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Original Article

Correlation Between Transcutaneous Bilirubin and Total Serum Bilirubin Before Initiation of Phototherapy in Neonates of Tertiary Care Centre of Nepal

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Abstract

Introduction: Jaundice is the predominant health issue within the initial week of an infant's life, impacting 60% of full-term and 80% of preterm newborns. Blood sampling for serum bilirubin measurement not only induces pain but also carries the potential for long-term consequences on neurodevelopment due to pain. Noninvasive transcutaneous bilirubin (TcB) devices, which serve as point-of-care instruments, not only save time but are also more cost-effective. This study's primary objective is to explore the correlation between Delta MBJ20 transcutaneous bilirubinometer measurements and TSB levels determined through the Diazo method.

Methods: This prospective observational research was conducted on newborn infants who received routine TSB tests during their care in the NICU, nursery, and neonatal ward at BPKIHS. TcB measurements were taken on both the sternum and forehead of neonates within a 30-minute window around the time of blood collection for the TSB assay, before phototherapy was initiated. The study involved analyzing a linear regression plot between the mean TcB readings from the forehead and sternum in relation to the mean TSB levels.

Results: Ordinary Least Squares (OLS) linear regression analysis for TSB and forehead TcB indicates a significant positive strong linear relationship between the two measurements ($r = 0.722$, $R2 = 0.52$, $P < 0.001$). A similar pattern of linear relationship was observed between the sternum TcB and TSB ($r = 0.771$, $R2 = 0.59$, $P < 0.001$).

Conclusion: TcB measurements from the forehead or sternum prove to be valuable non-invasive screening tools for non-severe hyperbilirubinemia in neonates.

Introduction

Jaundice is the most common morbidity in the first week of life, occurring in 60% of term and 80% of preterm newborn and it is the most common cause of readmission after discharge.[1-3] Approximately 5-10% of them have clinically significant jaundice that require treatment to prevent bilirubin induced neurological dysfunction (BIND). Few babies may develop severe neonatal jaundice (SNJ) that can result in irreversible neurodisability or even death. Therefore, it is crucial for paediatricians to assess jaundice and provide guidance on timely follow-up. Objective assessment of bilirubin levels, rather than relying solely on visual estimation, is essential. Identifying infants at a higher risk of SNJ and promptly initiating treatment, such as phototherapy or exchange transfusion (ET), if necessary, is critical. SNJ is recognized as the leading cause of preventable neurodisabilities, including conditions like cerebral palsy, deafness, and language problems.[2] A significant portion (85%) of these complications can be attributed to preventable healthcare factors, such as the absence of predischarge bilirubin evaluations, inaccurate bilirubin estimates, and delays in administering phototherapy or ET.[2] Newborn jaundice is known to have cephalo-caudal progression.[4] However, visual assessments of jaundice do not reliably correspond to measured serum bilirubin levels.[5] Blood sampling for serum bilirubin estimation is not only painful but also carries potential long-term consequences.[6,7] Fortunately, noninvasive transcutaneous bilirubin (TcB) devices have been developed. Transcutaneous bilirubinometry is based on optical spectroscopy, which relates the amount of light absorption by bilirubin to the concentration of bilirubin in the skin. This point-of-care device saves time compared to traditional methods.[8] It is also more cost effective and decreases the risk of trauma associated with blood sampling.[9] It also provides immediate results, reducing the risk of infections associated with invasive procedures.[10] It has been found to be effective in both hospital and outpatient settings and is more accurate than visual inspection for hyperbilirubinemia estimation.[11]

The TcB meter can be used as a screening tool to estimate the serum bilirubin level in newborns who are not clinically jaundiced or as a diagnostic tool in jaundiced newborns to assess the need for treatment.[12] The new American Academy of Pediatrics (AAP) 2022 guidelines recommend that transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) value be obtained for all neonates between 24 - 48 hours of life, and post-discharge surveillance be decided based on the difference between this value and the corresponding phototherapy (PT) cut-off.[13] TcB can be used in infants of 35 weeks or more of gestation and after 24 hr of age. TcB has a good correlation with TSB at lower levels, but it becomes unreliable once TSB level goes beyond 12 to 14 mg / dL. It is not useful for the babies undergoing phototherapy. Hour specific TcB can be used for prediction of the subsequent hyperbilirubinemia. TcB value below 50 centile for age would rule out the risk of subsequent hyperbilirubinemia with high probability (High negative predictive value).[14] Trends in TcB values by measuring 12 hr apart would have a better predictive value than a single value.[15]

The primary objective of this study was to investigate whether the Delta MBJ20 TcB measurement correlates with TSB levels measured through the Diazo method. The secondary objective was to determine if TcB measurements from the forehead (BCF) and sternum (BCS) yield comparable results. Since different levels of skin pigmentation may theoretically influence results, this study aims to investigate the reliability of a transcutaneous bilirubinometer (Delta MBJ20) for the screening of neonatal jaundice in in newborns of eastern Nepal.

Methods

Following the receipt of ethical approval from the Institutional Review Board (IRB) and securing informed consent from parents, we conducted a prospective observational study on newborn infants undergoing TSB tests as a routine component of their care in the NICU, Nursery, and Neonatal ward at B.P. Koirala Institute of Health Sciences (BPKIHS). The sample size was calculated based on study by Lilly et al. wherein correlation coefficients were 0.77 (sternum) and 0.72 (forehead).[16] So, keeping r as approximately 0.7, Fisher's arctanh transformation was applied, resulting in a minimum required sample size of 22. However, the study opted for a larger sample size of 100. All cases meeting inclusion criteria were enrolled in the study. Paired TcB and TSB measurements was performed on eligible infants. Within 30 minutes before or after blood collection for TSB assay, TcB measurements was performed on neonates prior to initiation of phototherapy. TcB was measured on the forehead and on the sternum using a Delta MBJ20. Three TcB measurements was done for each site and average was taken. The TcB machine was calibrated daily according to the manufacturer's instructions. The blood sample was collected by venous sampling as medically indicated. TSB levels was determined in hospital bioche mistry laboratory by automated biochemistry by Diazo method. The flow chart of the study is represented in Figure 1.

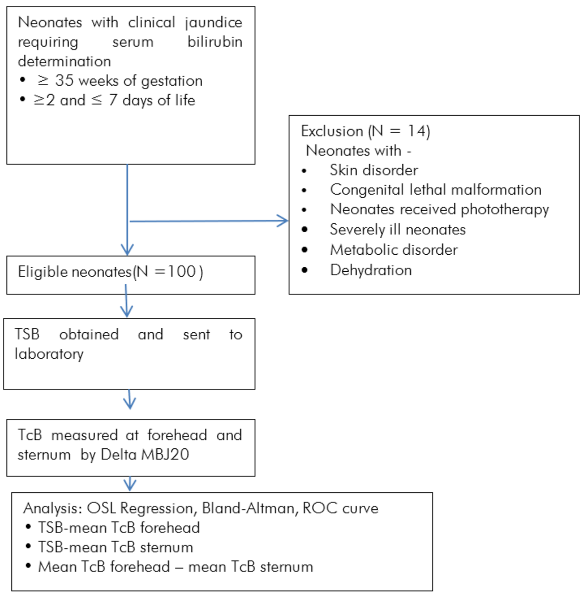


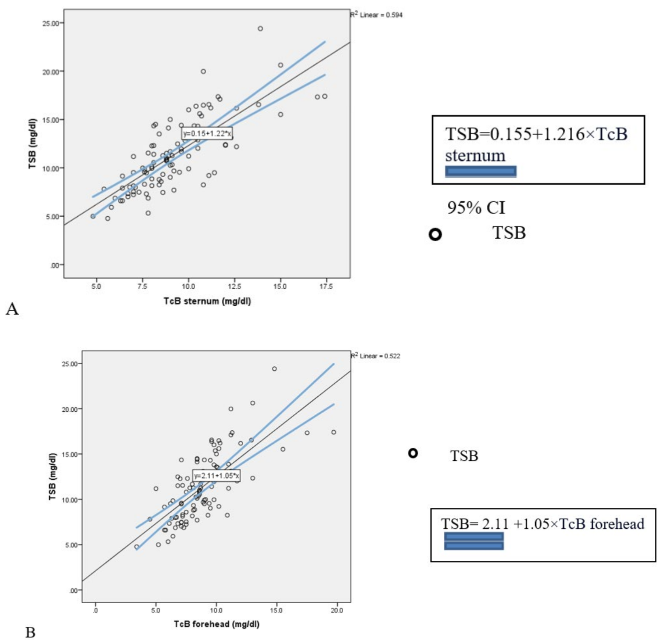
Fig 1: The flow chart of the study

Results

Table 1: Demographic characteristics (N = 100)

	N (%)
Gender	
Female	44 (44.0)
Male	56 (56.0)
Birth weight	
< 2500gm	27 (27.0)
≥ 2500gm	73 (73.0)
Gestational age (weeks)	
35 - 36	20 (20.0)
37 - 42	80 (80.0)
ABO setting	11 (11.0)
Rh setting	7 (7.0)
Mode of delivery	
SVD	72 (72.0)
LSCS	28 (28.0)
Feeding	
Adequate	66 (66.0)
Inadequate	34 (34.0)
Mother with DM	5 (5.0)
Mother with hypothyroidism	6 (6.0)
Birth trauma	1 (1.0)
Baby with hypothyroidism	2 (2.0)

Out of 100 neonates meeting inclusion criteria, most of the neonates were of normal birth weight, term and born via normal vaginal delivery.



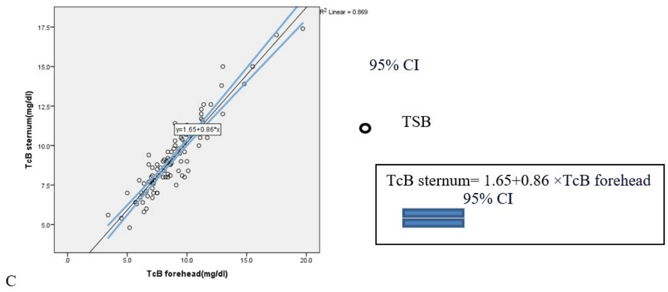
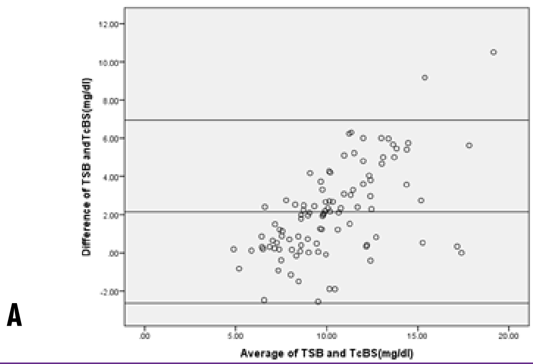
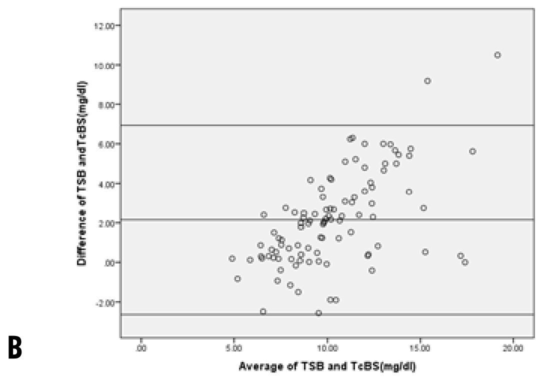


Figure 2: Linear regression plot for (A) TSB versus the sternum TcB, (B) TSB versus the forehead TcB and (C) sternum TcB versus forehead TcB

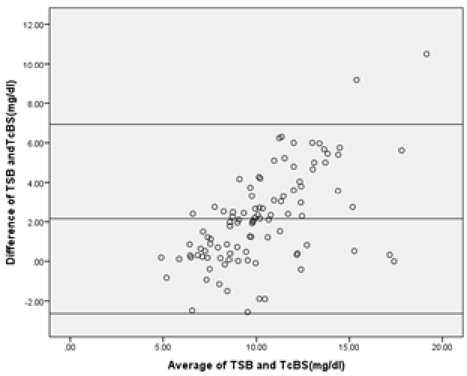
OLS linear regression analysis for TSB and forehead TcB indicates a significant positive strong linear relationship between the two measurements (r = 0.722, R2 = 0.52, P < 0.001) A similar pattern of linear relationship was observed between the sternum TcB and TSB (r = 0.771, R2 = 0.59, P < 0.001). Even stronger pattern of linear relationship was observed between the sternum TcB and forehead TcB (r =.932, R2 = .87, P < 0.001). (Figure 1)



2/100 =2% values outside limits of agreement
Mean difference = 2.15
95% limits of agreement (-2.62,6.93)



4/100 =4% values outside limits of agreement
Mean difference = 0.36
95% limits of agreement (-1.47,2.20)



C

7/100 =7% values outside limits of agreement
Mean difference = 2.51
95% limits of agreement (-2.57,7.60)

Figure 3: Bland-Altman plot showing (A) the difference and average of the TSB and sternum TcB, (B) the difference and average of the TSB and forehead TcB and (C) the difference and average of the sternum TcB and forehead TcB.

The Bland-Altman plot for TSB versus the sternum TcB, TSB versus the forehead TcB and sternum TcB versus forehead TcB showed a very good agreement between the tests, with only 2 / 100 (2%) of the tests being located outside the limits of agreement for TSB versus the sternum TcB, only 4 / 100 (4%) of the tests being located outside the limits of agreement TSB versus the forehead TcB and only 7 / 100 (7%) of the tests being located outside the limits of agreement sternum TcB versus the forehead TcB.

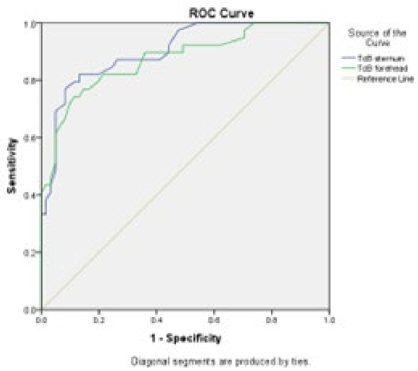


Figure 4: Comparison of the area under receiver operating characteristics (ROC) curve between the forehead TcB and sternum TcB at TSB level of 12 mg/dl

Using a common cut-off for phototherapy TSB of 12 mg / dl, the area under the ROC curve was 87.5%, 95% CI .802, 0.947, p value .000 for forehead TcB and area under the ROC curve 90.3%, 95% CI .843, .962, P value .000 for sternum TcB. (Figure 4). Best sensitivity and specificity-the forehead TcB compared to the TSB at the cut-off level TSB = 8.95 mg / dl and sternum TcB compared to the TSB at the cut-off level TSB = 9.30 mg / dl.

Table 2: Diagnostic accuracy of the forehead TcB compared to the TSB at the cut-off level TSB = 8.95 mg / dl and sternum TcB compared to the TSB at the cut-off level TSB = 9.30 mg / dl.

	Forehead TcB (%)		Sternum TcB (%)	
	Estimate	95% CI	Estimate	95% CI
Sensitivity	71.79	55.13, 85.00	82.05	66.47, 92.46
Specificity	90.16	79.81, 96.3	86.89	75.78, 94.16
Positive predictive value	82.35	68.04, 91.10	80.00	67.35, 88.58
Negative predictive value	83.33	75.06, 89.25	88.33	79.35,93.72

Sensitivity and specificity of the sternum TcB compared to the TSB at the cut-off level TSB = 9.15 mg/dl were 82.1% and 83.6% respectively whereas sensitivity and specificity of the sternum TcB compared to the TSB at the cut-off level TSB = 9.45 mg / dl were 79.5% and 86.9% respectively.

A

B

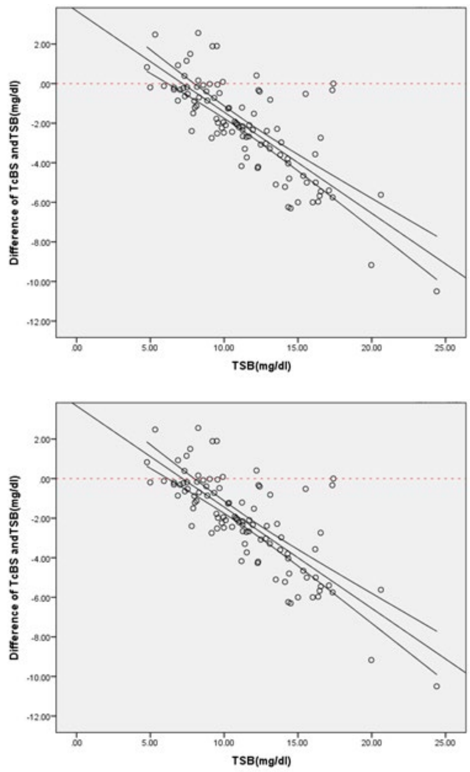


Figure 5: Characterisation of the difference between (A) sternum TcB-TSB and (B) the forehead TcB-TSB throughout the measurement range of TSB. The area between upper and lower line represents the 95% CI.

Figure 5 illustrates the difference between TcB and TSB values throughout the measurement range of TSB. For both TcB measurements (at the forehead and the sternum), the fit line indicates that at lower TSB values, TcB overestimates TSB. At around TSB values of 6 mg / dl, TcB measurements started to underestimate the TSB values. The underestimation of TSB values by TcB is gradually greater as the TSB values increase.

Discussion

This study revealed a strong linear correlation between TSB and both mean TcB measurements at the forehead ($r = 0.722$) and sternum ($r = 0.771$). These findings mirror those of a previous study by Taylor et al, which included data from 27 nursery sites and 925 matched TcB and TSB measurements from both the chest and forehead. Taylor's study used two different TcB devices, BiliCheck and JM-103, and found a robust correlation between TSB and TcB values.[17] Similarly, in Iran, Mansouri et al conducted a study with a wider range of neonatal ages (1 to 22 days) and also reported a strong correlation between TSB and TcB measurements from the forehead in 200 neonates.[18] Our results align with similar studies conducted in other Asian countries, including Thailand, India, and Hong Kong.[19-21] In our research, we observed that sternal TcB measurements exhibited a better correlation with TSB compared to measurements from the forehead. This outcome corresponds with the results of other studies.[16,22,23] For instance, Kosarat and Khuwuthyakorn's study in 2016, which involved 257 neonates, found a higher correlation coefficient ($r > 0.8$) between sternal TcB and TSB.[22] Chimhini et al reported a similar finding on Zimbabwean neonates where it indicated that the sternum was a more accurate indicator of neonatal jaundice than the forehead.[16] El-Kabbany et al's study in Egypt also demonstrated a significant correlation between TSB and both forehead and sternal TcB measurements, with sternal measurements being more accurate.[23] However, Rubaltelli et al reported a strong positive linear relationship between TSB and TcB, with the TcB measurements from the forehead ($r = 0.89$) performing slightly better than sternal measurements ($r = 0.88$).[24]

The exact reason for this difference between sternal and forehead TcB measurements remains unclear. One hypothesis suggests that it may be due to the fact that the sternum is typically covered, while the forehead is exposed to sunlight and ultraviolet rays. Exposure to ultraviolet rays can stimulate melanin production. This results in reduction of the basal yellow skin colour.[25] In some studies, gestational age, as well as postnatal age, have been shown to have an effect on TcB. This could be attributed to maturation of skin seen in term babies and changes in albumin binding which occurs with maturity.[25]

The Bland-Altman plot for TSB versus the sternum TcB, TSB versus the forehead TcB and sternum TcB versus forehead TcB showed a very good agreement between the tests which is in alignment to finding in study done on Malay neonates.[26] Using a common cut-off for phototherapy, TSB of 12 mg / dl, the area under curve was 87.5%, 95% CI .802, .947, p value .000 for forehead TcB and area under the ROC curve 90.3%, 95% CI .843, .962, p value .000 for sternum TcB. This is similar to findings in study on Malay neonates wherein good discriminations ability was observed for both the TcB forehead {receiver operating characteristics (ROC) curve= 89.8%} and sternum (ROC curve = 89.7%) at a TSB level of 205 µmol / L (12 mg / dl).[26] In study done among Zimbabwean neonates the ROC curves showed that the accuracy of the two diagnostic tests were good with no significant difference between the two, $p = 0.2954$.[16]

In our study, we found that the best sensitivity and specificity were achieved with the forehead TcB compared to TSB at a TSB cutoff of 8.95 mg / dl, and with sternal TcB compared to TSB at a TSB cutoff of 9.30 mg / dl. These results align with a study among Malay neonates, which reported sensitivity ranging from 84.4% to 85.3% and specificity ranging from 77.4% to 76.4%.[26] Similarly, a study among term Zimbabwean neonates found sensitivity for the sternum at 76% and specificity at 90%, while sensitivity for the forehead was 62% and specificity was 95%.[16]

The difference between TcB and TSB values throughout the measurement range of TSB. For both TcB measurements (at the forehead and the sternum), the fit line indicates that at lower TSB values, TcB overestimates TSB. At around TSB values of 6 mg / dl, TcB measurements started to underestimate the TSB values. The underestimation of TSB values by TcB is gradually greater as the TSB values increase. This finding is similar to that of study among Malay neonates.[26]

It's essential to note that our study had limitations, as it was conducted in a single setting with a relatively small sample size, and the neonates were limited to a specific population within one hospital. Future research should encompass a more diverse range of races and skin tones, as these factors may influence the performance of transcutaneous bilirubinometers. Additionally, further studies should investigate TcB's relationship with TSB in smaller premature neonates, high-risk neonates, and those with illnesses. Evaluating the pre- and post-phototherapy relationship between TcB and TSB could provide a more comprehensive understanding of the utility of TcB devices in our population.

Conclusion

TcB measurements from the forehead or sternum prove to be valuable non-invasive screening tools for non-severe hyperbilirubinemia in neonates. However, it is advisable to exercise caution and not solely rely on TcB when dealing with patients suffering from severe hyperbilirubinemia.

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Conflict of Interest None

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