



# Agreement between Transcutaneous Bilirubin and Serum Bilirubin Measurements Before, During and After Phototherapy in Term and Preterm Neonates a Prospective Cohort Study in an Asian Multi-Ethnic Population

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## Abstract

**Background:** Neonatal jaundice occurs commonly in neonates. Serum bilirubin, the gold standard method of assessing the severity of jaundice is a painful, time consuming and costly procedure. Transcutaneous Bilirubin (TcB) has been touted as an alternative method of detecting neonatal jaundice.

**Objectives:** To determine the agreement between transcutaneous bilirubin and serum bilirubin measurements before, during and after phototherapy in term and preterm neonates and to evaluate factors that may influence the correlation between TcB and TSB.

**Methods:** A total of 1541 paired bilirubin readings were obtained from 566 neonates managed for jaundice in the Department of Neonatal and Developmental Medicine at the Singapore General Hospital over a 4 month period. Neonates requiring an assay of bilirubin were prospectively enrolled and bilirubin was measured using TSB and TcB methods. Bland-Altman plots of difference in TcB and TSB versus the average of TcB and TSB were used to assess the degree of clinical agreement between TcB and TSB measurements. Limits of agreement of  $\pm 35 \mu\text{mol/L}$  were considered to be clinically acceptable.

**Results:** Bland Altman analysis revealed good clinical agreement between TcB and TSB measurements before and after phototherapy in both term and preterm neonates. The intra-class correlation coefficient for TcB at the sternum, forehead and inter-scapular was good at 0.937 before and 0.960 after phototherapy. The difference in TcB and TSB in neonates of Malay and Indian ethnicity are statistically higher compared to the Chinese ( $p=0.001$ ).

**Conclusion:** Agreement between TcB and TSB measurements is good before and after phototherapy, hence TcB is recommended in screening for jaundice and trending of jaundice after phototherapy.

**Keywords:** Newborn or neonates; Term and preterm; Bilirubinometry or transcutaneous bilirubin; Serum bilirubin, Phototherapy

## What is already known on the topic?

1. Transcutaneous bilirubin measurement is a good alternative to total serum bilirubin measurement in neonates with gestational age 35 weeks or more before phototherapy.
2. Conflicting reports on factors affecting the agreement between transcutaneous bilirubin measurement and total serum bilirubin.
3. Previous studies were done using the JM-103 and BiliCheck. These devices are no longer available for clinical use.

What this paper adds

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1. Transcutaneous bilirubin measurement via the JM-105 bilirubinometer is a valuable alternative screening tool to total serum bilirubin for both preterm and term neonates in a multi-ethnic Asian population before and after phototherapy.

2. There is no significant difference in clinical agreeability between transcutaneous bilirubin and total serum bilirubin measurements based on different sites of measurement including sternum, forehead and inter-scapular regions.

3. Malay and Indian ethnicity have statistically significant higher difference in transcutaneous bilirubin and total serum bilirubin measurements compared to Chinese. Gestational age and birth weight do not significantly affect the agreement between the two methods of measurement.

## Introduction

Neonatal jaundice is one of the most common problems encountered in the neonatal period, with about 10% of term and 25% of near-term neonates developing significant hyperbilirubinemia that requires phototherapy [1]. Delay in the diagnosis of jaundice and in initiation of treatment increases neonatal morbidity and mortality. Measurement of Total Serum Bilirubin (TSB) remains as the gold standard for detecting hyperbilirubinemia; however the sampling of TSB is resource-intensive and painful, leading to unnecessary delay in hospital discharge and parental anxiety [2]. Transcutaneous Bilirubin (TcB) measurement was developed as an alternative way of monitoring hyperbilirubinemia more than 30 years ago. This method has the advantage of being pain-free; non-invasive hence reduces risk of trauma and infection, and time-saving [3]. However, its use was previously limited by the lack of accuracy [4]. With technological advances, the American Academy of Paediatrics (AAP) in 2004 recommended that TcB be used as an alternative mode of assessing jaundice in neonates born more than or equal to 35 weeks' gestation. Several studies proposed that differences in sensitivities of the instruments, and the location of the TcB record may account for variations in the correlations between TcB and TSB [3,5-8]. Studies evaluating factors influencing the accuracy of TcB measurement reported conflicting results [9-15]. While some studies have reported good accuracy of TcB measurements in both term and preterm neonates, these data were largely limited to the Western population [10,12,13,15]. Study by Afanetti et al. [10] comparing Caucasians with non-Caucasians neonates showed good correlation between TcB and TSB regardless of skin colour. In contrast, Taylore et al. [12] showed greater discrepancies between TcB and TSB in the African-American newborns. A local study by Tan et al. [4] on forty preterm Chinese infants showed significant difference between TSB and TcB, but systematic review by Nagar et al. [5] involving preterm infants reported good correlation of TcB measurement with TSB. In addition, reports on the accuracy of TcB measurement during and post phototherapy have shown in consistent and conflicting results. Casnocha et al. [13] reported poor correlation between TcB and TSB measured 2 hr post phototherapy but Tan et al. [14] showed good correlation between TcB and TSB 18 to 24 hr after cessation of phototherapy. Given the limited and conflicting evidence of correlation between TSB and TcB in Asian neonates, our study was designed with the primary objective of determining the agreement between TCB and TSB measurements in term and preterm neonates before, during and after phototherapy in a multi ethnic Asian population. Our secondary objectives included the evaluation of factors that may influence the agreement between TcB and TSB, inclusive of correlation by sites of measurement of TcB,

namely sternum, forehead and inter-scapular.

## Materials and Methods

The study was approved by the Institutional Review Board. Neonates admitted to the Neonatal Department of the Singapore General Hospital from May to August 2015 who required an assay of total serum bilirubin were included. Except for neonates with hemodynamic instability, extensive bruising and/or haemangiomas over the forehead, sternum or inter-scapular area, all eligible neonates were enrolled with written informed consent obtained from the parent. Traditionally TSB measurement was done for all neonates with clinical jaundice and decisions on monitoring and treatment of jaundice were made by the attending physicians following departmental guidelines. Depending on the severity of neonatal jaundice, neonates receive their first repeat TSB measurement at 6 to 12 or 18 to 24 hrs post-initiation of phototherapy with subsequent repeats performed 24 hourly unless otherwise clinically indicated. Post-cessation of phototherapy, TSB measurements were assayed 24 hours later with further repeats performed as clinically indicated.

During the study period, neonates whose parents consented to participate will have their bilirubin levels measured via two methods:

1. Invasive laboratory TSB method where bilirubin was sampled through a heel prick filling a capillary tube with 0.2 cm<sup>3</sup> of blood and level was determined using direct spectrophotometry [16,17]. The machine was calibrated daily to ensure accuracy.

2. Non-invasive TcB method where transcutaneous estimation of bilirubin level was done using the Draeger JM-105 bilirubinometer (Draeger Medical Systems, Inc.) that was calibrated daily as per manufacturer's guidelines. Measurements were obtained from the forehead, the sternum, and the inter-scapular areas with the probe placed perpendicular to the skin. Three measurements were taken in succession from each site and readings from the respective sites recorded as the device calculates the mean of three independent determinations.

For TcB and TSB measurements obtained during phototherapy, the phototherapy light was temporarily stopped during the sampling and resumed immediately afterwards. TcB levels were obtained within 30 min of TSB assay by either of two investigators (SC and MGT). Raw values from both methods were recorded immediately on a study-specific form. Demographic data inclusive of gender, gestational age, birth weight and ethnicity were collated and recorded. The exact timing of phototherapy and cessation of phototherapy were compiled and recorded. The gestational maturity of neonates born <37 weeks' gestation was assessed using the Dubowitz or the New Ballard scoring method [18,19]. Mother's date was adopted as the best estimate when scored date was within 2 weeks of mother's dates and scored date was used as the best estimate of gestational maturity if scored date differed from mother's date by more than 2 weeks. To evaluate the inter-operator variability, 28 paired TcB measurements assayed by the two operators (SC and MGT) were compared against the measured TSB readings and variation calculated using Intra Class Correlation (ICC).

## Statistical analysis

Using the Bland-Altman sample size methodology, a sample size of 383 paired readings was targeted to study the agreement between TcB and TSB based on clinically acceptable limits of agreement of  $\pm 35 \mu\text{mol/L}$  [15]. Using the tolerance of difference between the 2

**Table 1:** Demographics and characteristics of study population.

Characteristics	Preterm (GA <37 weeks) (n=143)	Term (GA ≥ 37 weeks) (n=423)
Gestational age (weeks)	33 (3)	39 (1)
Birth weight (g)	2030 (618)	3152 (427)
Male (%)	69 (51.1)	214 (53.5)
<b>Ethnicity</b>		
Chinese	74 (51.7)	197 (46.6)
Malay	47 (32.9)	116 (27.4)
Indian	13 (9.1)	38 (9)
Others	9 (6.3)	72 (17)
<b>Mode of delivery</b>		
Spontaneous	36 (25.2)	163 (38.5)
Operative Vaginal	7 (4.9)	55 (13)
Caesarean	81 (56.6)	166 (39.2)
Unknown	19 (13.3)	39 (9.2)
<b>Nos. of TSB measurement</b>		
1	24 (16.8)	205 (48.5)
2	32 (22.4)	110 (26)
3	23 (16.1)	49 (11.6)
4	11 (7.7)	28 (6.6)
≥5	53 (37.1)	31 (7.3)
Phototherapy initiated	73 (51.0)	133 (31.4)
Duration of phototherapy (hrs)	40 (34.1)	34 (29.5)

**GA:** Gestational Age; **TSB:** Total Serum Bilirubin; Values are numbers (%) or mean (SD)

methods of  $\pm 35 \mu\text{mol/L}$  with an anticipated SD of the difference of  $25.5 \mu\text{mol/L}$  (based on manufacturer's information), the accepted width of the 95% confidence interval for the upper limit and lower limit of agreement was  $+8 \mu\text{mol/L}$ . The Bland-Altman plots of difference between the two methods against the average of TcB and TSB were used to assess for the degree of clinical agreeability between TcB and TSB measurements [20]. Intra-Class Correlation (ICC) was used to evaluate the agreement between the TcB readings sampled from the 3 sites; forehead, sternum and inter-scapular. The univariate Generalised Estimating Equation (GEE) model was utilised to assess the effects of factors that may influence the difference in TcB and TSB measurements. For each factor, the coefficient,  $\beta$  and its 95% CI for direction of association was measured for statistical and clinical significance. Factors predictive of difference in TcB and TSB were evaluated using the multivariate GEE model. Statistical significance was set at  $p < 0.05$ . All analyses were performed using SAS v9.4 (SAS Inc. Cary, NC USA), [21].

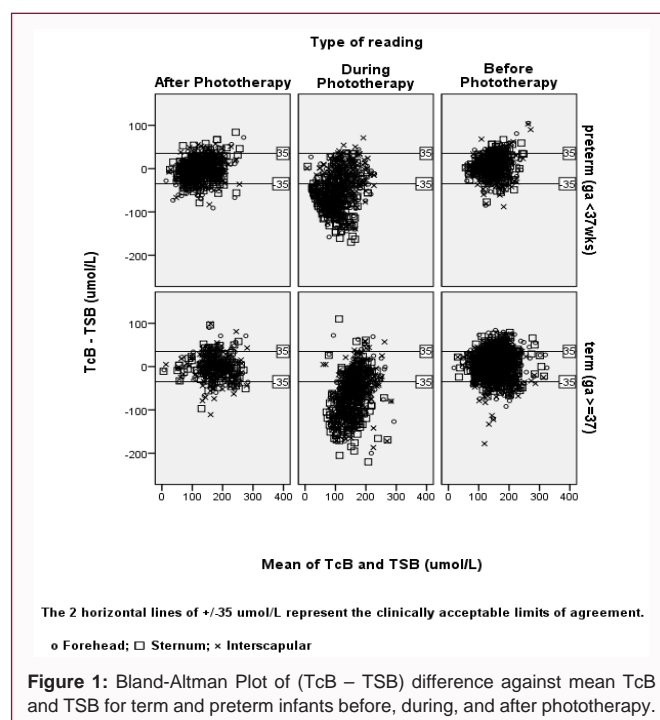
## Results

A total of 1541 paired bilirubin (TSB and TcB) readings were

**Table 2:** Comparison of TcB with TSB by sites of assay before, during, and after phototherapy in preterm babies.

Bilirubin Values Timing of Assay (N)	TcB (ummol/L)			TSB (umol/L)	Difference in TcB and TSB (umol/L)		
	Forehead	Sternum	Inter-scapular		Forehead	Sternum	Inter-scapular
Before Phototherapy (N=215)	148 (41)	152 (41)	149 (41)	144 (37)	4 (24)	8 (23)	5 (27)
During Phototherapy (N=205)	86 (53)	62 (43)	113 (52)	135 (45)	-49 (39)	-73 (41)	-22 (39)
After Phototherapy (N=242)	118 (46)	132 (48)	136 (43)	132 (41)	-14 (24)	0 (25)	5 (22)

Values are mean (SD); N = Numbers



obtained from 566 neonates. Of which 662 readings were assayed from 143 preterm neonates and 879 readings assayed from 423 term neonates. A total serum bilirubin of  $< 250 \mu\text{mol/L}$  was determined in 99% and 96.6% of the preterm and term neonates respectively. Table 1 shows the demographic characteristics of enrolled neonates, both preterm and term. The gender distribution and ethnicity of neonates resembled largely that of the local national population. Inter-rater variability of TcB readings between the two investigators (SC and MGT) were insignificant with ICC of 0.95, 0.97, and 0.90 for readings measured from the forehead, sternum, and the inter-scapular region respectively.

## Before and after phototherapy

Of the preterm neonates, 83.4% and 83.6% of the readings before and after phototherapy respectively were within the clinically acceptable limit of  $\pm 35 \mu\text{mol/L}$ . Among preterm neonates, the mean difference between TcB and TSB readings for the different sites before phototherapy ranged from  $4 \mu\text{mol/L}$  to  $8 \mu\text{mol/L}$ . After phototherapy, the mean difference ranged from  $-14 \mu\text{mol/L}$  to  $5 \mu\text{mol/L}$  (Table 2). Among the term neonates, 78.9% and 77.2% of the readings before and after phototherapy respectively were within the clinically acceptable limit of  $\pm 35 \mu\text{mol/L}$ . The mean difference between TcB and TSB readings ranged from  $0 \mu\text{mol/L}$  to  $9 \mu\text{mol/L}$  before phototherapy and  $-4 \mu\text{mol/L}$  to  $0 \mu\text{mol/L}$  after phototherapy (Table 3). There was no discerning difference in TcB and TSB readings by sites of assay of TcB. The intra-class correlation coefficient for TcB at the 3 sites was 0.937 before phototherapy and 0.960 after phototherapy (Figure 1).

**Table 3:** Comparison of TcB with TSB by sites of assay before, during, and after phototherapy in term babies.

Bilirubin Values Timing of Assay (N)	TcB (ummol/L)			TSB (umol/L)	Difference in TcB and TSB (umol/L)		
	Forehead	Sternum	Inter-scapular		Forehead	Sternum	Inter-scapular
Before Phototherapy (N=532)	157 (43)	152 (43)	148 (40)	148 (42)	9 (28)	4(25)	0 (31)
During Phototherapy (N=230)	148 (44)	117 (52)	122 (55)	189 (39)	-41 (40)	-73 (54)	-67(53)
After Phototherapy (N=117)	175 (54)	175 (51)	171(52)	175 (53)	0(28)	0 (27)	-4 (32)

Values are mean (SD); N = Numbers

**Table 4:** Univariate and multivariate GEE analysis of factors associated with increased difference between TcB and TSB (TcB-TSB).

Factors	Univariate GEE		Multivariate GEE	
	β (95% CI)	p-value	β (95% CI)	p-value
Ethnicity				
Chinese	Reference		Reference	
Malay	22.5 (14.4, 30.7)	0.001	19.2 (14.2, 24.1)	0.001
Indian	32.8 (24.1, 41.5)	0.001	22.1 (14.9, 29.3)	0.001
Others	17.7 (7.5, 27.8)	0.001	8.6 (1.6, 15.6)	0.016
Gestational maturity				
Preterm (GA < 37 wks)	Reference		Reference	
Term (GA ≥ 37 wks)	5.1 (-0.2, 10.4)	0.059	1.8 (-2.9, 6.6)	0.455
Time of life (days)	-1.0 (-1.7, -0.3)	0.003	-0.5 (-1.1, 0)	0.071
Gender				
Male	Reference		---	---
Female	2.2 (-3.0, 7.4)	0.415		
Sites of assay				
Forehead	Reference		---	---
Sternum	1.4 (-1.6, 4.4)	0.374		
Inter-scapular	-2.2 (-5.9, 1.6)	0.258		
Birth weight (100g)	0 (-0.4, 0.4)	0.937	---	---
TSB (umol/L)	-0.1 (-0.2, -0.1)	0	-0.1 (-0.2, -0.1)	0
Types of reading				
Before phototherapy	Reference		Reference	
After phototherapy	-10.8 (-17.7, -4.0)	0.002	-9.1 (-15.9, -2.3)	0.009

---; Factor was not entered in multivariate GEE model

Compared to the Chinese, neonates of Malay, Indian and other ethnic groups had statistically higher difference in TcB and TSB ( $p=0.00$ , Table 4). The difference in TcB and TSB varied significantly with the day of life at which bilirubin was sampled ( $p=0.003$ ), and exposure to phototherapy ( $p=0.002$ , Table 4). Gestational maturity, birthweight, gender and TcB sampling sites had no influence on difference in TcB and TSB readings. On multivariate analysis, the only factors that contributed to significant difference in TcB and TSB were ethnicity and exposure to phototherapy (Table 4).

### During phototherapy

A total of 435 paired readings were available for comparisons with TSB during phototherapy. Analysis showed that TcB underestimated jaundice level in all neonates during light therapy with mean difference ranging from -22  $\mu\text{mol/L}$  to -73  $\mu\text{mol/L}$  in preterm neonates (Table 2) and -41  $\mu\text{mol/L}$  to -73  $\mu\text{mol/L}$  in term neonates (Table 3).

## Discussion

Our study showed good agreement between TcB measured using the Draeger JM-105 and TSB measurements assayed by direct

spectrophotometry, before and after phototherapy in both preterm and term infants. Similar to the diverse ethnic population reported by Taylor et al. [12]. 46.6% of our study population were Chinese with the remaining being Malays, Indians and other ethnicity. However in their study, TcB measurements were derived using different brands of bilirubinometer performed by different healthcare professionals on different anatomical sites inclusive of the forehead, chest to multiple sites compared with TSB assayed using mix of methods performed within 2 hr of each measurements. Using a clinically acceptable limit of  $\pm 35 \mu\text{mol/L}$ , Taylor et al. [12] showed that 28.8% of the overall TcB readings differed from matched TSB values. This is congruent with our study where 21.1% of the overall TcB readings in term neonates differed from matched TSB levels. In our study, the Draeger JM-105 measures the TSB values in preterm neonates with accuracy similar to that obtained in term neonates. Of our preterm neonates, the results of difference in TcB and TSB pre-phototherapy measured on the forehead and the sternum of 4  $\mu\text{mol/L}$  (SD, 24.0  $\mu\text{mol/L}$ ) and 8  $\mu\text{mol/L}$  (SD, 23.0  $\mu\text{mol/L}$ ) respectively compared favourably with the pooled estimate of -0.06  $\mu\text{mol/L}$  (SD, 29.5  $\mu\text{mol/L}$ ) and 3.8  $\mu\text{mol/L}$  (SD, 26.  $\mu\text{mol/L}$ ) respectively reported by Nagar et al. [5] involving



preterm babies using either the Draeger JM-103 or the BiliCheck device. Our study also included three sites of measurement; the sternum, forehead and inter-scapular regions. The results show that intra-class correlation coefficient for TcB at the 3 sites was 0.937 before phototherapy and 0.960 after phototherapy, with no significant difference between the 3 sites used ( $p < 0.05$ ). This is similar to report by Yaser et al. [22] in which there were no significant difference in correlation coefficients from three similar sites. These findings suggest that TcB may be measured from any of the 3 body sites studied, thereby reducing unnecessary stress on the babies from repositioning that may be required to get an accurate measurement from a specific body part. In our study, TSB and TcB measurements were repeated 24 hr post-cessation of phototherapy. The agreement between TSB and TcB after phototherapy concurred with that reported by Justin-Reicher et al. [23], who evaluated agreement between TSB and TcB 8 hours after cessation of phototherapy. However, investigation on agreement at specific hours after cessation of phototherapy in an Asian multi-ethnic population is limited, hence further study is recommended. Similar to several studies our results showed poor correlation between TcB and TSB during phototherapy [14,24,25]. Jangaard et al. [26] in their study on the use of the BiliCheck in 24 preterm and term jaundiced infants showed better accuracy in term infants not receiving phototherapy and when TcB is measured from skin unexposed to light during phototherapy. But with the small population size, their results were inconclusive. In contrast, Cucoy et al. [27] showed acceptable correlation in preterm infants even during phototherapy. Studies on the use of TcB assayed from the unexposed skin during phototherapy concluded that TcB can be used for evaluation of bilirubin during phototherapy [14,26]. Inconsistency in reports on correlation between TcB and TSB during phototherapy maybe related to differences in the methods of assay of TcB (exposed versus unexposed skin) used in the studies. Phototherapy reduces serum bilirubin through its effect on the skin. Photo light induces the conversion of bilirubin to its photo-isomers, lumirubin and photo-bilirubin which are readily excreted through the kidneys and liver [27-29]. Equilibrium between cutaneous and serum bilirubin occurs as the concentration of bilirubin in the skin and the systemic circulation changes during light therapy but the time required to achieve a state of equilibrium remains unknown. Further exploration is necessary before the use of TcB during phototherapy may be considered. Our study is unique in revealing race as an important factor affecting the agreement between TcB and TSB. Using the Draeger JM-105, TcB tended to overestimate bilirubin levels in Malays and Indian neonates with statistically significant higher mean difference between TcB and TSB in Malays and Indians compared to the Chinese neonates. While, this may lead to unnecessary blood taking for TSB when device is used in screening for jaundice in Malay and Indian neonates, the adoption of the same TcB level to determine the need for TSB assay increases the margin of safety when device is used in these neonates. Our finding is in contrast with studies by Afanetti et al. [10] and Samiee-Zafarghandy et al. [30] which concluded that skin colour was not a factor affecting reliability of transcutaneous bilirubin measurement. Differences in population studied as well as variations in the brand of bilirubinometer used in the studies can contribute to the conflicting reports on influence of skin colour on accuracy of TcB measurements. Larger studies with diverse ethnic groups are more likely to yield differences as compared to small studies involving limited ethnic distribution. Earlier transcutaneous devices correlated yellow coloration of skin with bilirubinaemia. Newer devices are able to filter bilirubin in the subcutaneous tissue from

melanin; haemoglobin etc. and different brands of the transcutaneous device have varying sensitivity to varying degree of skin maturity. There are several limitations in our study. Our results were derived using the Draeger JM-105 bilirubinometer. Comparisons with other devices were not performed; hence findings must be applied with caution when using other brands of bilirubinometer. Secondly, our study included relatively small sample of preterm infants, especially the extremely preterm infants. Thirdly, more than 95% of the TSB readings were  $< 250 \mu\text{mol/L}$  and the maximum reading that we have for phototherapy was less than  $350 \mu\text{mol/L}$ , thus study does not include analysis for correlation at higher bilirubin levels.

## Conclusion

The new JM-105 bilirubinometer is a valuable and reliable tool for assessing jaundice in both term and preterm neonates. This painless, cost effective and time saving procedure is recommended for neonates before and after phototherapy. Further research is needed before the device may be recommended for use during phototherapy.

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