Original Article

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Accuracy of Transcutaneous Bilirubin Measurement from Unexposed Skin with a New Generation Device in Neonates Receiving Phototherapy

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Abstract

Aim: Transcutaneous bilirubin (TCB) measurement methods cause false results during and after phototherapy (PT), so bilirubin levels are followed by total serum bilirubin (TSB) measurement, which causes taking blood samples and increases the risk of infection. We compared the TCB measurements made with Bilicare™ and TSB measurements by preventing PT exposure of a part of the skin in newborns receiving PT and evaluating the reliability of the measurements made with Bilicare™ after PT.

Methods: This study was conducted between 01 February-30 June 2020 as a single-center cross-sectional study. The study included newborns aged 35 weeks and up who were admitted to a neonatal intensive care unit for PT. TSB measurements were reviewed by the hospital automation system. Bilicare™ bilirubin meter was used for TCB measurements. Simultaneous TSB and TCB measurements were made before PT. The skin area to be measured was covered with a radio-opaque patch. After PT, simultaneous TSB, exposed skin area TCB, and patched skin area TCB were measured. Simultaneous TSB and TCB measurements were repeated 24 h after the end of PT. The relationship between these data was evaluated statistically.

Results: This study was conducted with 171 late preterm and term newborns with a gestational age of ≥35 weeks. 79 (46.1%) were female and 92 (53.9%) were male newborns. The mean gestational age was 38.3±1.15 weeks. When maternal and newborn blood groups were evaluated, 107 (62.5%) had no blood incompatibility, 53 (30.9%) had ABO incompatibility incompatibility, 9 (5.2%) had Rh incompatibility, 1 (0.6%) had subgroup incompatibility, and 1 (0.6%) had ABO incompatibility and Rh incompatibility. The correlation coefficient (r) of TSB and TCB measurements made before PT was 0.97 and a strong correlation was found. A correlation coefficient (r) of 0.98 and a strong correlation between closed skin area TCB measurement and TSB measurement immediately after PT were detected. The correlation coefficient (r) was 0.96 and a strong correlation was found between the TCB and TSB measurements performed 24 h after the PT was terminated.

Conclusion: This study shows that TCB measurements made from unexposed areas can be safely measured in patients with PT.

Keywords: Jaundice, phototherapy, transcutaneous bilirubin, total serum bilirubin

Introduction

Jaundice is one of the most common clinical cases in the neonatal period requiring follow-up. Although hyperbilirubinemia is usually temporary, it can reach levels that require phototherapy or transfusion. Bilirubin levels in newborns can reach levels that necessitate phototherapy in 10% of term newborns and 25% of preterm newborns (1). Total serum bilirubin (TSB) measurement is the gold standard in neonatal jaundice. It is diagnosed with TSB measurement, and the TSB level should be examined periodically during phototherapy to prevent excessive or inadequate treatment (2). Blood samples should be taken from the newborn, and samples must be transported quickly without exposure to light and evaluated in the biochemistry laboratory for measuring TSB. Additionally, venous or capillary blood collection is an invasive procedure that causes disruption of skin integrity, an increased risk of sepsis, anemia, and pain in newborns (3).

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New generation transcutaneous bilirubin (TCB) meters show jaundice of subcutaneous tissue by measuring the optical density of light between 450 nm-550 nm wavelength regions (4). Bilicare™ is the only TCB meter that uses LED light resource. Unlike other new generation devices, the measurement is made from the scaphoid fossa of the auricle. It is fixed with the help of a clamp on the device. Pressure is applied automatically, not by the user. The transmitted light passes through the tissue. Some of it is absorbed by the bilirubin in the tissue, and some is reflected back to the outside. A receiver in the sensor collects and analyzes the reflected light. It is possible to get results quickly without invasive procedures with TCB measurement methods (5). With the widespread use of TCB measurement methods, the incidence of severe hyperbilirubinemia, re-hospitalization, and the number of babies receiving phototherapy has significantly decreased (6). Thanks to the advantages of TCB measurement, the use of TCB measuring devices has increased recently. In this study, we determined the correlation between TCB measurement and TSB measurements and the reliability of TCB measurement in newborns receiving phototherapy.

Methods

Study Design

After this study was planned, approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital with a decision dated April 29, 2020 and numbered 2020-38. Both verbal and written informed consent were obtained from the families of the babies. This study was conducted between 01 February-30 June 2020 as a single-center cross-sectional study.

This study was conducted on 171 infants with phototherapy indications hospitalized in the Neonatal Intensive Care Unit of University of Health Sciences Turkey, Haseki Research and Training Hospital, Pediatrics Clinic. Newborns with a gestational age of ≥35 weeks, scheduled for blood collection due to jaundice, and scheduled for phototherapy in the neonatal intensive care unit were included in the study. Gestational age was calculated according to the last menstrual period. Babies with a postnatal age greater than 28 days, skin diseases, ear structure anomalies, and previous blood transfusions were excluded from the study.

Bilirubin Measurement Technique

After the venous blood sample was taken from the babies whose TSB level was to be determined, the sample was transferred to the biochemistry laboratory of our hospital with unadulterated gel BD (Beckton Dickinson, New Jersey, USA) vacutainer biochemistry tubes. Samples were centrifuged at 1500 g for 10 min and TSB was measured spectrophotometrically after diazo reaction in a biochemistry autoanalyzer (Beckman Coulter™ AU5800 model Kyoto/Japan). Two consecutive measurements were made from the auricle scaphoid fossa with the Bilicare™ TCB measuring device within one minute after blood samples were taken, and the device was set to display the average of these two measurements. The average value shown by the device was recorded. Just before the onset of PT, the scaphoid fossa of the right auricle was covered with a non-translucent (radio-opaque) patch that was easily removable and did not damage skin integrity (Figure 1). Before PT, all newborns were stripped except for the diapers. Phototherapy was started while the newborns wore eye patches. After 4 h of PT, venous blood samples were taken from the newborns and sent to the biochemistry laboratory of our hospital in unadulterated gel BD vacutainer biochemistry tubes. The patch was removed from the auricle. Two consecutive measurements were made with the TCB measuring device from the exposed and covered auricles during PT. Average values were recorded. Venous blood samples were taken from all newborns 24 h after PT. Samples were delivered to the biochemistry laboratory of our hospital with unadulterated gel vacutainer biochemistry tubes. TCB was measured using Bilicare™ from the right ear simultaneously with venous blood collection.

Figure 1. Measurement method with Bilicare™ transcutaneous bilirubinometer

Statistical Analysis

The analyses were performed using SPSS 15.0 Statistics for Windows. Descriptive statistics: numbers and percentages for categorical variables, and mean and standard deviation for numerical variables were given. Comparisons of numerical variables in two independent groups were made using the Student's t-test in two groups when the normal distribution condition was met, the One-Way ANOVA test in more than two groups, the Mann-Whitney U test in two groups when the normal distribution condition was not met, and the Kruskal-Wallis test in more than two groups. In the non-parametric test, subgroups analyzed in more than two independent groups were made with the Mann-Whitney U test and interpreted with Bonferroni correction. Dependent group analyses were performed when the differences in numerical variables provided the normal distribution condition, paired t-test, and when the normal distribution condition was not met, with the test. The relationships between numerical tests were analyzed using Pearson correlation coefficient when the parametric test conditions were met if not Spearman correlation analysis was performed.

Results

The study was conducted with 171 late preterm and term newborns with a gestational age of ≥35 weeks. All the patients were hospitalized in our clinic and received phototherapy. Seventy-nine (46.1%) were female and 92 (53.9%) were male newborns. The mean gestational age was 38.3±1.15 weeks, and the mean birth weight was 3135±412 grams (Table 1). The distribution of Bilicare™ and TSB values measured before PT, after PT from the exposed and covered skin, and 24 h after PT is shown in Table 2 and Figure 2.

Before PT, there was a strong (r=0.976) and statistically significant positive correlation between Bilicare™ and TSB measurements (p<0.01). There was a strong (r=0.984) and statistically significant positive correlation between Bilicare™ and TSB measurements from the unexposed skin area after phototherapy (p<0.01). Additionally, there was a strong (r=0.965) and statistically significant correlation between Bilicare™ and TSB measurements at 24 h after PT (p<0.01) (Table 3).

TSB values were divided into two groups as ≤12 mg/dL and >12 mg/dL, and the measurements were evaluated between these two groups by Sperman Correlation Analysis. In the group with a TSB value of ≤12 mg/dL, there was a strong (r=0.953) and statistically significant positive correlation between Bilicare™ and TSB measurements before PT. There was a strong (r=0.920) and statistically significant positive correlation between Bilicare™ and TSB measurements from the unexposed skin area. Additionally, there was a strong (r=0.947) and statistically significant positive correlation between Bilicare™ measurements at 24 h after PT and the TSB measurements (p<0.01) (Table 3).

In the group with a TSB value >12 mg/dL, a strong (r=0.925) and statistically significant positive correlation

Table 1. Epidemiological features of cases

	Mean ± SD	
Birth week	38.3±1.5	
Age (days)	3.5±3.6	
Birth scale	3135±412	
Gender	n	%
Girl	79	46.1
Male	92	53.9
Delivery type		
NSVD	100	58.4
C/S	71	41.6
Birth week		
Late preterm	19	11.1
Early term	76	44.5
Full term	70	40.9
Late term	6	3.5
Jaundice in siblings		
None	158	92.5
Not received treatment	10	5.8
Received treatment	3	1.7
Blood type incompatibility		
None	107	62.5
ABO incompatibility	53	30.9
Rh incompatibility	9	0.6
Subgroup incompatibility	1	0.6
ABO+Rh incompatibility	1	9.1
Coombs test		
Positive	11	6.5
Negative	160	93.5
Consanguineous marriage		
Yes	45	26.3
No	126	73.7
Postnatal age (hours)		
0-24. hour	35	20.4
25-48. hour	34	19.8
49-72. hour	10	5.8
73-96. hour	16	9.3
97-119. hour	11	6.4
120. hour and above	65	38

SD: Standard deviation, NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section

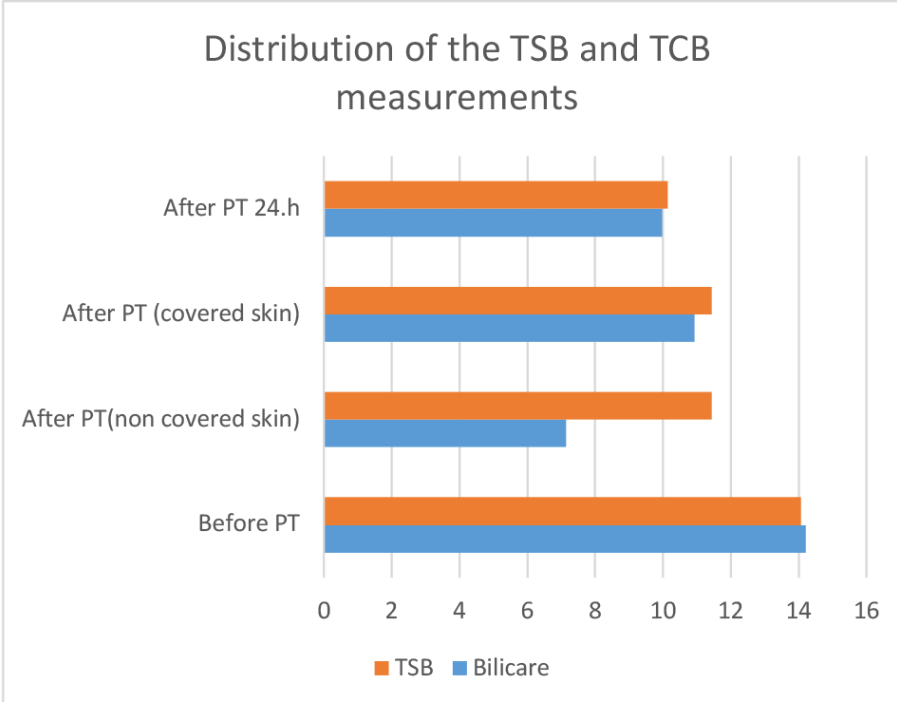

Figure 2. Mean values of TSB and TCB measurements in different time periods
TCB: Transcutaneous bilirubin, TSB: Total serum bilirubin, PT: Phototherapy

was found between the measurements made with Bilicare™ before phototherapy and TSB measurements, a strong (r=0.972) and statistically significant positive correlation was found between the measurements made with Bilicare™ from the unexposed skin area after phototherapy and TSB measurements; and a strong (r=0.955) and statistically significant positive correlation was found between Bilicare™ measurements at 24 h after PT and the TSB measurements (p<0.001) (Table 3).

Table 2. Distribution of the TSB and TCB measurements	
Before PT	**Mean. ± SD**
Bilicare™	14.21±4.71
TSB	14.08±4.63
After PT (exposed skin)	
Bilicare™	7.15±3.60
TSB	11.44±4.06
After PT (unexposed skin)	
Bilicare™	10.94±3.94
TSB	11.44±4.06
After PT 24. hour	
Bilicare™	9.98±2.54
TSB	10.15±2.61
SD: Standard deviation, TCB: Transcutaneous bilirubin, TSB: Total serum bilirubin, PT: Phototherapy	

Discussion

Today, TCB measuring devices are routinely used in the follow-up of neonatal jaundice. TCB measuring devices have provided us with the advantage of determining and monitoring the bilirubin level of newborns in their mother's arms without invasive intervention. However, current guidelines emphasize that TCB measurement is not sufficient when deciding on the need for treatment and that the result should be confirmed with TSB measurement. Additionally, it is recommended that patients who have received PT should be followed up with a TSB measurement. In the Guidelines for Approach, follow-up, and Treatment of Neonatal Jaundice published by the Turkish Neonatal Society in 2014, it is recommended that newborns who receive PT should be followed up with TSB measurement (7). Studies have shown that TCB measurements performed during and after PT in newborns may give inaccurate results (8). For this reason, frequent TSB measurement is performed in the follow-up of patients receiving PT, especially those with high bilirubin levels. In this study, we tested the reliability of the TCB measuring device in infants receiving PT to increase patient comfort and decrease the frequency of invasive procedures. The presence of hyperpigmentation, hair growth, and birthmarks in the skin area where TCB measurement is performed may affect the results. It has also been shown that there may be differences in TCB

measurement results according to different skin colors between races (9). The patients included in our study did not have any skin anomalies in the scaphoid fossa of the auricle.

In this study, we investigated whether the measurement results made with the new generation TCB measurement device Bilicare™ were correlated with TSB measurements in newborns with a gestational age of ≥35 weeks, TSB levels of 3.5-24.00 mg/dL, and newborns receiving phototherapy. During PT, we prevented the contact of one auricle with photons using a radio-opaque patch, and we measured TCB from this ear with Bilicare™ and simultaneously measured TSB from the other ear after PT. We found a strong correlation between the two measurements as well as between the Bilicare™ and TSB measurements performed 24 h after PT. Additionally, TCB measurement is considered unreliable in patients with a TCB level of 12 mg/dL or above, and TSB measurement is recommended in these patients. In newborns with a TCB level of 12 mg/dL and above, we found a significant positive correlation between TSB and TCB measurements performed before PT, from the unexposed skin area immediately after PT, and 24 h after PT (r: 0.925, r: 0.972, r: 0.955, p<0.001).

Table 3. Correlation of TSB and TCB measurements

All cases		
	Before PT TSB (mg/dL)	
	r	p
Bilicare™ (Before PT)	0.976*	<0.001
	After PT TSB (mg/dL)	
	r	p
Bilicare™ (Unexposed skin)	0.984*	<0.001
	After PT 24. hour TSB (mg/dL)	
	r	p
Bilicare™ (24. hour)	0.965*	<0.001
Cases with TSB measurements 12 mg/dL and under		
	Before PT TSB (mg/dL)	
	r	p
Bilicare™ (Before PT)	0.953*	<0.001
	After PT TSB (mg/dL)	
	r	p
Bilicare™ (Unexposed skin)	0.920*	<0.001
	After PT 24. hour TSB (mg/dL)	
	r	p
Bilicare™ (24. hour)	0.947*	<0.001
Cases with TSB measurements above 12 mg/dL		
	Before PT TSB (mg/dL)	
	r	p
Bilicare™ (Before PT)	0.925*	<0.001
	After PT TSB (mg/dL)	
	r	p
Bilicare™ (Unexposed skin)	0.972*	<0.001
	After PT 24. hour TSB (mg/dL)	
	r	p
Bilicare™ (24. hour)	0.955*	<0.001

*Bilicare™ measurements and TSB measurements were evaluated with Spearman Correlation Analysis. There is a strong correlation between TSB and Bilicare™ measurements made before phototherapy,the unexposed skin at the end of phototherapy and 24 h after phototherapy. A strong correlation was found between TSB and Bilicare™ measurements at high bilirubin levels (>12 mg/dL).
TCB: Transcutaneous bilirubin, TSB: Total serum bilirubin, PT: Phototherapy

There are limited studies in the literature conducted with Bilicare™, which is a new TCB measurement system. Several studies have reported correlations between TSB and TCB measurements (10-12). In the 2017 study by Yamana et al. in Japan (n=82), the correlation coefficient (r) was 0.91. In the study by Kitsommart et al. (10) (n=93) in Thailand, the correlation coefficient (r) was found to be 0.76. In the 2016 study of Pratesi et al. (11) in Italy (n=458), the correlation coefficient (r) was 0.56, while the correlation coefficient (r) was reported to be 0.86 in the study of Chokemungmeepisarn et al. (12) (n=214). We think that racial differences and the use of different TSB measurement methods may have caused the difference between the correlation coefficients.

The preferred method of measurement in follow-up and treatment of babies receiving PT is TSB measurement. This is because PT rays can affect the results of skin measurements. However, when skin areas are covered and not affected by PT, similar to the method in our study, it is still unclear whether measurements made from these skin areas are reliable. In the study by Costa-Posada et al. (13), a radio-opaque patch was placed on the sternum of 217 newborns before PT, and consecutive measurements were made with the Drager JM-105 TCB meter from the area closed with the patch after PT. These measurements were compared with TSB measurements made at 48, and 72 h. At the 24th hour, a difference of 0.74±1.35 mg/dL was found between bilirubin levels in the patch-covered area, and a strong correlation was found between all measurements and TSB measurements from the patch-covered area. In this study, we found a difference of 0.20±0.61 and a strong correlation in the measurements we made at the 24th hour. The difference between the results may be due to the different TCB measurement devices used and the different TSB measurement methods.

In the study conducted by Casnocha Lucanova et al. (14) in Slovakia, 150 term newborns were examined, and measurements were made from the forehead, sternum, and lower abdomen covered by the diaper with a Billcheck TCB meter 2 h after the end of phototherapy. A difference of 2.9±0.2 mg/dL was found between the measurements

made from the area covered by the diaper and the TSB measurements. In this study, we found a difference of 0.5±0.66 mg/dL between Bilicare™ measurement from the area covered with the radio-opaque patch and TSB levels. We think that the difference between the results may be because the light transmittance of the diaper is higher compared to the radio-opaque patch. Furthermore, different TCB measurement methods were used, and the measurements in this study were made immediately after PT.

In a study by Radfar et al. (15) in Iran, a radiopaque patch was placed in the lower abdomen area covered by the diaper of 134 term and 36 preterm newborns, and Billcheck TCB measurements were compared with TSB measurements. In the Unlthissent study, measurements were made at least 6 h after PT and TSB measurement was performed on blood samples taken from the heel and evaluated with a non-chemical spectrophotometric device. A strong correlation was found between the measurements.

In the study by Alsaedi (16) in Saudi Arabia, 151 term newborns were included in the study. Consecutive measurements were made with the Billchek TCB meter using a radio-opaque patch, and TCB measurements from this area after PT were compared with TSB measurements (16). The correlation coefficient (r) was reported as 0.85 in the comparison before PT, and the correlation coefficient (r) of the measurements after PT was reported as 0.80. It was found that the measurements made on the covered area unexposed to photons strongly correlated with TSB measurements. Similar to this study, the results show that there is a strong correlation between measurements.

We found a strong correlation between TCB measurements made from the covered skin area and TSB measurements in babies who received PT. Additionally, we found that TCB measurements were correlated with TSB measurements in babies for whom treatment was planned before PT. We found a strong correlation between TSB and TCB measurements 24 h after phototherapy. This study shows that TCB measurements made from skin areas covered against exposure during PT are safe and reliable. However, further studies and meta-analyses with larger patient series are needed before TCB measurements from unexposed skin areas become part of routine newborn practice.

Study Limitations

The main limitation of our study was that only one device was used on a small group of patients. It was a single-center study. A multicenter study with a larger number of patients would reveal more valuable results. Despite these limitations, the comparison of measurements at high bilirubin levels is valuable in terms of demonstrating the safety of the measurement technique. Measurements made 24 h after the end of the phototherapy are important in terms of providing data that the applied method can be reliable in terms of bilirubin-level monitoring.

Conclusion

We found a strong correlation between TCB measurements made from the unexposed skin area and TSB measurements in babies who received PT. Additionally, we found that TCB measurements were correlated with TSB measurements in babies for whom treatment was planned before PT. We found a strong correlation between TSB and TCB measurements 24 h after phototherapy. This study shows that TCB measurements made from skin areas covered against exposure during PT are safe and reliable. However, further studies and meta-analyses with larger patient series are needed before TCB measurements from unexposed skin areas become part of routine newborn practice.

Ethics

Ethics Committee Approval: Study approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital with a decision dated April 29, 2020 and numbered 2020-38.

Informed Consent: Both verbal and written informed consent were obtained from the families of the babies.

Authorship Contributions

Concept: I.Y., D.O., M.E., Design: I.Y., D.O., M.E., E.A., Data Collection and/or Processing: I.Y., E.A., Analysis and/or Interpretation: I.Y., D.O., Literature Research: I.Y., D.O., M.E., E.A., Writing: I.Y., D.O., M.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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