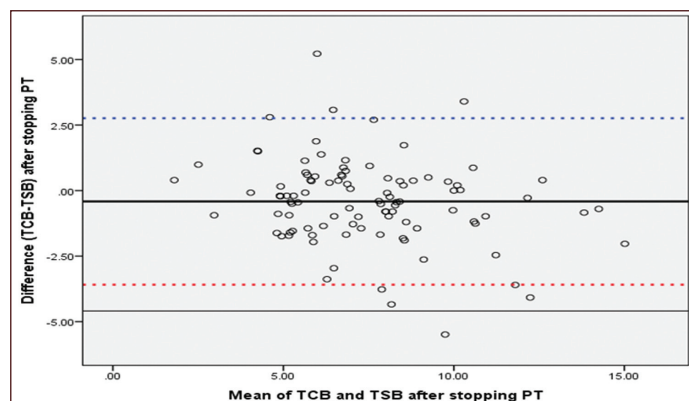


**[Table/Fig-6]:** Bland-Altman plot showing TcB difference between TcB and TSB before PT on Y-axis against mean TcB and TSB before PT on X-axis.



**[Table/Fig-7]:** Bland-Altman plot showing difference between TcB and TSB during PT on Y-axis against mean TcB and TSB during PT on X axis.

After discontinuation of phototherapy, the +1.96 standard deviation was 2.63, and the -1.96 standard deviation was -3.34. Only five fall outside the standard deviation line of difference, indicating that the differences are normally distributed even after discontinuation of phototherapy [Table/Fig-8].



**[Table/Fig-8]:** Bland-Altman plot showing difference between TcB and TSB after stopping PT on Y-axis against mean TcB and TSB after stopping PT on X-axis.

## DISCUSSION

Transcutaneous Bilirubinometer (TcB) is a sensitive screening method for estimating bilirubin levels in both term and preterm newborns. However, there is limited data on TcB estimation in preterm newborns within the Indian population.

Therefore, the main aim of our study was to compare TcB measurements with Total Serum Bilirubin (TSB) levels in preterm neonates before, during, and after phototherapy. The values obtained from TcB and TSB were paired each time.

Regarding the usefulness of covering the skin exposed to phototherapy, Hegyi T et al., showed that TcB measurements on uncovered skin change during phototherapy, while measurements on covered skin continue to reliably predict TSB [23]. To avoid this bias, all the study participants were checked for TcB levels over the covered area of the sternum.

In the present study, using a dependent t-test, the mean and standard deviation of TcB before, during, and after phototherapy were found to be 12.05±2.41, 9.66±2.34, and 7.23±2.41 mg/dL, respectively. The mean and standard deviation of TSB before, during, and after phototherapy were 11.28±2.69, 10.16±2.36, and 7.65±2.78 mg/dL, respectively. These results were statistically significant with p-values of 0.0001, 0.0187, and 0.0117, respectively. Comparable results were obtained in a study conducted by Tiwari MM et al., which showed the mean and standard deviation of TSB before, during, and after phototherapy to be 19.21±3.44, 15.76±2.79, and 12.89±2.44, respectively, and the mean and standard deviation of TcB before, during, and after phototherapy to be 18.34±2.99, 15.48±2.36, and 12.31±2.28, respectively [24]. It is important to note that the major population in that study were term newborns.

Based on Karl Pearson's correlation coefficient, a positive correlation between TcB and TSB was found in the present study before ( $r=0.8319$ ,  $p$ -value  $<0.001$ ), during ( $r=0.6069$ ,  $p$ -value  $<0.001$ ), and after phototherapy ( $r=0.8154$ ,  $p$ -value  $<0.001$ ). The Bland-Altman plot showed strong agreement between TcB and TSB before, during, and after phototherapy. Similar observations were also made in other studies shown in [Table/Fig-9] [19,24-26].

Study	Study period/ place of the study	Number of subjects	r-value		
			Before PT	During PT	After PT
Tiwari M et al., [24]	December 2015 to November 2017 SRTR, GMC, Ambajogai	N=172	0.806 $p<0.0001$	0.694 $p<0.0001$	0.785 $p<0.0001$
Panburana J et al., [25]	September 2007 to October 2008 Srinakharinwirot University, Bangkok	N=224	0.81 $p<0.001$	-	-
Pendse A et al., [19]	September 2014 to February 2015 KEM hospital, Mumbai	N=30	0.903 $p<0.001$	-	0.918 $p<0.001$
Povaluk P et al., [26]	April 2008 to October 2008 Hospital Universitário Evangélico de Curitiba	N=44	0.8794 $p<0.0001$	0.8599 $p<0.0001$	-
Present study	November 2019 to December 2020 SDMCMS&H Dharwad	N=100	0.8319 $p<0.001$	0.6069 $p<0.001$	0.8154 $p<0.001$

**[Table/Fig-9]:** Review of literature: comparison of TcB and TSB values in different studies [19,24-26].

A study by Nagar G et al., conducted in babies less than 32 weeks of gestational age concluded that BiliChek is a reasonably accurate early screening device before the initiation of phototherapy [17]. The results of our study also indicate that TcB measurements

provide reliable estimation before, during, and after phototherapy in premature infants with a gestational age of 30 to 34 6/7 weeks.

A study by Bhutani VK et al., found that the correlation between multiple near-simultaneous TcB measurements and TSB (HPLC) was linear and significant. Similar correlations were also observed when TcB values were compared with TSB values obtained by DPD diazo methods and other techniques [27]. Mishra S et al., demonstrated that the routine use of TcB, compared with visual assessment of bilirubin, reduced the need for blood sampling to estimate TSB in preterm neonates with jaundice [28].

The above findings indicate that TcB can be used as a non-invasive tool for estimating neonatal jaundice.

### Limitation(s)

The study population mainly consisted of individuals from the South Indian region, and therefore, the findings may not be universally applicable. Additionally, only the Dragger JM-103 jaundice meter was used to test TcB levels. It is worth noting that different TcB machines may provide different values, but this aspect was beyond the scope of the present study.

### CONCLUSION(S)

The TcB levels measured using a transcutaneous bilirubinometer were comparable to TSB levels in preterm newborns. Additionally, the study showed a strong linear correlation between TSB and TcB levels before, during, and after phototherapy. Therefore, the transcutaneous bilirubinometer, being a non-invasive method for estimating bilirubin levels, can be used as a potential screening tool in high-risk and preterm neonates. This can help initiate early interventions such as phototherapy and monitor bilirubin levels after phototherapy is initiated.

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