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Research Article

A CORRELATION STUDY BETWEEN TRANSCUTANEOUS BILIRUBIN AND TOTAL SERUM BILIRUBIN LEVELS AMONG NEONATES

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ABSTRACT

Objective: The availability of modern bilirubin meters that measure bilirubin concentration in dermal and subcutaneous tissues has made it possible to obtain serial, non-invasive (i.e., painless) TcB (transcutaneous bilirubin) measurements. However, concerns have been raised regarding the appropriateness of comparing these TcB values to serum bilirubin values. This study aims to find a correlation between transcutaneous bilirubin and total serum bilirubin.

Methods: Prospective analytic study carried out in NICU of Govt. RDBP Jaipuria Hospital. Newborn babies up to the 10th postnatal day of life with visually found jaundice had been enrolled in the study. TcB was measured over mid-sternum with Dräger JM 105™ device. Simultaneous total serum bilirubin (TSB) measurements had been done. Pearson's correlation coefficient and Bland–Altman analysis had been done. ROC curves of mean TcB at different TSB level had been constructed.

Results: In the study, 120 babies had been included. A significant correlation was founded between TcB and TSB measured values. Pearson's correlation coefficient was 0.892 ($p<0.001$). The average error in evaluating hyperbilirubinemia with TcB compared to TSB was 0.101, with limits of agreement between −3.73 and +3.55. The AUOC at three TSB levels (>10 mg/dl, >12 mg/dl, and >15 mg/dl) was 0.860, 0.892, and 0.849.

Conclusion: In our study, TcB measurements correlated well with TSB measurements and validated its use as a screening tool for the evaluation of jaundice in newborns.

Keywords: Neonatal jaundice, Transcutaneous bilirubin, Total serum bilirubin.

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INTRODUCTION

The term jaundice was taken from the French word "Jaune," meaning yellow. The term hyperbilirubinemia is being referred to as icterus which came from Greek literature. The clinical manifestation of hyperbilirubinemia is jaundice, a yellow discoloration of the skin that results from an increased concentration of bilirubin in the blood. Among all the infants born every year, between 60 and 80% will manifest jaundice during the 1st week of life [1]. Premature neonates, infants from certain ethnic groups, and infants with a significant risk profile are at greater risk of developing potentially hazardous levels of bilirubin that may pose a direct threat of brain damage [2]. The mainstays in preventing and managing bilirubin encephalopathy are phototherapy and exchange transfusion, which have been subjects of rigorous investigation over the past 60–70 years [3,4]. Three methods are being used to estimate or measure directly the bilirubin levels in neonates: Visual assessment, transcutaneous measurement of bilirubin, and analysis of blood serum. Transcutaneous bilirubin meter provides a non-invasive method for the estimating serum bilirubin using a handheld electronic device that measures the amount of bilirubin in the skin and subcutaneous tissues. Transcutaneous bilirubin (TcB) measurements and gestational age are used by the physician or nurse to assign risk of clinically significant hyperbilirubinemia. Total serum bilirubin (TSB) measurement requires drawing blood from the neonate and estimating risk of increasing hyperbilirubinemia by plotting the TSB measurement on an hour-specific nomogram [5]. Painless, non-invasive screening by the use of transcutaneous bilirubin meter is becoming more acceptable, especially for the term and near-term neonates [5,6]. Our concern was regarding the appropriateness of comparing these TcB values to serum bilirubin values.

This study aims to find a correlation between transcutaneous bilirubin and total serum bilirubin. Bilirubin levels obtained using a transcutaneous bilirubin meter could help diagnose neonatal hyperbilirubinemia in the early stages, thus enabling timely intervention and better outcome in newborns with hyperbilirubinemia.

MATERIALS AND METHODS

This prospective observational study had been conducted in the Department of Paediatrics at Govt. RDBP Jaipuria Hospital, Jaipur, Rajasthan, which is a 500-bedded tertiary care center attached to RUHSCMS, Jaipur, Rajasthan. The study period was September 2018–May 2019. The study population was 120 neonates fulfilling inclusion criteria who required phototherapy in the NICU of Govt. RDBP Jaipuria Hospital, Jaipur.

Inclusion criteria

Inclusion criteria were clinically jaundiced neonates who had not received phototherapy yet and developed jaundice within 10 days of life, admitted for phototherapy in the NICU of Govt. RDBP Jaipuria Hospital, Jaipur.

Exclusion criteria

The following criteria were excluded from the study:

1. Neonate whose age was more than 10 days of life.
2. Infants who had received phototherapy from outside.
3. Infants who needed exchange transfusion.
4. Severe multiple anomalies.
5. Conjugated hyperbilirubinemia.
6. Those who had culture-proven sepsis.
7. Who refused to give consent.

Methodology

Ethical clearance had been obtained from the ethical committee of RUHSCMS. Parental/guardian's consent for enrolment had been taken only after fully explaining the objectives, procedure, risk, and benefits of the study. TSB estimation and TcB readings had been taken as soon as a baby with jaundice was admitted or as more quickly as jaundice appeared in an already hospitalized baby. On the basis of the AAP (American Academy of Pediatrics), nomogram who require phototherapy had been admitted, sequential serum bilirubin estimation and TcB readings had been taken in them. Detailed history and examination of babies had been done. After obtaining informed consent from parents, blood samples had been drawn from a peripheral vein. Blood samples had been taken within ½-h of taking TcB. TcB was analyzed by Dräger Jaundice Meter Model JM-105™ and TSB using the Diazo test. Using JM-105™, three readings at mid sternum were taken in a quiet child, and the mean of each was recorded, which had been displayed on the device's LCD screen. While giving phototherapy, 3 times the area equivalent to the area of JM-105™ probe on the sternum was covered with maxicor electrode covered with aluminum foil. Monitoring of phototherapy had been done as 12–24 hourly TSB levels and TcB measurement from the patched site. Phototherapy was discontinued once two TSB values 12 h apart fall below current age-specific cutoffs. The data were analyzed using SPSS (Statistical Package for the Social Sciences) version 26.

RESULTS

In the present study, 120 babies had been included. The male: female ratio was 1.3:1. Among 120 neonates, 43 were preterm and 77 were full term. The gestational age ranged from 30 to 42 weeks with a mean of 38.40±2.54 (SD) weeks. Mean birth weight was 2538±480 (SD) g; range 885 g–3335 g. The TSB levels ranged from 5.4 to 21.3 mg/dl with a mean of 12.87±4.11 (SD) mg/dl. The TcB levels ranged from 5 to 19.6 mg/dl with a mean of 12.96±3.80 (SD).

Table 1 shows that among the inborn group, 54.05% were male and 45.95% were female, and among the outborn group, 58.70% were male and 41.30% were female. Out of 120 neonates, 55.83% were male and 44.17% were female, as depicted in Table 1. Thus, males outnumbered females in the present study. In Table 1, we observed that the percentage of early preterm (10.81%) and late preterm (29.73%) in the inborn group outweighs that in the outborn group, that is, 4.35% and 23.91%, respectively. Second, we observed that percentage of the terms in the outborn group is highest among all other categories followed by the terms in the inborn group.

Correlation coefficient estimation

In Fig. 1, there was a significant correlation found between TcB and TSB measured values. Pearson's correlation coefficient (r) was 0.892 with the hypothesis test of correlation showing p≤0.001. This indicates that there was a strong linear association between the two variables in our sample, and the same holds for the underlying population. The linear regression equation was Y=0.97X+0.24. This equation can be used for predicting TSB from TcB with a high degree of accuracy. The coefficient of determination (r^2) was 0.797. Thus, 79% of the variance for serum bilirubin concentration could be anticipated by TcB values.

In Fig. 2, Pearson's correlation coefficient (r) was 0.832 with hypothesis test of correlation showing p≤0.001 for the preterm neonates, and the linear regression equation was Y=0.92X+0.80. The coefficient of determination (r^2) was 0.693. This shows a strong linear association between the two variables in our sample.

Similarly, we also calculated the correlation coefficient for term neonates. In Fig. 3, Pearson's correlation coefficient (r) was 0.915, which was higher than preterm neonates, and the linear regression equation was Y=0.99X+0.03. The coefficient of determination (r^2) was 0.837.

ROC curves to determine cutoff values for transcutaneous bilirubin

ROC curve had been constructed to determine the cutoff with maximum sensitivity and specificity to determine transcutaneous bilirubin values. In Figs. 4-6, the area under operator characteristic curve (AUOC) was 0.860 (95% CI=0.817–0.903), 0.892 (95% CI=0.847–0.937), and 0.849 (95% CI=0.807–0.891) at TSB predictive values of >10 mg/dl, >12 mg/dl, and >15 mg/dl, respectively. Thus, TcB could be considered good at separating sample values for different predictive values of TSB. The analysis of ROC curves showed 95% sensitivity and 80.2% specificity for a cutoff point of >10 mg/dl. For cutoff value, >12 mg/dl produced a sensitivity of 88.4% and specificity of 79.4%, while for cutoff value, >15 mg/dl showed a sensitivity of 85% and specificity of 90%.

DISCUSSION

Early newborn discharge after delivery is a common practice because of social reasons and economic constraints. An association between decreased length of stay and the risk of readmission during the neonatal period with hyperbilirubinemia had been shown. Measurement of transcutaneous bilirubin is gaining popularity in NICUs and wards for early prediction, effective preventive measures, and early treatment, thereby reducing mortality and morbidity. However, it's use is still restricted partially due to lack of data and the affordability of the device in the developing countries. TcB estimation reduces the burden of blood analysis for serum bilirubin estimation, and it is non-invasive, so reduces the need of painful venipuncture. TcB also produces immediate results. Therefore, we conducted this study to determine if the correlation between TcB and TSB is satisfactory.

This study had been conducted in the NICU of Govt. RDBP Jaipuria Hospital, Jaipur. In the study of 120 neonates, 43 were preterm and 77 were full term. The gestational age ranged from 30 to 42 weeks with a mean of 38.40±2.54 weeks. In a similar study conducted by Gagan Mahajan *et al.* [7] in 2004, gestational age varied from 28 to 42 weeks with a mean of 36.8±2.9 weeks. While in a study conducted by Surana *et al.* [8] in 2017, gestational age ranged from 30 to 42 weeks with a mean of 38.23±2.01 weeks. Both the studies show results which were comparable with our study.

Table 1: Distribution of the study population on the basis of gender, gestational age, and birth weight

Gender	Inborn		Outborn		Total	
	No.	%	No.	%	No.	%
Male	40	54.05	27	58.70	67	55.83
Female	34	45.95	19	41.30	53	44.17
Early preterm (28–<34 weeks)	8	10.81	2	4.35	10	8.33
Late preterm (34–<37 weeks)	22	29.73	11	23.91	33	27.50
Term (37–42 weeks)	44	59.46	33	71.74	77	64.17
Birth weight<1000 g	1	1.35	1	2.17	2	1.67
1000 g–1499 g birth wt.	3	4.05	1	2.17	4	3.33
1500 g–2499 g birth wt.	26	35.14	5	10.88	32	26.67
2500 g–4000 g birth wt.	44	59.46	39	84.78	82	68.33
Total	74	100	46	100	120	100

In our study, mean birth weight was 2538±480 g; range 885 g–3335 g, while in a similar study by Gagan Mahajan *et al.* [7], mean birth weight in grams was 2264.9±634.4 g; range 1000 g–3600 g. In a survey conducted by Surana *et al.* [8], mean birth weight was 2.403±0.61 kg; range 1 kg–4 kg. Joshi *et al.* [9] did a retrospective study in Bhopal in 2012 with 441 newborns and found that the mean weight was 2.72±0.41 kg. A recent study in South India by Kumar *et al.* [10] reported that the mean birth weights were 2.934 kg and 2.889 kg, respectively, in males and females. The results obtained from our study were much comparable to the above studies.

Out of 120 neonates, 67 were male, 53 were female, and the male: female ratio was 1.3:1. Thus, males outnumbered females in our study. In a survey conducted by Gera and Mehta [11] at SMS Medical College, Jaipur, the sex ratio for year 2013–15 was 928 females to 1000 males (1.08:1, M: F) and according to National Family Health Survey (NFHS)-4, the sex ratio for India is 919 females per 1000 males (1.09:1, M: F). Thus, our data are much comparable to state and national statistics.

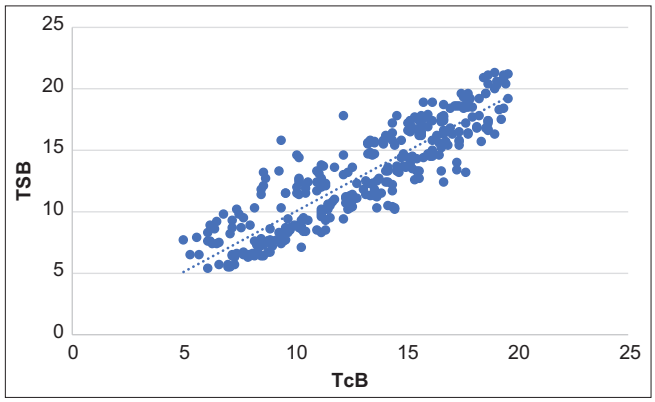

Fig. 1: Correlation between TcB and TSB (mg/dl)

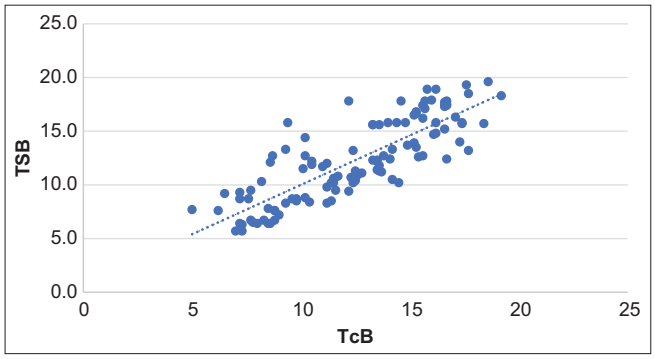

Fig. 2: Correlation between TcB and TSB (mg/dl) for preterm neonates

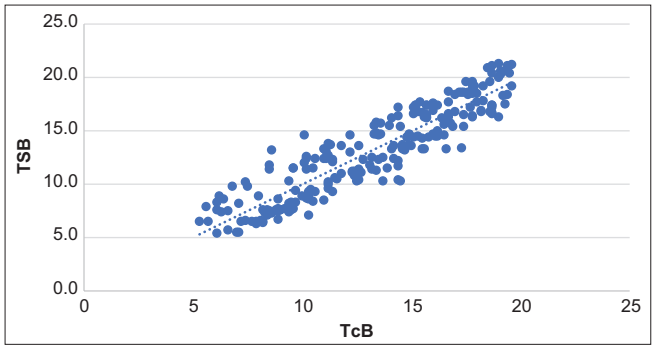

Fig. 3: Correlation between TcB and TSB (mg/dl) for term neonates

In our study, percentage of babies in the inborn group was 40.54% and 28.26%, in the outborn group was 59.46% and 71.74%, and overall 35.83% and 64.17%, respectively, in weight <2500 g and >2500 g category. Incidence of LBW babies reported previously varies from 24 to 30%; however, it was 35.83% at our center, which is a little higher [12-14]. In a study done in Jaipur by Gupta *et al.* [15], percentage of LBW babies was 20.2%. The prevalence of LBW in the study countries

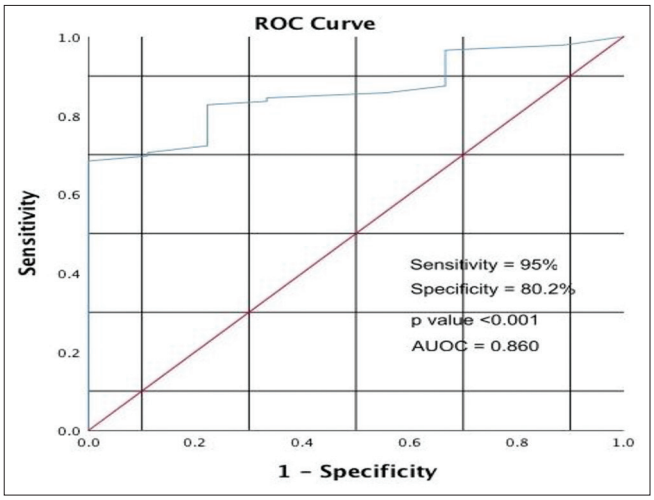

Fig. 4: ROC curve for TSB value >10 mg/dl

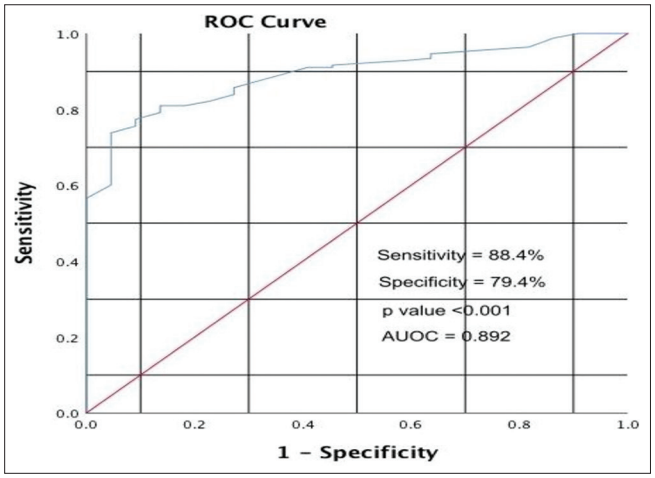

Fig. 5: ROC curve for TSB value >12 mg/dl

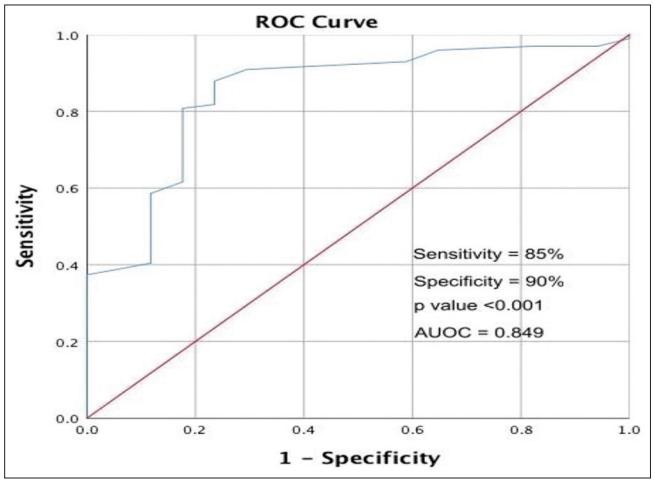

Fig. 6: ROC curve for TSB value > 15 mg/dl

was 15.9% (range, 9.0–35.1%) in a secondary study on distribution and determinants of low birth weight in the developing countries by Human *et al*. [16] from 2010 to 13. At 28%, India had the third highest percentage of LBW newborns, behind only Mauritania (35%), Pakistan, and Yemen (32% each) according to UNICEF17. The higher % of LBW babies can be explained by the fact that ours is a tertiary level NICU and high-risk delivery referral center for both obstetric and fetal complications [17].

We found a high correlation between TcB and TSB measurements in neonates (r=0.892). In another study in 2017 done by Surana *et al*. [8] on 160 neonates of all gestational age, the correlation coefficient (r) was 0.836 between TcB and TSB, which is very similar to our study. Several studies had been done in this regard. In a study done by Hesaraki [18] in 2017, 120 neonates were included, and results showed a correlation coefficient of 0.885, which is very much comparable to our study. In the study done by Douglas *et al*. [19] on 430 neonates in a multiethnic newborn population, the correlation coefficient was 0.83, which is comparable to our study. In 2004 in India, Gagan Mahajan *et al*. [7] conducted a study in which a total of 104 neonates with grossly uniform skin color had been evaluated. The correlation coefficient observed in babies who received phototherapy for a duration of 12–48 h, ranged from 0.829 to 0.857 ($p<0.001$), which is much comparable to our study. Minor differences between the mentioned studies could be attributed to differences in the type of bilirubin meters, skin color, ethnicity, laboratory methods, kits, etc.

In our study, we also calculated correlation coefficients separately for preterm and term neonates, which were 0.832 and 0.915, which were statistically significant. In a similar survey done by Hesaraki [18] in 2017, in Iran, the correlation coefficients observed for preterm and term neonates were 0.502 and 0.885, respectively. While in another study done by Pendse *et al*. [20] on 30 preterm neonates, in 2017; in KEM Hospital, Mumbai, the observed correlation coefficient was 0.97 and 0.88, respectively, for 28–32 weeks and 32–37 weeks of gestation. Pendse *et al*. observed a higher correlation coefficient for the 28–32 weeks gestation group, while the study done by Hesaraki shows a statistically significant but lower correlation coefficient in the preterm group than the term group. Our analysis also indicates a slightly lower correlation coefficient for the preterm than the term group, this might be due to skin immaturity and lower amount of subcutaneous tissue in preterm neonates.

In our study, we also plotted a ROC curve for TSB >10 mg/dl, TSB >12 mg/dl, and TSB >15 mg/dl and compared them with other studies. In the present study, it was found that AUOC ≥0.8 for different predictive values of TSB >10 mg/dl, >12 mg/dl, and >15 mg/dl which was similar to the values reported by Surana *et al*. [8], Maisel *et al*. [20], Bental *et al*. [21], Panburana *et al*. [22], and Akharia Moe *et al*. [23]. This indicates that transcutaneous bilirubinometer is good at separating samples with value less than x from samples having values more than x. As seen in this study, TcB measurement showed sensitivity of 85%–95% at different cutoff TSB values of >10 mg/dl, >12 mg/dl, and >15 mg/dl. In this study, we found that there is a good sensitivity and specificity for three different cutoff TSB values. The specificity level varies in different studies ranging from 35% to 100%. The survey done by Holland *et al*. [24] and EYW Ho *et al*. [25] reported decreased specificity with increasing serum bilirubin concentration. However, this study showed higher specificity for all the three TSB cutoff limits. These results are similar to studies done by Bental *et al*. [21] and Panburana *et al*. [22].

This higher specificity observed in our study might be due to the advancement and upgradation of the new device JM-105™. The higher specificity even at higher levels of TSB suggests that newer models with advancing technology could be accepted safely to rule out disease among neonates who appear to be clinically jaundiced. Our study found that TcB measurement is helpful as an alternative, quick, and convenient screening tool. Further studies from other parts of countries needed to be done, and the standardized scores should be developed at a national level which could be implemented. Limitations of the present study are lack of comparison with other sites such as forehead and interscapular area.

This study has significant implications for the developing countries where the rate of prematurity is high, necessitating prolonged NICU admissions, phlebotomy losses, and unavailability of micro-methods for bilirubin estimation in most laboratories.

CONCLUSION

The data demonstrated a strong correlation between TCB and TSB, and the sensitivity and specificity of TcB for all the TSB cutoff values was high. Hence, we conclude that due to its simplicity and painlessness, serial cutaneous bilirubin measurements would be helpful in the following neonatal jaundice. TcB value estimation is a useful non-invasive screening tool in detecting neonatal hyperbilirubinemia and should be used routinely before discharging the baby from the hospital.

RECOMMENDATIONS

- Clinical assessment of jaundice by visual inspection is not accurate as a screening tool because of its very low sensitivity. In the study, we found high sensitivity and specificity of TcB for all cutoff levels so that TcB measurement can be a good screening tool.
- TcB measurement can also be done for screening of jaundice in low-risk preterm neonates as our study showed a statistically significant correlation coefficient for both preterm and term population.
- TcB is also a helpful tool in follow-up of those neonates who were discharged and had jaundice but not in the range of phototherapy nomograms. The benefits to infants, parents, and care providers of a quick, non-invasive estimate of the TSB are abundant.

Transcutaneous bilirubin meter should be done to monitor the treatment so that invasive blood sampling can be minimized.

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CONFLICTS OF INTEREST

None declared.

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ETHICAL APPROVAL

This study had been approved by ethical committee of Govt. RDBP Jaipuria Hospital, Jaipur.

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