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Comparison of the Non-Invasive Transcutaneous Bilirubin (TcB) and Total Serum Bilirubin (TSB) Measurements among Preterm Infants: A Prospective Cohort Study in Singapore General Hospital

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Abstract

Introduction: AAP recommends the use of transcutaneous bilirubinometry (TcB) in screening of jaundice in newborns >35 weeks' gestation. At Singapore General Hospital (SGH), TcB has been used to screen jaundice in neonates born >35 weeks' gestation within 2 weeks of postnatal age. To establish the agreement between TcB and TSB in neonates born preterm, a prospective cohort study was conducted from October 2020 to January 2022 to evaluate the agreement between transcutaneous bilirubin (TcB) and serum bilirubin (TSB) levels before, during and 24 hours after cessation of phototherapy.

Methods: Eligible neonates with birth gestational age of 23 to 36+6 weeks born at Singapore General Hospital from July 2020 to July 2022 were enrolled. Bland-Altman method was employed to consider within subject variability for multiple measurements before, during and after phototherapy. Mean differences with corresponding 95% limits of agreement (LOA) were calculated for babies stratified by gestational age and ethnicity. Receiver operating characteristic (ROC) analysis and area under the curve (AUC) were calculated to determine sensitivity of TcB. TcB was measured over the baby's sternum.

Results: Of the 161 babies studied, 989 readings were obtained. Mean difference with 95% Level of agreement (LOA) was the least for post phototherapy cohort in both gestational age and ethnicity sub-groups respectively which was corroborated by Bland Altman's correlation. Area under curve (AUC) of 0.84 was achieved with 90% sensitivity for TSB measurements (phototherapy cut off) of >100 umol/L at 23-32 weeks' gestation and >170 umol/L at 35-36 weeks' gestation.

Conclusion: Transcutaneous bilirubinometry could be considered for screening and monitoring of babies >23 weeks, 24 hours after discontinuation of phototherapy, to minimize pain and blood loss in these vulnerable babies.

Keywords: Transcutaneous bilirubin (TcB); Preterm; Serum bilirubin (TSB); Neonatal jaundice

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Introduction

Neonatal Jaundice (NNJ) or hyperbilirubinemia is common in neonates. Incidence varies across the globe. Exclusive breastfeeding, race/ethnicity, and genetic factors that affect bilirubin production and metabolism play major role in the incidence. It is more prevalent in the east Asian population compared to Caucasians. Incidence can be as high as 60% to 70% of neonates with peak levels occurring around day 5 of life [1]. Rare complications include bilirubin induced neurologic disorder (BIND), acute bilirubin encephalopathy and chronic bilirubin encephalopathy (kernicterus). The incidence is proportional to the serum bilirubin levels. While these complications have decreased with the introduction of phototherapy and the use of Rh(D) immunoglobulin, early identification, and timely intervention of significant jaundice in neonatal period remain key in prevention of these

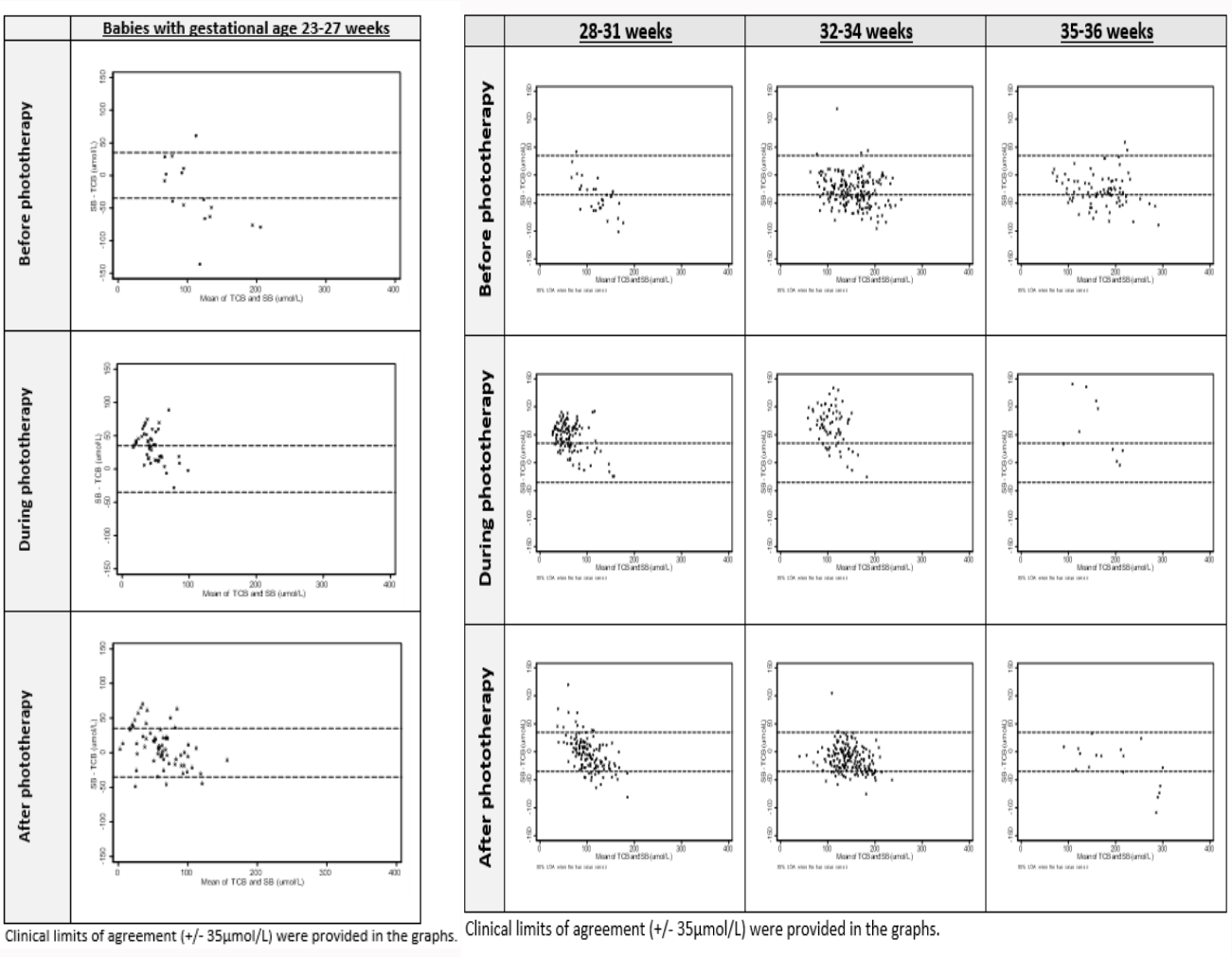

Figure 1: Bland-Altman plot comparing TcB and TSB before, during and after phototherapy, stratified by gestational age.

rare complications.

Universally, measurement of total serum bilirubin (TSB) is the gold standard method used to assess the severity of jaundice. The test involves a prick to obtain a capillary specimen of 0.2cc of blood. Transcutaneous bilirubin (TcB) has been shown to correlate with TSB in babies born at gestation of 35 weeks and more with r of 0.89, hence recommended and used in screening of jaundice in babies born more than or equal to 35 weeks' gestation within 14 days of life [4].

Transcutaneous bilirubinometry works based on optical spectroscopy principle and relates the optical absorption of bilirubin in the (sub)cutaneous tissue to its serum levels. A correlation between TcB and TSB of approximately r=0.8 has been obtained in studies involving preterm neonates [2,3]. Despite reports of good correlation between TcB and TSB in studies involving preterm neonates, its use is not widely practised. In Singapore, transcutaneous bilirubinometer is used among neonates with a birth gestational age of more than or equal to 35 weeks. Our study aims to evaluate the accuracy of TcB levels among all preterm neonates to extend its use to newborns less than 37 weeks gestation.

Methods

A prospective cohort study was conducted in the Department of Neonatal and Developmental Medicine of Singapore General Hospital from March 2020 to January 2022. Study was approved by the Institutional review board (IRB) (IRB 2020-2586). Written informed consent was sought from parents for this study. JM-105 TcB device [5] (Drager Medical Systems Inc., Telford, Philadelphia) was used to measure TcB. Measurements of the TcB on the sternum were obtained before, during and 24 hours after phototherapy in eligible preterm infants. Paired serum bilirubin levels were obtained for comparison (within 30 minutes of TcB measurement).

Inclusion criteria

All stable preterm infants of less than 37 weeks of gestation were included where parents have consented, TcB will be assayed when TSB is done.

Exclusion criteria

All unstable preterm infants (needing inotropic support, FiO2 requirement >50%), infants with skin hemangiomas/naevus or extensive bruising at the site of TcB measurement, early jaundice less than 24 hours of life or hyperbilirubinemia warranting an exchange transfusion were excluded.

Statistical analysis

Data was summarized using number (percentage) for categorical

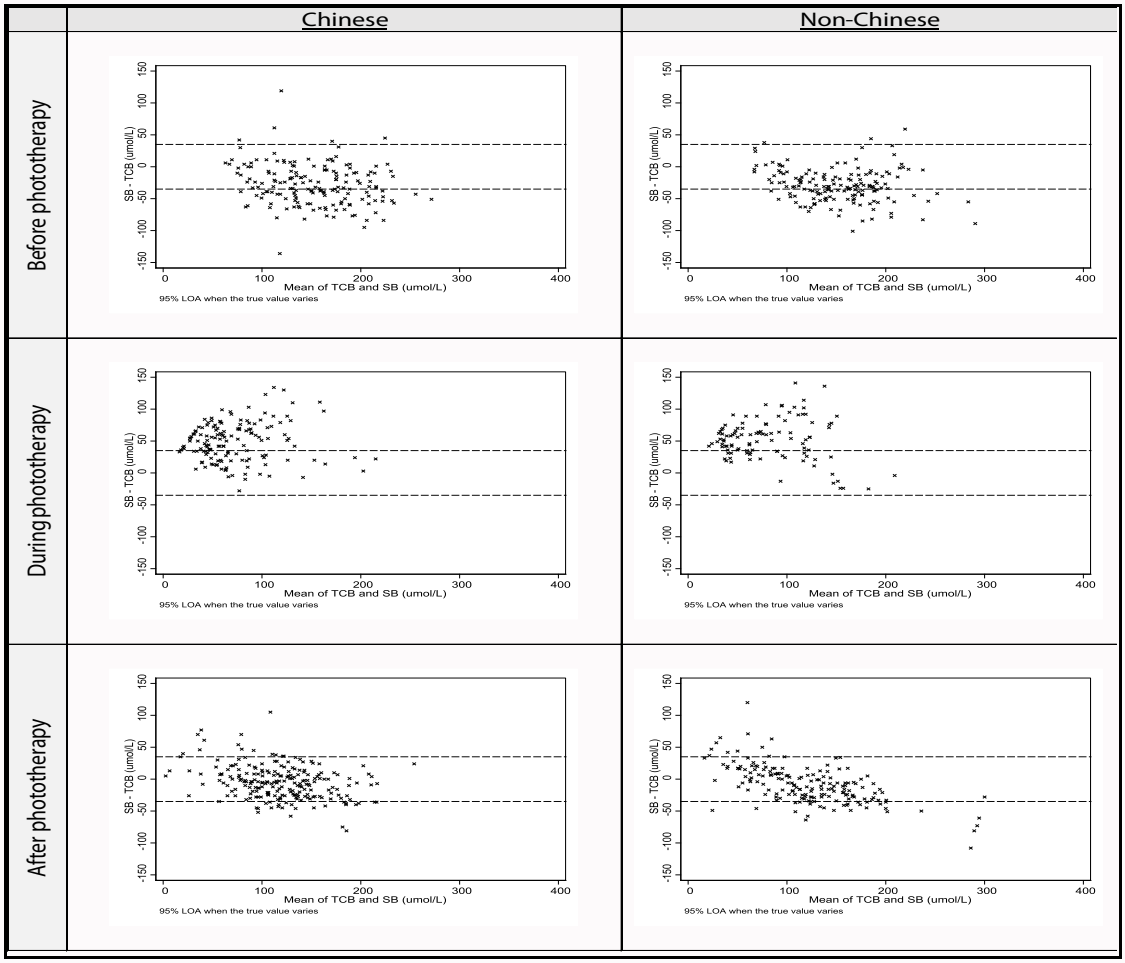

Figure 2: Bland-Altman plot comparing TcB and TSB before, during and after phototherapy, stratified by ethnicity.

variables, or median (range) for continuous variables. Bland–Altman was employed to consider within subject variability for multiple measurements before, during and after phototherapy. Mean differences with corresponding 95% limits of agreement (LOA) were calculated for babies stratified by gestational age and ethnicity. (Clinical limits of agreement of +/- 35µmol/L was taken as clinically acceptable. Receiver operating characteristics (ROC) analysis and area under the curves (AUC) were also calculated to determine the sensitivity of TcB. The TCB cut points were also determined with at least 90% sensitivity to detect a TSB of >100 µmol/L at 23–32 weeks' gestation and a TSB of >170 µmol/L at 33-35 weeks. Ethnicity plays a significant role in the development of jaundice in South Asia. Skin pigmentation could affect the correlation of TcB and TSB[7]. All analyses were performed on STATA 17 (Stata Corp 2021. Stata Statistical Software: Release 17. College Station, TX: Stata Corp LLC). P <0.05 is considered significant.

Results

The baseline characteristics of the four subgroups of preterm babies are as shown in Table 1. Racial distribution reflected Singaporean population with Chinese being the predominant race. Paired samples of TcB and TSB were obtained for all preterm babies less than 37 weeks gestation. Table 2 shows the mean difference between SB and TcB with the corresponding 95% limits of agreement (LOA) before, during and after phototherapy based on gestational age groups. The mean difference was minimal post phototherapy in all gestational age groups especially in the very preterm group. In the pre-phototherapy group acceptable mean difference was noted in the moderate to late preterm group. Mean difference was noted to increase during phototherapy in all gestational age groups. Table 3 shows the mean difference between TSB and TcB with the corresponding 95% limits of agreement (LOA) before, during and after phototherapy based on ethnicity. The mean difference between the TcB and TSB is minimal post phototherapy and within acceptable limits pre phototherapy. Mean difference increases during phototherapy in all ethnic groups. (Figures 1 and 2) depict the Bland- Altman correlation based on gestational age and ethnicity corroborating the findings in (Tables 2 and 3).

- Multiple reading was performed for the same patient.
- Readings were normally distributed, but median (range) presented for consistency.

Using the recommended cut-off TSB of >85 umol/L, in preterm infants born at 23+0-27+6 weeks' gestation sternum TcB had an AUC of 0.873 (95% CI: 0.796, 0.950). In these infants, a sternum TcB cut point of 74 µmol/L (based on Youden's index) had a sensitivity of 77.8% (95% CI: 70.7, 84.9), specificity 87.6% (95% CI: 82.0, 93.2), PPV 61.8% (95% CI: 53.5, 70.1), NPV 93.9% (95% CI: 89.8, 98.0), and respective positive and negative likelihood ratios of 6.28 (95% CI: 3.63, 10.9) and 0.25 (95% CI: 0.12, 0.52) to detect the recommended

Table 1: Baseline Characteristics.

Characteristics	GA 23+0-27+6 weeks (n = 21)	GA 28+0-31+6 weeks (n = 35)	GA 32+0-34+6 weeks (n=74)	GA 35+0-36+6 weeks(n=35)	p-value
Gender, n (%)					
Male	11 (52.4)	18 (51.4)	49 (66.2)	18 (51.4)	0.34
Female	10 (47.6)	17(48.6)	25 (33.8)	17 (48.6)	
Race, n (%)					
Chinese	13 (61.9)	17 (48.6)	38 (51.4)	18 (51.4)	0.97
Malays	2 (9.5)	7 (20)	16 (21.6)	9 (25.7)	
Indians	4 (19.1)	9 (25.7)	15 (20.3)	6 (17.1)	
Others	2 (9.5)	2 (5.7)	5 (6.8)	2 (5.7)	
Mode of delivery, n (%)					
Caesarean	6 (28.6)	27 (77.1)	16 (21.6)	4 (11.4)	0.23
Spontaneous	4 (19.1)	7 (20)	4 (5.4)	3 (8.6)	
Operative Vaginal	11 (52.4)	1 (2.9)	54 (73.0)	28 (80.0)	
Birthweight (g); median (range)	773(562, 1200)	1190(545, 1710)	1985(1195, 2640)	2365(1505, 3705)	0.0001
Multiple pregnancy, n (%)	6 (28.6)	6 (17.1)	29 (39.2)	6 (17.1)	0.04
No. of bilirubin readings taken n (%)[1]					<0.001
Before phototherapy	16 (12.1)	33 (11.3)	200 (44.2)	84 (75.7)	
During therapy	50 (37.9)	122 (41.6)	72 (15.9)	10 (9.0)	
After phototherapy	66 (50)	138 (47.1)	181 (40.0)	17 (15.3)	
Hours of life, median (range) @TcB & TSB sampling					
Before phototherapy	25 (16,384)	24(24,72)	60(15, 384)	57.5(12, 264)	0.0001
During phototherapy	160.5(16,384)	137.5(32,456)	114(8,336)	103(66, 240)	0.17
After phototherapy	252(64,528)	312(21,648)	240(74, 552)	216(114, 336)	0.0001
Transcutaneous bilirubin (TcB) umol/L; median (range)					
Before phototherapy[2]	107.5(53,245)	150(56,219)	166.5(58, 277)	190(64, 335)	0.0001
During phototherapy	24.5(0,99)	35(0,169)	73(10, 195)	108.5(38, 211)	0.0001
After phototherapy	57.5 (0,162)	102.5 (0,226)	148(44, 261)	(86, 340)	0.0001
Serum bilirubin (SB) (umol/L); median (range)					
Before phototherapy	93.5(50,166)	99 (55143)	141(52, 235)	157.5(69, 256)	0.0001
During phototherapy	61(33,114)	82.5(48,160)	139.5(93,195)	206(107, 226)	0.0001
After phototherapy	63 (0,151)	99.5(48, 167)	140(36, 213)	198(95, 286)	0.0001

Table 2: Mean difference between TSB and TcB based on gestational age groups.

Gestational Age (GA)	Before phototherapy	During phototherapy	After phototherapy
23+0-27+6 weeks	-28.8 (-128.3, 70.7)	34.6 (-12.8, 81.9)	8.1 (-46.8, 63.0)
28+0-31+6 weeks	-38.2(-99.0,22.7)	46.3(-4.2,96.9)	-3.2(-61.1,54.8)
32+0-34+6 weeks	-27.5(-81.0,26.0)	65.6(-0.9,132.1)	-12.5(-57.5,32.4)
35+0-36+6 weeks	-26.9(-83.0,29.3)	62.0 (-51.5,175.5)	-23.1(-104.4,58.2)

TSB threshold of >85 μmol/L.

Preterm infants born at 28+0-31+6 weeks' gestation using the recommended TSB cut point of >100 μmol/L, prior to phototherapy, sternum TcB had an AUC of 0.82 (95% CI: 0.77, 0.87). A sternum TcB cut point of 106 μmol/L (based on Youden's index) had a sensitivity of 64.5% (95% CI: 54.9, 73.4), specificity 86.3% (95% CI: 80.5, 91.0), PPV 74.0% (95% CI: 64.0, 82.4), NPV 80.2% (95% CI: 73.9, 85.5), and respective positive and negative likelihood ratios of 4.72 (95% CI: 3.20, 6.98) and 0.41 (95% CI: 0.32, 0.453 respectively to detect the recommended TSB threshold of >100 μmol/L among infants born at 28-31 weeks.

In preterm infants born at 32-36 weeks' gestation, using the recommended TSB cut point of >170 μmol/L, sternum TcB had an AUC of 0.85 (95% CI: 0.81, 0.90). A sternum TcB cut point of 185 μmol/L (based on Youden's index) had a sensitivity of 81.3% (95% CI: 73.7, 87.5), specificity 75.1% (95% CI: 70.7, 79.1), PPV 50.5% (95% CI: 43.6, 57.3), NPV 92.8% (95% CI: 89.6, 95.3), and respective positive and negative likelihood ratios of 3.27 (95% CI: 2.72, 3.93) and 0.25 (95% CI: 0.17, 0.36) to detect the recommended TSB threshold of >170 μmol/L among infants born at 32+6–36+6 weeks.

Table 3: Mean difference between TcB and TSB stratified based on ethnicity.

	Mean difference (SB-TCB) (95% Limits of agreement)		
Ethnicity	**Before phototherapy**	**During phototherapy**	**After phototherapy**
Chinese	-27.7 (-90.8, 35.4)	48.5 (-11.9, 108.9)	-4.7 (-56.6, 47.2)
Non-Chinese	-29.2 (-81.1, 22.6)	52.3 (-11.4, 116.0)	-8.4 (-67.0, 50.2)

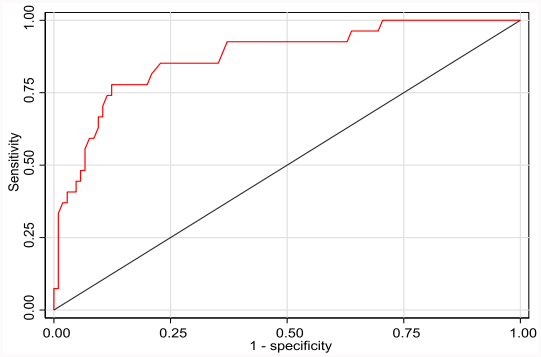

Figure 3: Receiver operating curves for TcB measured at the sternum at the recommended TSB threshold of >85 µmol/L at 23-27 weeks' gestation.

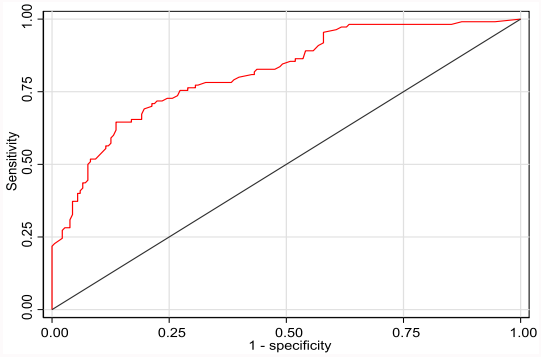

Figure 4: Receiver operating curves for TcB measured at the sternum at the recommended TSB threshold of >100 µmol/L at 28-31 weeks' gestation.

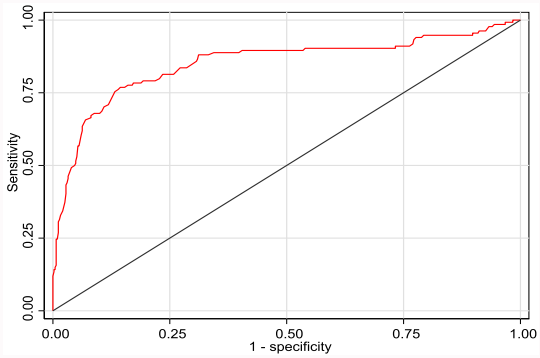

Figure 5: Receiver operating curves for TcB measured at the sternum at the recommended TSB threshold of >170 µmol/L at 32+0–36+6 weeks' gestation.

Discussion

Our study showed that the correlation between TcB and TSB is good in preterm babies with gestational age more than or equal to 23 weeks before and after phototherapy. This has been reflected in the results through various statistical analyses. The correlation coefficient of 0.84 for babies ≥23 weeks gestation prior to phototherapy resembles that of other studies in literature. Mor Cucuy et al. [2] reports a correlation coefficient of 0.777 in their cohort. Hassan Shabuj et al. [3] reports a correlation coefficient (CC) of 0.82 between TcB and TSB in their meta-analysis of 28 studies in preterm infants irrespective of the equipment used or the site of performing the measurement. Hence, we did not compare different sites or use other equipment.

Our study corroborates that the correlation between TcB and TSB is re-established post phototherapy which is shown by the good correlation across various preterm subgroups studied. Though the correlation is affected during phototherapy especially in the exposed areas, it improves within 24 hours after discontinuation of phototherapy [8]. Maya-Enero et al. [9] showed that skin tone did not affect the correlation between TcB and TSB, though in babies with darker skin tones TcB could overestimate TSB [10]. Correlation between TcB and TSB was reliable in both pre and post phototherapy cohorts irrespective of the race/ethnicity in our study.

In our study, the correlation between TcB and TSB was suboptimal in the 'during phototherapy' group irrespective of gestational age or ethnicity/race. Similar observations were reported in study by Nagar et al. [11] with r of 0.65 in areas of the body exposed to phototherapy and r of 0.71 in areas of body not exposed to phototherapy.

Some of our limitations include small number of extreme preterm babies. We also did not analyse subgroups based on birthweight or risk factors like haemolytic conditions, intraventricular haemorrhage, or conditions like delayed cord/cord milking that may contribute to neonatal jaundice. Ethnicity may not be indicative of skin tone; hence skin pigmentation may be determined to better define skin tone. However, this was not included in our study. Correlation between TcB and TSB in the covered areas were not evaluated in our study as effort was made to optimise the exposure to phototherapy in all babies requiring phototherapy.

Conclusions

Transcutaneous Bilirubinometer (TcB) use can be extended to monitor preterm babies >23 weeks, 24 hours after discontinuation of phototherapy. TcB can serve as a tool for screening and monitoring of jaundice pre and post phototherapy in babies >23 weeks. This would minimize the pain and invasive blood taking for the vulnerable preterm babies.

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