Reducing the "ouch" after phototherapy in neonates!! – A prospective observational study to prove the correlation of transcutaneous and serum bilirubin after cessation of phototherapy

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ABSTRACT

Background: Neonates receiving phototherapy (PT) for neonatal hyperbilirubinemia are often discharged late and multiple blood samples are taken during and after discontinuation of PT. Clinicians often have reservations in replacing total serum bilirubin (TSB) with transcutaneous bilirubinometer (TcB). **Objective:** The objective of the study was to study the correlation between TcB values with TSB in infants before PT and during rebound bilirubin assessment in term and late preterm babies. **Materials and Methods:** The study was conducted in a tertiary newborn center from November 2014 to June 2016. The babies above 34 weeks gestation period significant hyperbilirubinemia were included in the study and exclusion criteria included babies with established direct hyperbilirubinemia, neonatal septicemia, major congenital/gastrointestinal malformations, and those on PT. TSB and TcB were taken at 24 h of age in all babies and rebound values, both TSB and TcB, in 54 babies who required PT. Statistical analysis was done using Spearman's correlation and Bland Altman plots. **Results:** TcB and TSB showed good correlation (Spearman R=0.917) at 24 h of age before initiation of PT but with poor agreement (mean difference overestimating by 1.5 mg/dl). The correlation of TcB and TSB at the time of rebound estimation was 0.994 with good agreement (mean difference overestimating by 0.6 mg/dl). **Conclusion:** Pediatricians should take steps in reducing "ouch" for rebound bilirubin.

Key words: *Jaundice, Phototherapy, Rebound bilirubin, Serum bilirubin, Transcutaneous bilirubin*

Neonatal hyperbilirubinemia is a matter of concern for pediatricians worldwide. There is an unusual delay in the baby's discharge with extra blood sampling to check the bilirubin levels at frequent time intervals. This adds to the concern and worry of the parents too [1]. Although transcutaneous bilirubinometer (TcB) measures the bilirubin levels in a safe, cost effective, and less invasive manner, there is uncertainty about replacing TcB with total serum bilirubin (TSB) [2,3].

Phototherapy (PT) has been widely used in pathological jaundice to reduce the bilirubin levels. Due to this, frequent blood sampling is carried out to check for reduction in bilirubin values. Once PT is stopped, sampling of rebound bilirubin is required. Most of the times, the parents are reluctant for further sampling, and hence, the baby's condition or severity of jaundice cannot be reassessed, thus worsening the scenario.

The correlations between TcB and TSB have been researched and studied extensively. Studies have shown poor correlation during PT, but there are few studies that show the correlation before and after PT. The objective of the study is to find the correlation between TcB values with TSB in infants before PT and during rebound bilirubin assessment in term and late preterm babies.

MATERIALS AND METHODS

This was a prospective observational study from November 2014 to June 2016 in a neonatal unit of a medical college hospital in South India. Inborn babies more than 34 weeks gestational age and having neonatal hyperbilirubinemia (NNH) were included in the study. Babies with established direct hyperbilirubinemia, neonatal septicemia, major congenital/gastrointestinal malformations, and those who were already on PT were excluded from the study. Based on a study conducted by Chakrabarti, correlation between transcultanoeus bilirubinometry and TSB after PT was r=0.3959 [4].

Sample size was calculated using the formula:

$$N = [\frac{(Z\alpha + Z\beta)}{C(r)}]^2 + 3$$

$$C(r) = \tfrac{1}{2} \ln [\frac{1+r}{1-r}]$$ r=correlation coefficient=0.3959

Zα=1.96 at 95% C.I., Zβ=0.84 at 80% power

Minimum sample size needed, n=48.

In the present study, 54 samples were collected. The study protocol was approved by the institutional review board and

ethics committee. Written informed consent was obtained from the parents. The clinical and dimorphic profile of the mother and the baby was collected using a pro forma.

TcB was estimated with Drager Jaundice Meter JM-105 by placing the instrument on the baby's sternum. Sternum was taken as the principal site of measurement as several studies have shown excellent correlation with TcB compared to the other sites [5,6]. An average of three readings was taken as the TcB value. After each baby, the probe was cleaned with a sterile gauze before using for the next baby.

After the mother was explained about the procedure, 1 ml of venous blood was collected in a Microtainer clot activator tube for assessing TSB level under strict aseptic precautions after the mother was explained about the procedure. The blood samples were taken to the hospital laboratory within an hour to prevent degradation and processed. Serum bilirubin measurements were done 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 TSB was 30 min.

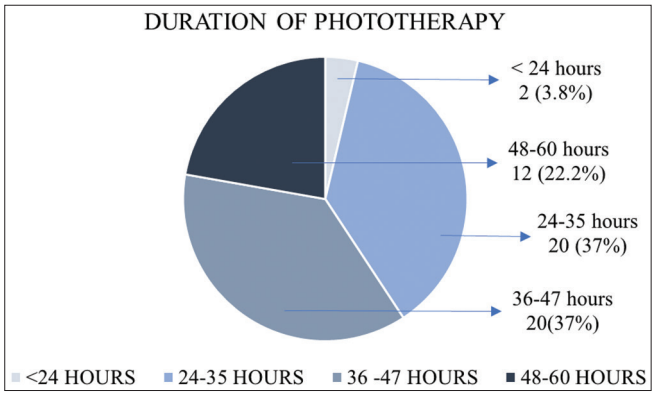

Figure 1: Distribution of cases as per the duration of phototherapy

All babies were visually examined every 6 hours on the 1st day of life by a trained physician and twice a day thereafter. At 24 h, TSB and TcB were done for all babies. If PT was required, it was started according to the AAP guidelines [7]. PT lights used were the standard CFL 101 model (Phoenix Ltd) consisting of six CFL lights providing blue light at −30 μW/cm²/nm with an intensity of up to 40 μW. A pre-set height of 45 cm from the bed was made for the PT lights. The eyes and genitalia of the babies were covered before starting the procedure. PT units were maintained and used according to the manufacturer's guidelines. Rebound TcB and TSB were taken for all babies, 12 h after stopping PT.

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

RESULTS

Of 1950 babies delivered in our hospital during the study period, 396 babies had non-significant hyperbilirubinemia and 54 babies had significant hyperbilirubinemia and these were recruited in the study after considering the inclusion and exclusion criteria. Out of these, 23 (42.6%) were male and 31 (57.4%) were female. A total of 10 babies (18.5%) were late preterm and 42 (77.8%) were from 37 to 39 weeks of gestation. Only 2 (3.7%) post-dated babies developed significant hyperbilirubinemia. Before starting PT, the mean TSB was 8.41±1.23 mg/dl and mean TcB was 9.93±1.43 mg/dl. After PT, the mean TSB was 14.95±3.48 mg/dl and mean TcB was 15.58±3.57 mg/dl. The duration of phototherapy for all cases are shown in Figure 1, 52 babies received more than 24 h of phototherapy.

Rebound bilirubin was done in all infants receiving PT 8–12 h after discontinuation. The agreement between TcB and TSB was done using Bland–Altman plots. It showed excellent agreement for after phototherapy values (Rebound) with TcBI overestimates

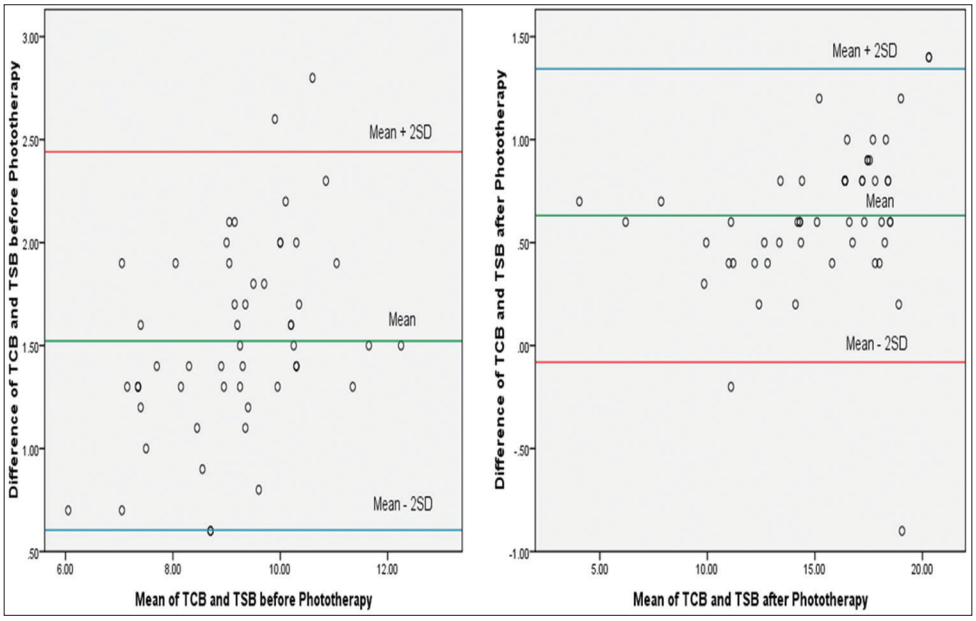

Figure 2: Bland–Altman plot showing agreement between total serum bilirubin and transcutaneous bilirubinometer before and after phototherapy in the study population

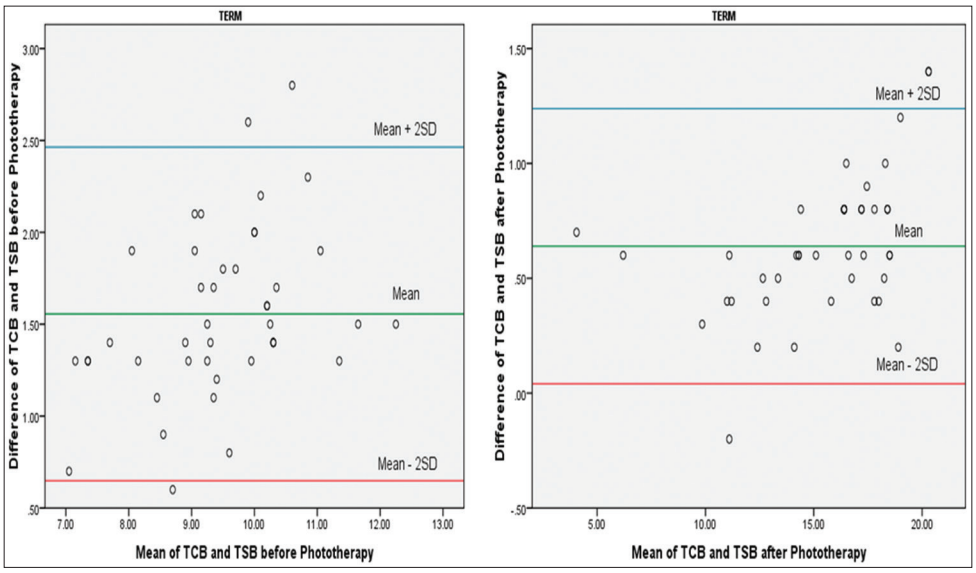

Figure 3: Bland–Altman plot showing agreement, in term babies, between total serum bilirubin and transcutaneous bilirubinometer before and after phototherapy

Table 1: TSB and TCB levels before and after PT

Study population	Time	Bilirubin levels (mg/dl) Mean+SD			p-value
		TcB	TSB	TcB-TSB	
Entire Cohort (n=54)	Before PT	9.9 (±1.4)	8.4 (±1.2)	1.5 (±0.5)	<0.001
	After PT	15.6 (±3.6)	14.9 (±3.5)	0.6 (±0.4)	<0.001
Term babies (n=43)	Before PT	10.2 (±1.3)	8.7 (±1.1)	1.6 (±0.5)	<0.001
	After PT	15.7 (±3.6)	15.1 (±3.5)	0.6 (±0.3)	<0.001
Preterm babies (n=11)	Before PT	8.7 (±1.3)	7.3 (±1.1)	1.4 (±0.5)	<0.001
	After PT	15.1 (±3.6)	14.5 (±3.7)	0.6 (±0.6)	0.005

TSB: Total serum bilirubin, TcB: Transcutaneous bilirubinometer

only 0.6mg/dl above the mean, when compared to before phototherapy with 1.5mg/dl, as shown in Figure 2. This means that the rebound TcB can be used instead of TSB. This not only reduces the hospital stay but also unnecessary blood sampling in these babies for rebound values.

In term and preterm babies, there was over estimation by 1.5mg/dl before phototherapy and just 0.6mg/dl after stopping phototherapy as shown in Figures 3 and 4.

As shown in Figure 5, before phototherapy, the spearman correlation coefficients for the entire cohort, term and preterm babies were R= 0.917, 0.891 and 0.876. Once phototherapy was stopped, the correlation coefficients improved to R= 0.994, 0.994 and 1.0 respectively.

Table 1 shows that after PT, the difference between TSB and TcB remained higher compared to before PT for all the babies, irrespective of gestational age.

DISCUSSION

Transcutaneous bilirubinometry has been extensively used as a substitute for serum bilirubin as it is reliable, safe, quick, and cost effective. However, when the babies are subjected to PT, TSB still continues to be the ideal choice of many pediatricians for assessing the progression of jaundice. There have been conflicting ideas when their correlation is discussed with differing basic characteristics such as site of assessment, covered and exposed regions, type of lights, and type (continuous or intermittent) of PT. With the initiation of PT, a rapid decrement in dermal bilirubin is caused by photoisomerization of albumin-bound bilirubin in interstitial places and subcutaneous capillaries into lumirubin and other photoisomers [8]. Studies have shown that the rate of decrease of dermal bilirubin as measured by TcB is non-linear with respect to the duration of PT. TSB 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.

There have been studies showing the poor correlation between the two during the PT. However, once it is stopped, the correlation seems to improve as the bleaching effect is also reduced and hence overtime, the skin color returns to normal. There have been very few studies proving that post-PT, the correlation improves. In a meta-analysis, the correlation between TcB and TSB readings improved marginally following discontinuation of PT (r = 0.72, 95% CI 0.64–0.78) [9]. Tan and Dong noted further improvement in the correlation coefficients on the 2nd day after PT as compared to the first reading taken 18–24 h after discontinuation of PT [10].

In another study, though TcB underestimated TSB within the first 8 h after cessation of PT, thereafter, the difference returned

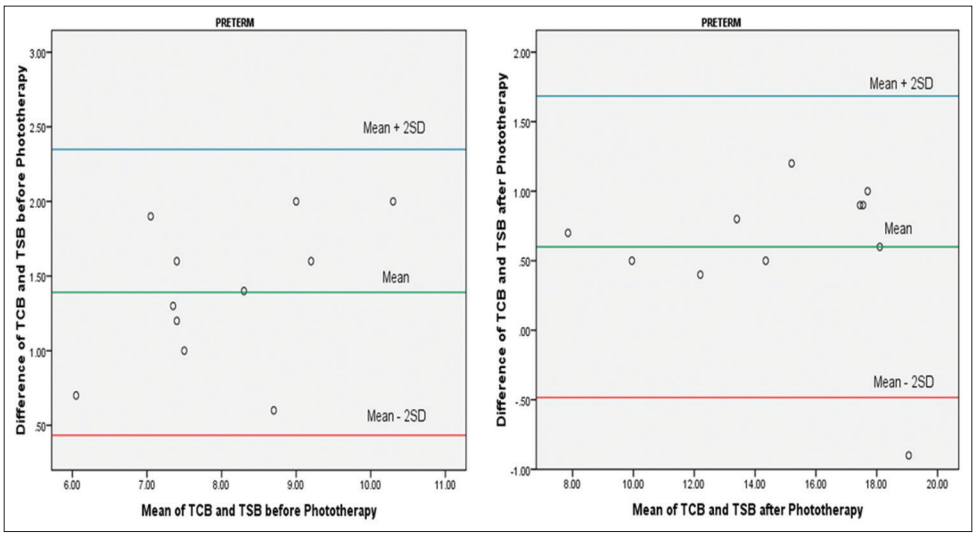

Figure 4: Bland–Altman plot showing agreement, in preterm babies, between total serum bilirubin and transcutaneous bilirubinometer before and after phototherapy

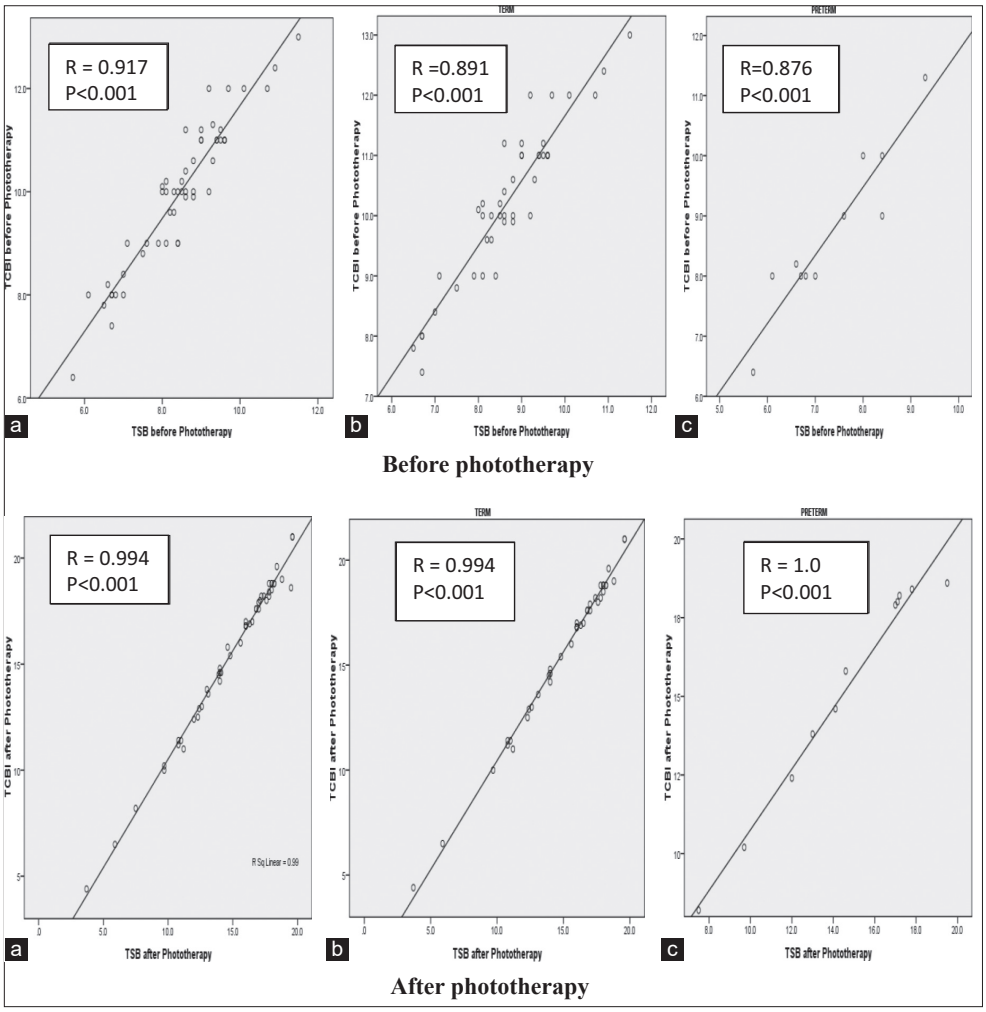

Figure 5: Graphs showing the Spearman correlation for the entire study population, term and preterm babies after phototherapy. (a) Entire cohort, (b) term babies, (c) preterm babies

to pre-treatment levels and thus 43% of post-PT punctures could have been avoided [11]. Juster-Reicher *et al*. showed that the correlation was low during the first 8h after PT (r=0.56), but thereafter the correlation returned to the range of 0.65–0.8 [12]. A study in preterm babies of 30–34 weeks gestation also showed a strong correlation between TcB and TSB measurements post-therapy (r=0.869, p<0.001) [13]. Nagar and Kumar showed that in post-PT phase, correlation coefficients improved significantly and were equivalent to the estimates before starting PT (r=0.88 at forehead and 0.87 at sternum) [14]. This study showed that once

PT was stopped, the correlation between TSB and TcB remained significant (r=0.990). All the rebound bilirubin values were taken at the end of 12 h of stopping PT. Thus, the blood samples post-PT could be reduced and even the duration of hospital stay.

The time duration at which correlation was higher between TcB and TSB, has always been a challenging conflict between many pediatricians. There was one prospective study by Casnocha Lucanova *et al*. that proved that 2 h post-PT, the correlation between TSB and TcB was poor. They attributed the reason for this early sampling due to early discharge of the babies [15]. On the other hand, Hulzebos *et al*. proved that the length of time after stopping PT did not appear to have a statistically significant effect on the mean differences between TSB and TcB [16]. Most of the above studies that prove correlation showed excellent correlation after 8 h of cessation of PT [10-12]. Our study showed a correlation at 12 h after PT was stopped.

This study was the first of its kind to be done in the South Indian population. However, it has some limitations too. First, it is not a population-based study and it represents the data of a single tertiary care hospital in South India. Small number of preterms in our study precludes any meaningful assessment in this subgroup, and larger studies in preterms of various maturity and nutritional states are, therefore, needed. We also studied only the correlation after 12 h of PT, but we did not follow these patients after 12 h post-PT to further study the correlation.

CONCLUSION

This study proves that post-PT, the correlation between TSB and TcB is excellent in both term and preterm babies, making TcB a much ideal choice for pediatricians all over the world. This not only reduces the duration and cost of stay of hospitalization of babies but also excess blood sampling post-PT. More studies with a bigger sample size are required.

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