How to Cite:
Amneenah, A. M. (2022). Comparison of diagnostic accuracy of transcutaneous bilirubinometry during phototherapy by using skin patch. *International Journal of Health Sciences*, *6*(S2), 7276–7288. https://doi.org/10.53730/ijhs.v6nS2.6779

Comparison of diagnostic accuracy of transcutaneous bilirubinometry during phototherapy by using skin patch

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***Abstract*---**Background: Neonatal jaundice is a very common condition. Serious unconjugated hyperbilirubinemia may result in neurological dysfunction as catastrophic as kernicterus. Phototherapy is the method of choice in treatment of hyperbilirubinemia. Aim and objectives: the aim of the study was to assess the accuracy of transcutaneous bilirubin measurement during phototherapy by using skin patch and comparing this with skin and serum bilirubin measurement at the same time. Subjects and methods: This was an observational prospective study was conducted in special care baby unit at Al-wahda teaching hospital –Derna-Libya over a period of nine months (June 1st 2021 to March 2022).Eighty (80) newborn (41 Male, 39 Female) were enrolled in the study .Transcutaneous bilirubin measurement from skin over sternum, skin under patch at Rt. Side of chest, simultaneously serum bilirubin sample were collected. Results: during phototherapy; the mean± SD TSB (14.94 ± 4.57 µmol/L) and mean± SD TCBC (13.52 ± 4.84) and at skin level was 9.45 ± 3.62. Bland–Altman plot showed significant agreement between TcB from patched site and TSB Conclusion: TCB measurements correlate strongly with TSB levels during and after PT. However, as a result of the wide and clinically relevant disagreement between TCB and TSB measurements during the PT phase, a TCB device cannot be recommended for monitoring bilirubin level during PT in our opinion. However, based on our results, we would advocate the use of TCB for TSB 'rebound' measurements at 12 hours after PT to avoid unnecessary serum sampling.

***Keywords*---**transcutaneous bilirubin, accuracy, skin patch, hyperbilirubinemia, neurological dysfunction, neonatal jaundice.

Introduction

Neonatal jaundice is a very common condition. It is detected in 84% of healthy infants. Serious unconjugated hyperbilirubinemia may result in neurological dysfunction as catastrophic as kernicterus. Phototherapy is the method of choice in treatment of hyperbilirubinemia. Although there is some evidence that phototherapy can produce oxidative injury, patients who received aggressive phototherapy were less likely to have neurodevelopmental impairment (Bhutani et al., 2013).

Transcutaneous measurement of bilirubin concentration has become a widely used screening test, which determines whether it is necessary to obtain a blood sample for total serum bilirubin (TSB) concentration. This noninvasive technique has been characterized as not reliable in infants undergoing phototherapy, because phototherapy 'bleaches' the skin (Sampurna et al., 2021). Although obtaining TSB is the most common way to measure bilirubin levels in infants, blood sampling can be painful and a time-consuming procedure. Studies have also reported concerns about frequent TSB measurements, such as the increased risk of infection and anemia, particularly among extremely preterm infants. Furthermore, repeated procedural pain and stress have been documented in preterm infants (Jegathesan et al., 2021).

Phototherapy (PT) is considered to be a safe and effective treatment for neonatal unconjugated hyperbilirubinaemia. The indication to commence treatment is based on the level of serum bilirubin, the age of the baby in hours and gestational age. Evidence is conflicting regarding the best therapeutic approach to hyperbilirubinaemia, especially in extremely low birth weight (ELBW) infants (Mitra and Rennie, 2017). However, aggressive PT was associated with a reduction in the rate of neurodevelopmental impairment alone. However, post-hoc analysis showed that in the smallest and sickest subgroup (mechanically ventilated infants with birth weight less than 750 g), aggressive PT may increase mortality while reducing neurodevelopmental impairment (Nagar et Al., 2016).

Measurement of total serum bilirubin (TSB) remains the gold standard for monitoring bilirubin levels during and after PT in term and preterm infants. However, obtaining heel stick or venous blood samples is painful, time-consuming, and increases the risk of local and systemic infection especially in preterm infants. A transcutaneous bilirubinometry (TCB) device works by directing light into the skin of the infant and measuring and analyzing the intensity of the returned wavelengths to estimate TSB (Hassan Shabuj et al., 2019). TCB has been recommended as a non-invasive, painless and time-saving test for bilirubin estimation in term and late preterm infants prior to commencement of PT. However, TCB measurements are not recommended in the first 24 hours of life or in preterm infants below 35 weeks of gestation according to the National Institute for Health and Care Excellence (NICE) guidelines (Rylance et al., 2014). We designed our study to assess the accuracy of transcutaneous bilirubin measurement during phototherapy by using skin patch and comparing this with skin and serum bilirubin measurement at the same time.

Subjects and Methods

This is a single-center, prospective observational cohort study performed in special care baby unit at Al-wahda teaching hospital –Derna-Libya over a period of nine months (June 1st 2021 to March 2022).Eighty (80) newborn (41 Male, 39 Female) were enrolled in the study. Transcutaneous bilirubin measurement from skin over sternum, skin under patch at Rt. Side of chest, simultaneously serum bilirubin sample was collected.

Inclusion criteria

- Age:0-28 days
- Both term and preterm
- Not started phototherapy

Exclusion criteria

- Babies already on phototherapy before skin patch applied.

Ethics approval

Both ethics and Research & Development committees approvals were obtained before starting this study.

Consent

Written information leaflets were given to parents of all babies admitted to NNU, which fulfilled the inclusion criteria and were invited to enroll for this study. Subsequently, written consent was obtained from those willing to participate.

Methods

Where a clinical decision was made to undertake TSB measurement, a simultaneous TcB measurement using BiliChek was also obtained. The decision to commence phototherapy was made by the clinicians based on the TSB result. The threshold used depends on gestational age [threshold = (Gestation × 10) − 100]; thus, for example the threshold for a 35-week gestation infant would be 250 μmol/L. If the baby did not require phototherapy, he/she was monitored clinically and any further decision to repeat TSB was made on clinical grounds by the medical and/or nursing staff. If, however, the baby required phototherapy, the TSB was repeated in 6–8 h (to ensure a downward trend and improvement in bilirubin levels) and then 12–24 h, till a decision was made to stop phototherapy.

TSB measurement

TSB was measured in the laboratory using a standard diazo method (Olympus AU640; Olympus Diagnostics, Watford, Herts, UK).

TcB measurement

When samples for TSB measurement were collected, a contemporaneous TcB measurement was also carried out within 15–30 min by applying BiliChek (Respironics Inc., Chichester, UK; http://www.respironics.co.uk/) to the infant's forehead with the infant lying supine. Disposable probe tips were calibrated as per the manufacturer's instructions before each TcB measurement. The tip was then applied with light pressure to the skin and the BiliChek device was automatically triggered for five consecutive spectral analyses, which are used to display a calculated averaged reading in either µmol/L or mg/dL.

Simultaneous multiple measurements were taken if the neonate required repeated TSB measurements, e.g. during phototherapy. The area of forehead used for TcB was not exposed to direct sunlight and/or phototherapy. If an infant required phototherapy, Bil*Eclipse*™ (phototherapy protective patch) was positioned over the measurement site prior to starting phototherapy. All phototherapy lights were turned off while a BiliChek measurement was taken. The BilEclipse protective patch was opened and after taking the BiliChek measurement, the flap was closed before recommencing phototherapy. Once phototherapy was discontinued, the BilEclipse flap was removed but subsequent BiliChek measurements were taken from the site on the forehead that had not been exposed to the phototherapy lights. Care was taken to avoid skin areas with bruising, birthmarks, haematomas or excessive hairiness. Gestation, birth weight, postnatal age and ethnicity were recorded.

Results

Table 1. Basic patient characteristics

Variable	Mean ±SD	Median (Range)
Age (days)	5.67 ± 4.49	4 (0.3 – 22)
Weight (gm)	2580.81 ± 913.16	2800 (650 – 4700)
	N	%
Sex Male Female	 41 39	 51.2% 48.8%
GA Preterm Term Post-term	 26 53 1	 32.5% 66.3% 1.3%

This table shows that patients age ranged between 0.3 – 22 days with mean weight was 2580.81 ± 913.16 gm and 51.2% of the patients were males while 66.3% of patients were term, 32.5% were preterm.

Table 2. Blood group distribution

Blood group	Patients (n=80)	
	N	%
A^+	20	25

A^-	2	2.5
B^+	27	33.8
B^-	2	2.5
AB^+	10	12.5
O^+	18	22.5
O^-	1	1.3

This table shows that the most common blood group among studied patients is B^+ (33.8%)

Table 3. Causes of admission

	Patients (n=80)	
	N	%
ABO/Rh incompatible	29	36.8%
Cold stress	1	1.3%
Convulsion	1	1.3%
Down syndrome	1	1.3%
Hip joint synovitis	3	3.8%
Hypocalcemic seizures	1	1.3%
IDM	9	11.3%
IUGR	1	1.3%
Meningitis	1	1.3%
Neonatal jaundice	14	17.5%
Pneumonia	2	2.5%
Prematurity	18	22.5%
Sepsis	3	3.8%
Respiratory distress	15	18.7%
Small for gestational age	1	1.3%
Transient tachypnea of newborn	5	6.3%
UTI	2	2.5%

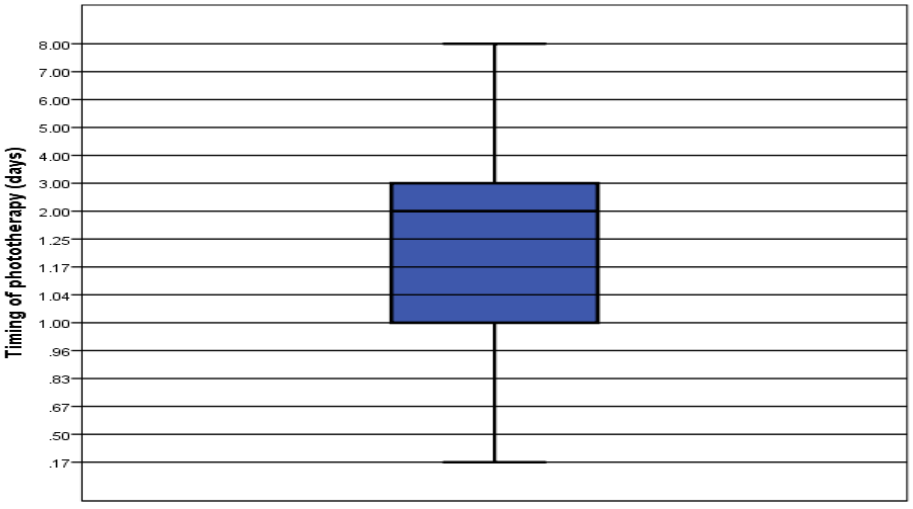

Figure 1. Timing of the phototherapy distribution among the studied patients

Table 4. Different measurements of total bilirubin

Variable	Mean ±SD	Median (Range)
Serum total bilirubin (mg/dl)	14.94 ± 4.57	15.2 (4.2 – 23)
TCTB (mg/dl)	13.52 ± 4.84	14.45 (1.5 – 23)
Skin (mg/dl)	9.45 ± 3.62	10.1 (0.7 – 16.5)

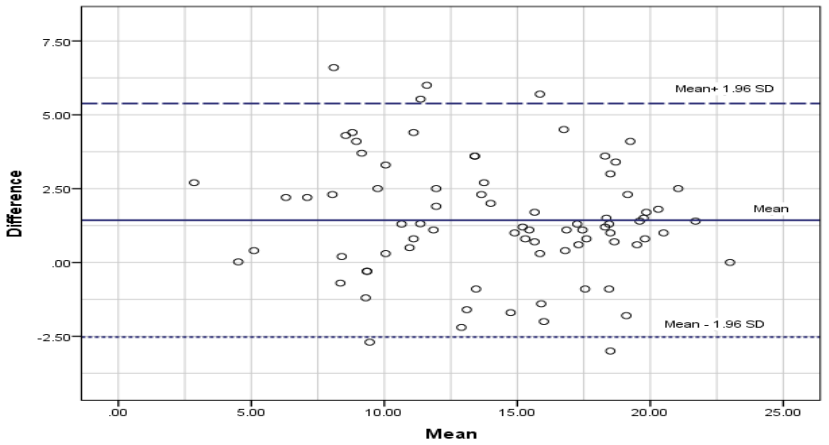

Figure 2. Agreement between serum total bilirubin and TCTB using Bland–Altman plot. Showing a fair agreement between total bilirubin in serum and TCTB after phototherapy.

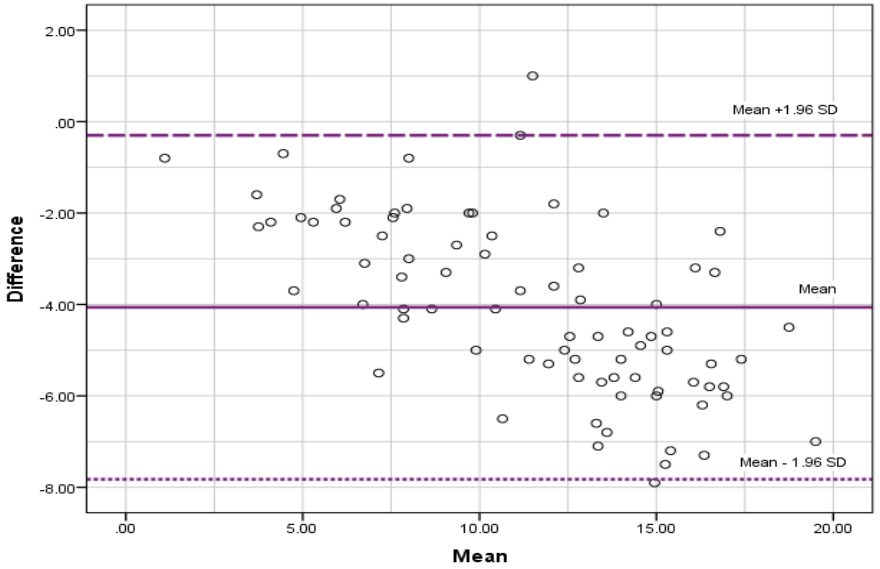

Figure 3. Agreement between skin bilirubin and TCTB using Bland–Altman plot. Showing a good agreement between skin bilirubin and TCTB after phototherapy.

Discussion

Since the 1980s, the phototherapy's influence on measurement results has been considered a major disadvantage of transcutaneous bilirubinometry. Transcutaneous bilirubin measurements may provide inaccurate results during or immediately after phototherapy. First, bilirubin concentration in subcutaneous tissue exposed to phototherapy decreases before TSB concentration. Second, it is possible that bilirubin concentration in subcutaneous tissue will rise with a time delay in the case of rebound serum bilirubin (Ho et al., 2021).

Transcutaneous measurement of bilirubin is useful as a screening device for neonatal hyperbilirubinemia. There is good evidence that a risk assessment that combines the result of a timed transcutaneous bilirubin level with risk factors for significant hyperbilirubinemia is effective at preventing later significant hyperbilirubinemia (Cloherty et al., 2015). In this study, we aimed to assess the accuracy of transcutaneous bilirubin measurement during phototherapy by using skin patch and comparing this with skin and serum bilirubin measurement at the same time. This was an observational prospective study was conducted in special care baby unit at Al-wahda teaching hospital –Derna-Libya over a period of nine months (June 1st 2021 to March 2022).Eighty (80) newborn (41 Male, 39 Female) were enrolled in the study .Transcutaneous bilirubin measurement from skin over sternum, skin under patch at Rt. Side of chest, simultaneously serum bilirubin sample were collected

Analysis of our findings revealed that patients age ranged between 0.3 – 22 days with mean weight was 2580.81 ± 913.16 gm and 51.2% of the patients were males while 66.3% of patients were term, 32.5% were preterm. In comparison with our findings, the study of Raba et al., 2020 where one hundred and ninety-six preterm infants with jaundice who received PT were enrolled to the study. The mean (±SD) gestational age and birth weight of our cohort were 30.4 weeks of gestation (±3.2) and 1605 g (±638), respectively. In another study done by Nagar and Kumar, 2022 was conducted on a total of ninety infants were enrolled in the study contributing data for various phases of the study. The mean (SD) birth weight (BW) was 1847 g (±478 g) and mean (SD) gestational age was 32.4 (±1.89 weeks) for the study participants.

Furthermore, a study of Ho et al., 2021 on a total of 40 neonates with neonatal hyperbilirubinemia who met the criteria for phototherapy between December 2017 and April 2018 in the NTUH Hsin-Chu branch were included. Thirteen of them were preterm infants with a mean gestational age of 34.3 weeks. In the study participants, ninety-six measurements of TSB (total serum bilirubin) and 384 measurements of TCB (transcutaneous bilirubin) were collected. In the present study, we found that the most common blood group among studied patients is B^+ (33.8%). This come in comparison with the study of Akanmu et al., 2015 which reported that a total of 9138 blood donors were ABO blood group typed. 4962 (54.3%) were blood group O. Blood group A was slightly more prevalent (23.0%) than blood group B (19.4%). AB blood group constituted only 3.3%. In consistent with our findings, Kalakheti et al., 2009 reported that among 200 babies 60% had 'O' positive and 40% had other than 'O' positive blood group (19% B +ve, 2% AB +ve and 19% A +ve).

In the current study, we found that major cause of NICU admission is ABO/Rh incompatible by 36.8%, followed by prematurity 22.5%, respiratory distress 18.7%, Neonatal jaundice by 17.5%, IDM by 11.3% and other causes as Small for gestational age, Transient tachypnea of newborn, UTI, Cold stress, Convulsion, Down syndrome, Hip joint synovitis, and Hypocalcemic seizures In a harmony with our findings, the study of Tekleab et al., 2016 reported that the most common primary diagnoses during admission to the neonatal care unit were prematurity with respiratory problem (36.6%), neonatal sepsis (22.7%), and asphyxia (16.2%). These three conditions comprised 75.5% of the causes for admission, and the remaining reasons for admission were Meconium Aspiration Syndrome (13.9%), hyperbilirubinemia (6.0%), and other conditions (4.6%). Hypothermia was diagnosed as comorbid illness in 60.6% of the neonates during admission. The proportion of prematurity, sepsis, and asphyxia as causes of admission vary across different centers. In Tanzania, Mmbaga et al., 2012 reported that asphyxia, prematurity, and sepsis accounted for 26.8%, 18.4%, and 15.4% of the causes of admission, respectively, where asphyxia and sepsis contributed a lesser proportion as a cause of admission when compared to ours. Also sepsis, prematurity, and asphyxia were described as major reasons for admission in Nigeria (Toma et al., 2013) and Pakistan (Ali et al., 2013), the proportion accounted by each disease entity as a cause of admission varies across the centers. Sepsis and prematurity were also major causes of morbidity in another study of Ahmadu et al., 2013 in Nigeria. The fact that prematurity, sepsis, and asphyxia are being common causes of neonatal morbidity in neonatal care centers of developing countries including ours could imply the lack of appropriate interventions in the antenatal, intrapartum, and postpartum neonatal care.

Transcutaneous bilirubinometer devices are widely applied to assess neonatal hyperbilirubinemia. However, the optimal skin site and timing of transcutaneous bilirubin (TCB) measurements for the strongest correlation with total serum bilirubin (TSB) levels after phototherapy are still unclear (Ho et al., 2021). In addition to above findings, during phototherapy; we found that the mean± SD TSB (14.94 ± 4.57 µmol/L) and mean± SD TCBC (13.52 ± 4.84) and at skin level was 9.45 ± 3.62. Bland–Altman plot showed significant agreement between TcB from patched site and TSB

On the other hand, Raba et al., 2020 reported that there were 328 simultaneous measurements (TSB and TCB) during the PT phase and 142 pairs of readings after discontinuation of PT. The PT was commenced at a mean (±SD) of 32.5 (±20) hours of life and the median duration of PT exposure was 24 hours (IQR 24–32). Moreover, Ho et al., 2021 reported that the average TSB level was 12.9 mg/dL, the authors measured TCB levels on their forehead and mid-sternum at 0 min and 30 min after cessation of phototherapy. The mean differences between TSB and TCB levels were 1.3 mg/dL, 0.9 mg/dL, 5.8 mg/dL and 5.3 mg/dL over the forehead (0 min), forehead (30 min), mid-sternum (0 min), and mid-sternum (30 min), respectively.

A recent study of Lucanova et al., 2016 reported an accuracy analysis of TCB measurements at uncovered skin sites with an interval of 2 h post phototherapy. However, the mean differences between the TCB and TSB levels varied widely

from -2.9 to -6.7 mg/dL in their study. The authors suggested that the TCB measurement was not suitable for neonates after phototherapy, even when measurements were recorded at covered sites and that measurement of TSB levels was necessary to ensure the selection of the appropriate treatment plan. In the study by Lucanova et al., 2016, the TCB data from the lower abdominal skin sites covered with a diaper were chosen for comparison with other uncovered sites at the forehead, sternum and abdomen. They found that even for measurements at the covered area, the reliability was inadequate. In our study, the forehead skin site covered by a gauze eye mask was adopted as the best measurement area. Based on the mean differences and correlations with the corresponding TSB level, the TCB measurement at the forehead at 30 min postphototherapy was the most accurate among the measurements tested. The skin depth, subcutaneous tissue and composition are different between the forehead and lower abdomen, which may explain the discrepancies in results between the study by Lucanova et al., 2012 and our study.

In the present study, Agreement between serum total bilirubin and TCTB using Bland–Altman plot. Showing a fair agreement between total bilirubin in serum and TCTB after phototherapy Agreement between skin bilirubin and TCTB using Bland–Altman plot. Showing a good agreement between skin bilirubin and TCTB after phototherapy. Similar to our study, Nagar et al., 2017 reported that a total of 66 and 65 pairs of TcB and TSB measurements for forehead and for sternum, respectively, were available for comparison during the PT phase. The TcB and TSB measurements correlated poorly during the PT phase particularly at sternum (r = 0.72 at forehead and 0.51 at sternum). The analyses of the BA difference plots revealed significant bias and imprecision in the TcB measurements. TcB underestimated jaundice level with mean TcB-TSB difference of −52.4 μmol/L at forehead ([SD: 40.7 μmol/L], 95% agreement limits −132 and 26 μmol/L) and −69.2 μmol/L at sternum ([SD: 42.5 μmol/L], 95% agreement limits −157and 19 μmol/L)

In the post-PT phase, Nagar et al., 2017 noted significant improvement in bias and precision in the TcB estimates as compared to estimates during the PT phase. The 95% limits of agreements indicate that the underestimation of bilirubin level with the use of TcB device during post-PT phase could be up to 88 μmol/L. These magnitude of underestimation noted here are similar those noted in a recent study involving term and preterm infants. Grabenhenrich et al., 2014 in this study showed that the risk of underestimation is particularly high in the first 8 h after stopping PT. Although we were unable to analyze our data according to the time cutoffs used in that study due to very few assessments conducted within 8 h of stopping PT, we also noted a better correlation between TcB and TSB when subjects were off-PT for ≥24 h as compared to <24 h.

Based on the data presented here, and in another recent study of Grabenhenrich et al., 2014 using similar TcB device, we propose that the blood sampling for bilirubin estimation in the post-PT phase could be avoided if the TcB reading is more than 85 μmol/L below the PT threshold. Similarly, a TcB reading above the PT threshold may be sufficient grounds to initiate PT without the confirmatory blood test (theoretically, some of these infants could be below the PT line as per their serum levels but are still likely to be reasonably close to the threshold for

starting PT). In the borderline cases, following a trend of TcB values over a period of time could help with a decision regarding the need for blood sampling.

Nagar et al., 2017 reported that during the PT phase, the mean±SD TSB (127±51 μmol/L) and mean±SD TCBC (102±62) were statistically significantly different ($p<0.0001$). Similarly, the difference between the mean±SD TSB (127±51 μmol/L) and mean±SD TCBU (79±70) was statistically significantly different during PT ($p<0.0001$). Although there was a significant correlation between TSB and TCB measurements during PT ($r=0.72$, 95% CI 0.66 to 0.77 from covered area; $r=0.75$, 95% CI 0.70 to 0.80 from uncovered area; $p<0.0001$), B-A plots showed significant bias and imprecisions in the TCB readings. TCB underestimated TSB level with a mean TCB–TSB difference of −25±43 from the covered area (95% agreement limits of 62 to −112, $p<0.0001$) and of −48±46 from the uncovered area (95% agreement limits of 45 to −140, $p<0.0001$), furthermore, Nagar et al., 2017 reported that during the post-PT phase, TSB±SD (153±51 μmol/L) and TCB±SD (143±63) measurements were statistically significantly different ($p=0.0001$). These measurements were taken at a median time of 12 hours (IQR 8–24) after PT. After cessation of PT, the correlation between TCB and TSB further improved ($r=0.87$, 95% CI 0.83 to 0.91, $p<0.0001$). The B-A plot also showed an improvement in the agreement between TCB and TSB, but TCB continued to underestimate TSB level by −10±31 (95% agreement limits of 52 to −72, $p=0.0001$). At 12 hours after cessation of PT, the correlation between TCB and TSB was improved compared with 8 hours after PT, with statistically significantly improving mean difference between TCB and TSB ($p<0.0001$)

Nagar and Kumar, 2017 performed a smaller study on 90 preterm infants with a mean gestational age of 32.4 weeks and a mean birth weight of 1847 g. They found that TCB cannot be recommended for bilirubin measurement during PT in preterm infants due to the high risk of underestimation of TSB by up to 132 and 157 μmol/L from covered and uncovered skin, respectively. Although their sample was smaller and infants older than our cohort, their results were quite comparable with our findings.

Similarly, Hulzebos et al., 2019 demonstrated that TCB underestimated TSB in very preterm infants during PT when measured on covered skin. The same research group proposed different cut-off rules to improve the prediction of PT thresholds when TCB was measured during PT on covered skin. Zecca et al., 2009 conducted a study on 364 preterm and term infants requiring PT. The mean gestational age and the mean birth weight of their sample were 34.6 weeks of gestation and 2371 g, respectively, which were higher than the mean gestational age and the mean birth weight of our cohort. They reported a smaller bias between TCB readings from covered skin and TSB compared with our results. Their results demonstrated that TCB from exposed skin underestimated TSB by 54±51 μmol/L, while TCB from covered skin underestimated TSB by 3.1±53 μmol/L. However, B-A plots showed a wide TCB–TSB disagreement with a risk of underestimation of TSB by up to 106 μmol/L from covered skin and 153 μmol/L from exposed skin.

The main strength of our study is that we compared four TCB measurements at different sites and time points after phototherapy with a concurrently obtained

standard TSB measurement. Other studies compared TCB and TSB measurements but not in the same series. Other strength of our study is that it is a large prospective observational study with a substantial number of paired TCB–TSB measurements in comparison with previous studies. We have also provided recent data on the agreement between TCB and TSB which are more helpful in clinical practice than correlation coefficient. Thus, our study added significant findings to the literature on the use of the TCB device in preterm infants during and after PT.

The present study has some limitations. First, we did not examine the effect of the duration and recommencement of PT on the TSB–TCB correlation. Also, TCB was only measured from exposed skin (sternum) after PT was discontinued, and the TCB measurements from the covered area (nappy area) could have different correlation and agreement with TSB.

In conclusion, TCB measurements correlate strongly with TSB levels during and after PT. However, as a result of the wide and clinically relevant disagreement between TCB and TSB measurements during the PT phase, Phototherapy may interfere with the accuracy of TCB measurement in neonates. The appropriate application of transcutaneous bilirubinometry could aid clinical practice and avoid unnecessary management. The accuracy of TCB measurement in extremely preterm infants needs to be more carefully interpreted. Future studies are needed to develop treatment guidelines for the use of TCB measurements and to assess the reliability of TCB measurements in extremely preterm infants.

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