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Can we Rely on Transcutaneous Bilirbinometry during Phototherapy?

By Dr. Pearl Mary Varughese

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Objective: To study the correlation between Transcutaneous bilirubinometer (TcB) values with serum bilirubin levels (TSB) in infants during phototherapy in term and late preterm babies.

Materials and Methods: The study was conducted in a tertiary new-born center from November 2014 to June 2016. The inclusion criteria included all babies above 34 weeks gestation and exclusion criteria included babies with established direct hyperbilirubinemia, neonatal septicemia, major congenital/ gastrointestinal malformations, and those on phototherapy.

Keywords: *serum bilirubin, transcutaneous bilirubin, phototherapy, jaundice, rebound bilirubin, newborns.*

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Abstract- *Background:* Neonatal jaundiceis one of the main reasons for prolonged hospitalization in newborns, and its progress and treatment depends on serum bilirubin values. Phototherapy remains the mainstay of treatment of pathological jaundice in newborn babies. Though, transcutaneous bilirubinometer has been used as a screening device for measuring bilirubin, its role during phototherapy has always been questioned.

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Materials and Methods: The study was conducted in a tertiary new-born center from November 2014 to June 2016. The inclusion criteria included all babies above 34 weeks gestation and exclusion criteria included babies with established direct hyperbilirubinemia, neonatal septicemia, major congenital/ gastrointestinal malformations, and those on phototherapy. The sample size was 550, and after taking into consideration the inclusion and exclusion criteria, 450 babies were recruited. TSB and TcB were taken at 24 hours of age in all babies. A photo-opaque patch was placed on the sternum. Transcutaneous bilirubin was measured both in covered and uncovered (forehead) regions, and simultaneous serum bilirubin is taken. The correlation was measured for TSB and TcB- exposed (TCB-E) and covered regions (TCB-C), in 54 babies who required phototherapy. Statistical analysis was done using Spearman's correlation, ROC curves and Bland Altman plots.

Results: TcB and TSB showed good correlation (0.948) at 24 hrs of age before initiation of phototherapy but with a poor agreement (mean difference overestimating by 1.5mg/dl). The correlation was better for TcBE and TSB within 24 hours of phototherapy, and as the duration increased, the correlation for TcBC was better than TCBE and serum bilirubin. Bland Altmann shows good agreement too.

Conclusion: During phototherapy, transcutaneous bilirubinometry can estimate bilirubin better in covered regions when compared to exposed regions.

Keywords: serum bilirubin, transcutaneous bilirubin, phototherapy, jaundice, rebound bilirubin, newborns.

I. Introduction

Neonatal jaundice or hyperbilirubinemia is observed during the first week of life in approximately 60% of term and 80% of preterm infants(1). Neonatal hyperbilirubinemia occurs when there is an imbalance between the production and elimination of bilirubin, a breakdown product of hemoglobin. Kernicterus, which is due to severe hyperbilirubinemia, is the most easily preventable cause of neonatal mortality and brain death. With the increasing demand for a shorter length of hospital stay for babies after delivery, there is an increased risk of unrecognized or delayed hyperbilirubinemia resulting in an increased incidence of babies affected with kernicterus(2)

The problem of finding an accurate and specific method of bilirubin assay has for 50 years occupied the attention of many workers. In the early days, jaundice was assessed by the clinical evaluation of the babies. The conventional method of measuring serum bilirubin requires repeated blood sampling, which causes undue pain to the babies and emotional stress to the parents(3).Over the last three decades, transcutaneous bilirubinometry has emerged as a safe, simple, cost-effective non- invasive modality in the screening and monitoring of jaundiced newborns(4),(5). But its clinical utility is limited to a screening method rather than a replacement for invasive blood sampling.

Phototherapy has been widely used in pathological jaundice to reduce bilirubin levels. During phototherapy, frequent blood sampling is necessary to measure infants' bilirubin levels and to assess treatment efficacy to manage hyperbilirubinemia adequately (6). The usefulness of transcutaneous bilirubinometer (TcB) measurements during phototherapy in South Indian new-borns remain unclear. This study is being done to find out the correlation of transcutaneous bilirubinometer index (TcBI) with serum bilirubin levels in term and late preterm neonates during phototherapy and to study the reliability of TcBI during phototherapy in exposed and unexposed regions.

II. Methods

Study Population: This was a prospective observational study on inborn babies more than 34 weeks gestational age, from November 2014 to June 2016 in a neonatal unit of a medical college hospital in South India. The exclusion criteria included babies with established direct hyperbilirubinemia, neonatal septicemia, major congenital/ gastrointestinal malformations, and those started on phototherapy.

The sample size was calculated using the formula:

$$n = \frac{Z^2 * \{p(1-p)\}}{d^2}$$

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Z^2=1.96 at 95% confidence interval

P= proportion of infants with hyperbilirubinemia = 20%, d= error margin or precision=4%

The minimum sample required was 385. In the present study, 450 samples were collected. The study protocol was approved by the institutional review board and ethics committee. Written informed consent was obtained from the mothers for using their baby's de-identified data. Confidentiality was maintained throughout the study. The clinical and dimorphic profile of the mother and the baby was collected using a proforma.

Transcutaneous bilirubin levels (TcB) were estimated with Drager Jaundice Meter JM-105 by placing the instrument on the baby's sternum. The sternum was taken as the principal site of measurement, as several studies have shown excellent correlation with TSB compared to the other sites(7)(8). An average of three readings was taken as the TcB value. After each baby, the probe was cleaned with sterile gauze before using it for the next baby.

Approximately 1 ml of venous blood was collected in a microtainer clot activator tube for assessing total serum bilirubin (TSB) level under strict aseptic precautions after the mother was explained about the procedure. Serum bilirubin measurements were measured using the Diazo method (modified Jendrassik-Grof method) in the automated analyzer Cobas Integra 400 plus from Roche Diagnostics. The maximum interval of time between the transcutaneous measurement and the collection of blood for total serum bilirubin was 30 minutes.

A disposable temperature probe cover (Phoenix Medical Systems Ltd) was used as the phototherapy patch on the sternum of the babies. The patch was secured to the skin using liquid adhesive present on the inner surface and would remain in place till the end of phototherapy. The patch measures 32mm in diameter with a thickness of 2mm. (Figure 3)

All babies were visually examined every 6 hours on the first day of life by a trained physician and twice a day after that. At 24 hours TSB and TcB were done on all babies and later repeated as per attending clinician's discretion. If phototherapy is required, the babies were started on phototherapy after informed consent was obtained, and AAP guidelines were followed(9). Phototherapy lights used were the standard CFL 101 model (Phoenix Ltd) consisting of six CFL lights providing blue light at -30 $\mu W/cm^2/nm$ with an intensity of up to 40μW.A pre-set height of 45cm from the bed was made for the phototherapy lights. The eyes and genitalia of the babies would be covered before starting phototherapy. Phototherapy units are maintained and used according to manufacturer guideline. The phototherapy patch would be placed on the sternum, and the transcutaneous bilirubin measurements are taken from both the covered regions (area under the patch) and the exposed regions (the forehead of the baby). (Figure 4 and 5)

Four hours after the starting of phototherapy, the blood samples were taken for hemolytic work up according to the Department protocol. The phototherapy light would be switched off before the blood samples were taken. During phototherapy, whenever the blood sample was taken for bilirubin values, simultaneously the TcBI-E and TcBI-C measurements were also taken.

Data were entered in Microsoft Excel and analyzed using the SPSS version 20.0 for Windows software. Pearson's correlation and Bland Altman analysis were used for studying the data.

III. Results

The total number of babies delivered at the Pondicherry Institute of Medical Sciences during the study period (November 2014- April 2016) was 1950. 567 babies were recruited, and after taking into consideration the inclusion and the exclusion criteria, 450 babies were included considering be the incidence of hyperbilirubinemia to 20%. Of this, only 54 babies developed hyperbilirubinemia. (Figure 1)

The mean serum bilirubin of the entire cohort before phototherapy was 6.2 ± 1.4mg/dl, and the simultaneous mean TcB value was 7.7 ± 1.4mg/dl. In the 54 babies with significant hyperbilirubinemia, 23 babies (42.6%) were males, and 31 babies (57.4%) were females. In the 54 babies with significant hyperbilirubinemia, 10 babies (18.5%) were late preterm babies, and 42 babies (77.8%) were from 37-39 ^{6} weeks of gestation. Only 2(3.7%) babies were post-dated who developed significant hyperbilirubinemia.

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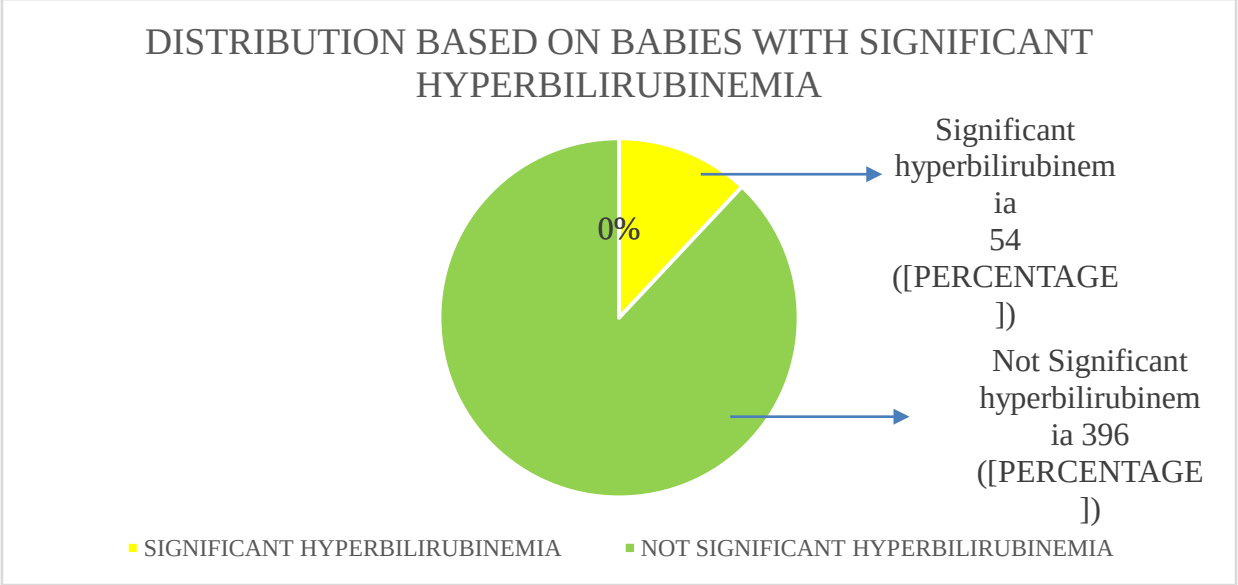


Figure 1: Distribution Based on Babies with Significant Hyperbilirubinemia

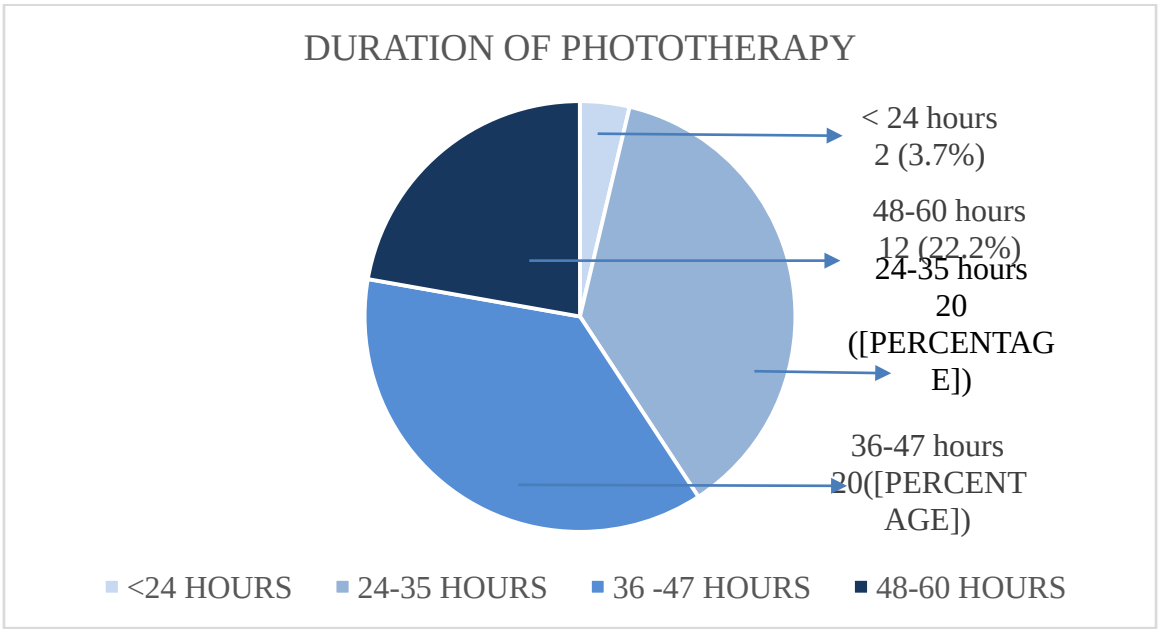


Figure 2: Distribution of Babies Based on Duration of Phototherapy

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Figure 3: Placing the patch on the sternum before phototherapy



Figure 4: Measuring TcBI C at the sternum after the patch is removed



Figure 5: Measuring TcBI E (Exposed) at the forehead of the baby

Table 1: Correlation of Tcbie (Exposed) and Tcbic (Covered) with Tsb at Different Time Intervals after Starting Phototherapy

Time		Number (%)	Correlation Co-efficient	Value
4 hours	TcBI-E (EXPOSED) WITH TSB	54 (100)	0.931	<0.001
	TcBI-C (COVERED) WITH TSB		0.886	
8-12 hours	TcBI-E (EXPOSED) WITH TSB	22 (100)	0.932	
	TcBI-C (COVERED) WITH TSB		0.885	
13- 24 hours	TcBI-E (EXPOSED) WITH TSB	39 (100)	0.980	
	TcBI-C (COVERED) WITH TSB		0.957	
25-36 hours	TcBI-E (EXPOSED) WITH TSB	6 (100)	0.829	
	TcBI-C (COVERED) WITH TSB		0.869	

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As shown in Figure 6, after 4 hours of starting phototherapy TcBI levels in both the covered and exposed regions showed good correlation with TSB (r= 0.931 and r= 0.886 respectively). After 8-12 hours of starting phototherapy, 22 babies were evaluated. The remaining 32 babies had lower risk, or the slower rise of bilirubin levels, so were pricked at a later time interval. There was a better correlation with serum bilirubin in exposed regions than covered regions within 12 hours of starting phototherapy with r= 0.932 and r= 0.885, respectively. As the duration of phototherapy increases, there was a significant correlation of TcB with TSB in both the exposed and covered regions (r = 0.980 in exposed regions and r= 0. 957 in covered regions). After 24 hours of starting phototherapy, though there is a significant correlation for both, the correlation was better in the covered regions (r = 0.829 in exposed regions and r= 0. 869 in covered regions). Further correlations as the duration of the phototherapy increases could not be done as there were very few cases.

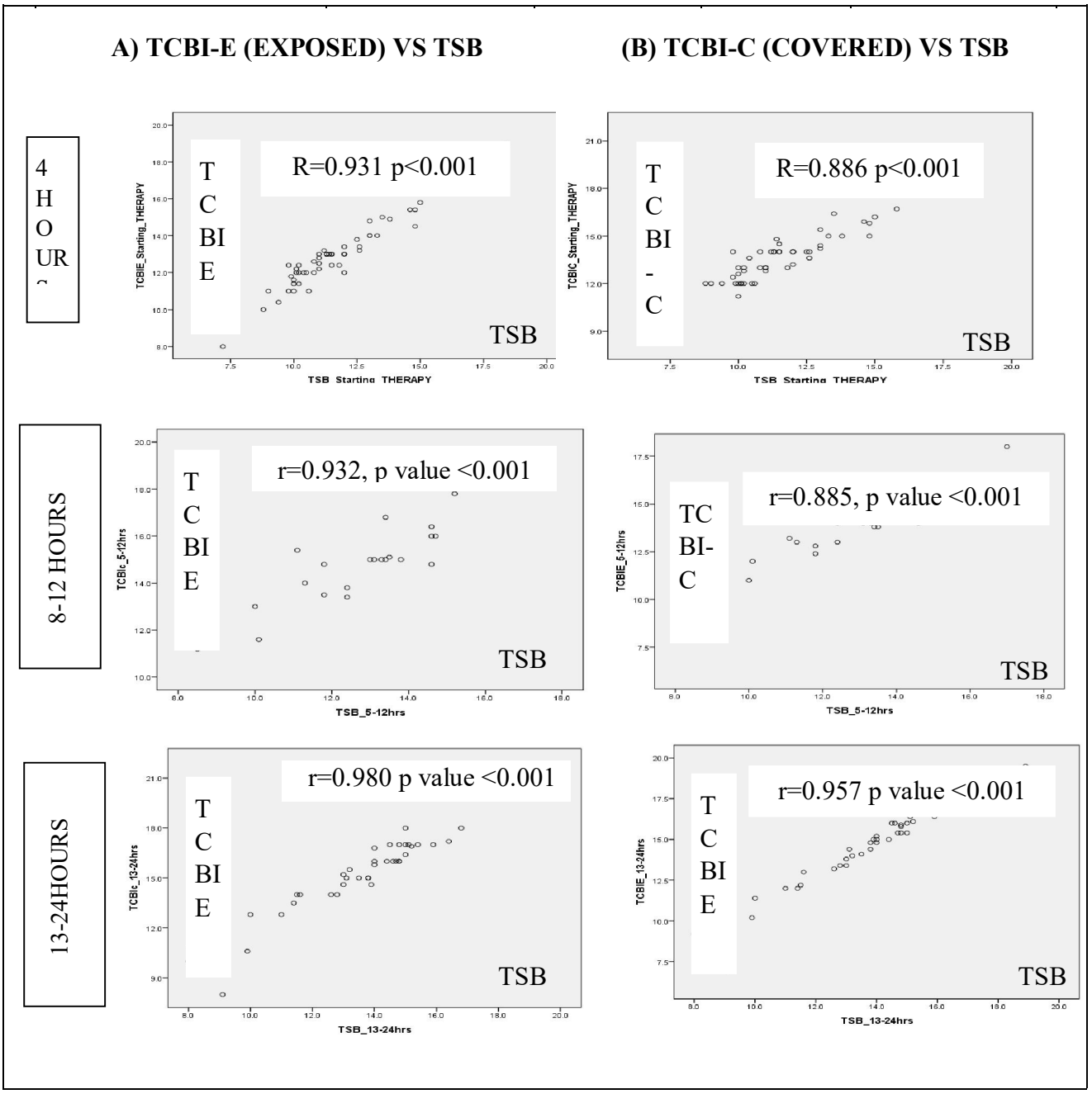


Figure 6: Graphs Showing Correlation of Tcbie and Tcbic with Tsb at Different Time Intervals during Phototherapy

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Table 2: Statistical Analysis According to the Bland Altman Plot for the Babies Who Had Significant Hyperbilirubinemia

TIME	VARIABLES	NUMBER (N)	MEAN (MG/DL)	STANDARD DEVIATION
4 hours after starting phototherapy	TcBI C with TSB	54	2.1	1.9
	TcBI E with TSB	54	1.3	0.6
13-24 hours after starting phototherapy	TcBI C with TSB	39	1.6	0.7
	TcBI E with TSB	39	0.7	0.6

As shown in table 2, 4 hours after starting phototherapy, the TcBIover- estimates TSB by 2.1 ± 1.9mg/dl in covered regions and by 1.3 ± 0.6mg/dl in exposed regions. Within 13-24 hours after starting phototherapy, the TcBI over- estimates TSB by1.6 ± 0.7mg/dl in covered regions and only by 0.7 ± 0.6mg/dl in exposed regions.

IV. Discussion

Transcutaneous bilirubinometry has been extensively used as a substitute for serum bilirubin as it is reliable, safe, quick, and cost- effective. But when the babies are subject to phototherapy, serum bilirubin continues to be the ideal choice of many pediatricians for assessing the progression of jaundice. There have been conflicting ideas when the correlation of transcutaneous bilirubin and serum bilirubin during phototherapy has been discussed with differing characteristics like the site of assessment, covered and exposed regions, type of lights, and type (continuous or intermittent) of phototherapy. With the initiation of phototherapy, a rapid decrement in dermal bilirubinis caused by photoisomerization ofalbumin-bound bilirubin in interstitial places and subcutaneous capillaries intolumirubin and other photo isomers (10). Studies have shown that the rate of decrease of dermal bilirubin as measured by TcBI is non – linear concerning the duration of phototherapy. Serum bilirubin shows an exponential decline that is independent of the logarithm of light dose. Skin bilirubin decreases more than the plasma bilirubin causing the bilirubin gradient between the two. The possible rationale behind the difference in shielded and exposed regions could be that TcB in exposed regions underestimates bilirubin levels owing to bleaching with phototherapy while dermal bilirubin at the shielded site, doe not participate in the phototherapy induced conversion of bilirubinto its photo isomers as much as the exposed skin (11). Vogl et al. using Gosset's icterometer, showed that light does not bleach the covered skin, and a clear demarcation exists between bleached and icteric skin(12).

With the forehead being covered, Zecca et al. concluded that transcutaneous bilirubin measurement of covered skin could be a reliable method for use during phototherapy, reducing blood sampling(13). Mitra Radfaretal. too proved that post-phototherapy correlation was 0.92 among term and 0.887 among preterm neonates in patched area (forehead), while it was 0.666 among term and 0.756 among preterm neonates post-phototherapy in unpatched areas(14). Most of the studies show that the covered regions had a better correlation to serum bilirubin values during phototherapy compared to the exposed regions in both term and preterm babies(15) (16) (17) (18).But a systemic review conducted showed that there was no statistically significant difference in the pooled estimates of the correlation coefficients in the covered regions and the exposed regions (r= 0.71 and 0.65 respectively)(19). But these results were conflicting to the results obtained by a few authors who proved that TcB could not be used as a surrogate measure of TSB once phototherapy has started (20). Murli et al. did notfind agreement between TcB and TSB in 34- 41week gestation neonates receiving phototherapy (21). Fok et al. and Tudehope et al. reported a lower correlation between TcB and TSB both in the exposed and unexposed areas of the skin of the forehead in term neonates receiving phototherapy (22) (23).

In our study though there is a statistically significant difference, the correlation is found to be better in exposed regions in the first 24 hours, and after 24 hours, the correlation not only decreased but is found to be better in covered regions than exposed.

This study was the first of its kind to be done in the South Indian population. Most of the studies showed correlation coefficients, but we have used both correlation coefficients and Bland Altman plots. Bland Altman plots do not depend on treatment thresholds and are more useful than correlations in clinical practice. But there were a few limitations in our study. Firstly, it is not a population-based study, and it represents the data of a single tertiary care hospital in South India. The sample size was small compared to other studies.

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Lastly, further correlations as the duration of the phototherapy increases (after 36 hours) could not be done as there was very few cases.

V. Conclusion

Significant correlations exists between TcB and serum bilirubin levels in both the exposed and covered group. But the exposed group is overestimating the bilirubin level at different points of time more than that of the covered group. Hence the TCB prediction of bilirubin is better in covered areas when compared to exposed areas after 24 hours of starting phototherapy.

Conflict of Interest: There was no conflict of interest.

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