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Original Article

Paediatrics Section

Comparison of Transcutaneous Bilirubin with Serum Bilirubin in a Tertiary Care Newborn Unit- A Cross-Sectional Study

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ABSTRACT

Introduction: Transcutaneous Bilirubin (TcB) is a non-invasive, point of care test for assessing bilirubin level. There has been renewed interest in use of this method with availability of newer generation transcutaneous bilirubinometer (Bilichek and JM-103). Indian studies evaluating TcB with newer generation bilirubinometer have limitations of small sample size, inclusion of mainly term neonates and focusing only on correlation between the two methods (ignoring agreement between the two).

Aim: To compare TcB measurement with Total Serum Bilirubin (TSB) in neonates (term as well preterm) with clinically significant jaundice.

Materials and Methods: This cross-sectional study enrolled 400 healthy neonates (<34 weeks-50, 34-37 weeks-152, >37 weeks-198) who were judged to have clinically significant jaundice and required TSB estimation. TcB was measured at forehead using TcB meter (DRAGER, JM-103) within 30 minutes of obtaining sample for TSB. TcB -TSB difference was computed. Pearson's correlation coefficient and Bland Altman analysis were used to assess the strength of association and agreement respectively between the two values.

Results: Mean (±SD) TcB-TSB difference was 0.68±2.12 mg/dL (range -5.6 to 6.9 mg/dL). Corresponding difference in preterm and term babies was 1.20±1.92 mg/dL (range -4.1 to 5) and 0.15±2.19 mg/dL (range -5.6 to 6.9 mg/dL) respectively. Correlation between TcB and TSB was good across various gestational ages (r value 0.75 overall and 0.71, 0.74 and 0.74 in 30-34 weeks, 34-37 weeks and >37 weeks gestational age, respectively) and between TSB values of 10-18 mg/dL (r-value 0.79). However, correlation was poor when TSB was less than 10 mg/dL and moderate at TSB level above 18 mg/dL (r value 0.36 and 0.65, respectively). Clinically relevant discrepancy of ≥±3 mg/dL between TcB and TSB was present in 17% of study subjects. The 95% limits of agreement between TcB-TSB and mean of TcB and TSB by Bland Altman analysis were estimated to be -3.48 to 4.84 suggesting poor agreement between two methods.

Conclusion: TcB correlates well with TSB in TSB range of 10-18 mg/dL but agreement between two methods is not good and underestimation by TcB at higher values of TSB is a concern. So, TcB is not a substitute for TSB and should never be used in isolation.

Keywords: Bilirubinometer, Hyperbilirubinemia, Jaundice, Neonate

INTRODUCTION

TcB measurement, being non-invasive, has always been an attractive option for assessment of jaundice in neonates. There has been a renewed interest, especially in resource poor settings, for TcB measurement with easy availability of newer generation transcutaneous bilirubinometer (Bilichek and JM-103). Studies done in western countries, using these newer devices have shown good correlation between TcB and TSB [1-5]. However, the hope that measurement with these devices, using innovative technology, would be independent of race, skin color and gestational age has not been fully realised with studies showing poor correlation in African-American neonates, those with dark skin tones and preterm babies [1,6-10]. So it is prudent to have local community data before wider application of TcB is done. Studies done in India to evaluate performance of TcB have been done using older generation bilirubinometer and/or had small sample size, inclusion of only term neonates and focus on only correlation between the two methods (ignoring agreement between the two) [11-16]. So, present study was done with an aim to compare TcB measurement with TSB in healthy neonates (term as well as preterm) with clinically significant jaundice.

MATERIALS AND METHODS

This cross-sectional study was conducted in inborn neonatology unit of a tertiary care institute in North India over a period of one

year from April 2016 to April 2017. Ethical approval was taken from Institutional ethical committee (IEC/SJH/VMMC/Thesis/June/2015-980). Sample size of 324 neonates was calculated to be sufficient to estimate mean error between standard method (TSB) and test method (TcB) (i.e., TSB-TcB) with stated precision based on following assumptions: SD of error = 1.8, Absolute precision in mean error= 0.2, desired confidence level = 95%. Hence 400 healthy neonates {198 Term (>37 weeks) and 202 Preterm (<34 weeks -50, 34-37 weeks-152)} who required estimation of serum bilirubin in view of clinically significant jaundice were enrolled in the study after taking informed consent from parents. Clinically significant jaundice was defined as jaundice appearing in first 24 hours of life or visual assessment of jaundice approaching the intervention range. Neonates with haemodynamic instability, conjugated hyperbilirubinemia and those who had already received some intervention (phototherapy/exchange transfusion) were excluded. For TSB estimation 1 mL blood was collected by venipuncture and sent to clinical biochemistry laboratory. Blood samples were analysed using fully automated clinical chemistry (photometric) analyser (HITACHI 912). TcB levels were measured at forehead (avoiding bruised and discolored areas), using transcutaneous bilirubin meter (DRAGER, JM-103) within 30 minutes of obtaining sample for TSB measurement by single trained paediatric resident in all cases. The device was calibrated as per manufacturer's recommendation. JM-103 was pre-set to take 3 measurements at the site and the mean of 3 values that appeared on display was taken as TcB. Intervention (phototherapy, exchange transfusion, no treatment), however, was decided based on TSB values.

STATISTICAL ANALYSIS

Data analysis was done using Stata 14.0 software. Pearson's correlation coefficient was used to assess the strength of association between TSB and TcB. As Pearson's correlation coefficient alone may be a poor indicator of agreement between diagnostic tests, Bland Altman technique was used to assess TcB and TSB comparability. 95% limits of Agreement for the error (TcB-TSB) was calculated and Bland-Altman type graphs with mean of TSB and TcB on X-axis and TcB-TSB difference on Y-axis were drawn to determine systematic error (bias) by the transcutaneous bilirubin meter (JM-103).

RESULTS

Total 400 neonates (192 boys, 208 girls) were included in the study. Mean gestational age of enrolled babies was 37 weeks (range 30-43 weeks) and mean birth weight was 2.508 kg (range1.1-4.2 kg). Of 400 enrolled neonates, 50 (12.5%) were between 30-34 weeks of gestation, 152 (38%) were between 34-37 weeks and remaining 198 (49.5%) were >37 weeks of gestation [Table/Fig-1]. Mean age of neonates at the time of measurements was 52 hours (range 18-160 hours). For neonates <34 weeks, 34-37 weeks and >37 weeks of gestation, mean ages at the time of measurement were 57 hours, 47 hours and 52 hours respectively. ABO/Rh incompatibility was present in 69 neonates and 36 neonates were born through meconium stained liquor.

Gestation age	Number (%)
30-34 weeks	50 (12.5%)
34-37 weeks	152 (38.0%)
>37 weeks	198 (49.5%)
Total	400

[Table/Fig-1]: Gestational age profile of study population.

Mean TSB was 13.9 (range 6.6-25.6). TSB was <10 mg/dL in 43 (Preterm-36, Term-7), 10-18 mg/dL in 329 (Preterm-162, Term-167) and >18 mg/dL in 28 (Preterm-4, Term-24) neonates. Mean TcB was 14.58 mg/dL (range 8.2-21). Mean (±SD) TcB-TSB difference was 0.68±2.12 mg/dL (range -5.6 to 6.9 mg/dL). Corresponding difference for TSB<10, 10-18 and >18 was 2.28±1.25 mg/dL, 0.69±1.97mg/dL and -2.04±2.17 mg/dL, respectively. Thus, TcB overestimates TSB at lower values (more so with TSB<10) and underestimates TSB at higher values. Mean (±SD) TcB-TSB difference in preterm and term babies was 1.20±1.92 mg/dL (range -4.1 to 5) and 0.15±2.19 mg/dL (range -5.6 to 6.9 mg/dL), respectively.

A total of 68 neonates (17%) had TcB-TSB difference ≥±3 mg/dL (overestimation in 47, 11.8% and underestimation in 21, 5.2%). The sensitivity and specificity of TcB (with margin of error ±3 mg/dL) at different ranges of TSB is shown in [Table/Fig-2]. The sensitivity and specificity of TcB was highest between TSB values of 10-18 mg/dL.

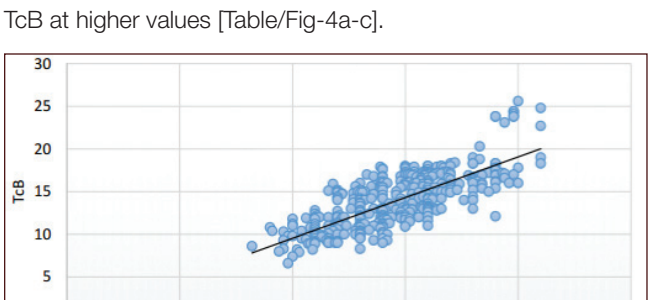
TSB range	Sensitivity	Specificity
<10 mg/dL	53.50%	71.75%
10-18 mg/dL	78.44%	86.87%
>18 mg/dL	78.21%	70.68%

[Table/Fig-2]: Sensitivity and specificity of TcB at various ranges of TsB.

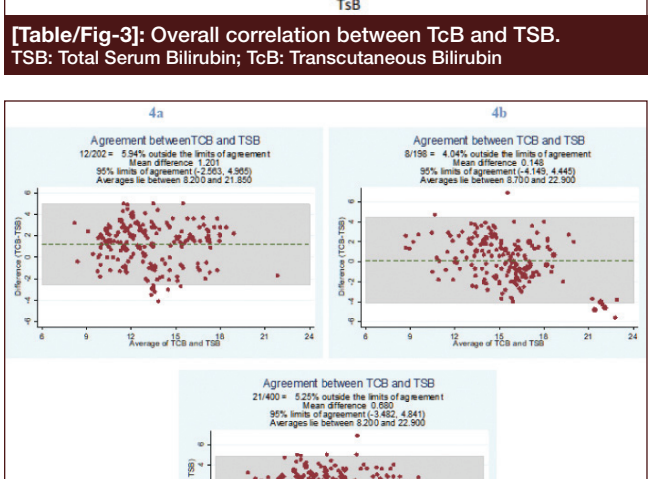
The overall correlation between TSB and TcB was good with Pearson's correlation coefficient (r) of 0.75 [Table/Fig-3]. Correlation coefficient for TSB values <10 mg/dL, 10-18 mg/dL and >18 mg/dL were 0.36, 0.79 and 0.65, respectively. There was good correlation between TSB and TcB across various gestational age groups (r value 0.71, 0.74 and 0.74 in <34 weeks, 34-37 weeks and >37 weeks respectively). In 36 babies with meconium staining, mean (±SD) TcB-TSB difference was 0.62±2.43 mg/dL with r of 0.76.

The 95% limits of agreement were estimated to be -3.48 to 4.84 mg/dL overall (-2.56 to 4.97 mg/dL in preterm and -4.15

to 4.45 mg/dL in term). Though, majority of readings were within limits of agreement, limits of agreement were very wide suggesting poor agreement between two methods. Also, when mean of TSB and TcB was more than 20 mg/dL, 7 out of 9 values of TcB-TSB difference were below lower limit of agreement, suggesting significant underestimation of TSB by TcB at higher values [Table/Fig-4a-c].



[Table/Fig-3]: Overall correlation between TcB and TSB.
TSB: Total Serum Bilirubin; TcB: Transcutaneous Bilirubin



[Table/Fig-4]: Bland–Altmann plots depicting difference between transcutaneous bilirubin (TcB) and TSB on Y-axis against mean of TSB and TcB on X-axis in preterm (4a), term (4b) and total population (4c).

DISCUSSION

Present study was done using newer generation bilirubinmeter (JM 103), had large sample size and included almost equal number of term and preterm babies. Though overall correlation between TcB and TSB was found to be strong across gestational age groups (r-0.74 to 0.75), correlation between the two methods was poor when TSB was less than 10mg/dL and moderate at TSB values above 18 mg/dL. Few Indian studies done using newer generation bilirubinmeter have shown good correlation between TcB and TSB with correlation coefficient varying between 0.76-0.90 as found in present study [12-17]. Out of these studies, Lodha R et al., reported correlation between TcB and TSB to be poorer when TSB was more than 13 mg/dL (Correlation coefficient 0.823 and 0.64 in all neonates and those with TSB > 13 mg/dL, respectively) similar to that found in present study [13]. Other Indian studies did not report correlation between TcB and TSB at different TSB levels [12,14-17]. In present study, TcB overestimated TSB at values <18 mg/dL (more so with TSB<10) and underestimated TSB at higher values. When TSB was > 18 mg/dL, TcB averaged 2.04 mg/dL lower than corresponding TSB value. Studies done in India have not reported TcB-TSB difference based on TSB values [11-17]. However, a recent study done by Taylor JA et al., observed similar trend and found that TcB-TSB difference became progressively less positive as TSB level increased and the least TcB-TSB difference was found when TSB was between 13-15 mg/dL. At TSB >15 mg/dL TcB underestimated TSB by an average of 1.4±2.4 mg/dL [1]. Similar results have been found in other studies that compared performance of TcB and TSB at higher values of TSB [1,5,18].

Clinically relevant difference (±3 mg/dL) between TcB and TSB, called discrepancy, was present in 17% of the study subjects. Taylor JA et al., reported similar results wherein they found discrepancy of ±3 mg/dL in 12.1% study subjects [1]. This clinically relevant discrepancy, especially underestimations, is a concern because failure to identify significant hyperbilirubinemia may be a serious consequence of TcB screening.

Bland Altman analysis revealed wide range of limits of agreement between TcB-TSB difference and mean of TSB and TcB overall as well as in preterm and term babies separately, despite there being good correlation between the two methods. Also, Bland Altman analysis showed 7 out of 9 values of TcB-TSB to be below lower limit of agreement when TSB was more than 20 mg/dL. Indian studies that have analysed agreement between two methods in addition to correlation found similar results [13-17]. Lodha R et al., emphasised poor agreement between TcB and TSB by Bland Altman (limits of agreement -3.6 to 3.6 mg/dL) despite there being good correlation between the two (r value 0.823) [13]. Rest of the mentioned studies, though found wide limits of agreement between two methods, mainly focused on correlation between the two [14-17].

Strengths of our study were inclusion of a large number of neonates across wide gestational age range. We also tried to analyse correlation between TcB and TSB across different ranges of TSB and used Bland Altman Analysis to assess agreement between TcB and TSB in addition to assessment of correlation. Present study highlights the drawback of assessing correlation as a sole method of agreement because while correlation may be good, difference between the two values may be too large to be acceptable clinically.

Limitation(s)

Despite having a good sample size, number of neonates with TSB >18 mg/dL was less in our study, probably because of early identification of significant hyperbilirubinemia in inborn neonatal unit.

CONCLUSION(S)

TcB correlates well with TSB in TSB range of 10-18 mg/dL in Indian population but agreement between two methods is not good and underestimation by TcB at higher values of TSB is a concern. So TcB is not a substitute for TSB, should be used as a screening tool only and management decisions should be based on TSB.

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