ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2024;95(1):34-40
DOI: 10.32641/andespediatr.v95i1.4851

ORIGINAL ARTICLE

Correlation between transcutaneous bilirubinometry and serum bilirubin in newborns ≥ 35 weeks

Correlación entre bilirrubinometría transcutánea y bilirrubina sérica en recién nacidos ≥ 35 semanas

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Received: Jun 29, 2023; Approved: November 3, 2023

What do we know about the subject matter of this study??

Some studies determine that transcutaneous bilirubin (TcB) underestimates total serum bilirubin (TSB) values, so its usefulness as a diagnostic test would be limited. On the other hand, other studies conclude that it overestimates TSB, so they consider TcB as an adequate screening method.

What does this study contribute to what is already known??

Based on the results of our study, it is concluded that TcB measurements using the Dräger jaundice meter JM-105 are closely correlated with TSB levels, making it useful as a screening technique, highlighting the excellent sensitivity and negative predictive value compared with other similar studies.

Abstract

Clinical control and monitoring of bilirubin in the neonatal stage are essential to avoid toxicity in the central nervous system. **Objective:** to determine the correlation between transcutaneous bilirubin (TcB) and total serum bilirubin (TSB) levels in newborns ≥ 35 weeks. **Patients and Method:** observational, cross-sectional, analytical, retrospective study that included 90 neonates of gestational age ≥ 35 weeks with mucocutaneous jaundice who underwent TcB and TSB measurement simultaneously between June 1, 2022, and January 31, 2023. Both variables were compared, determining their correlation. **Results:** the validity indicators were analyzed, obtaining 100% sensitivity and negative predictive value. The mean of TcB determinations was 14.84 mg/dl ± 2.27 and that of TSB was 13.1 mg/dl ± 2.39. The correlation obtained indicates that both variables are related, which is a direct correlation and, according to the prediction equation, there is an appropriate correlation between them. It was determined that TcB overestimated TSB in 95.56% of the determinations, and underestimated TSB in the rest (4.44%). Simultaneous measurements of TcB and TSB were different in all determinations with a mean difference of 1.72 ± 1.48. **Conclusions:** the non-invasive TcB method can be used as an initial screening tool for the neonatal population ≥ 35 weeks, given its adequate sensitivity and negative predictive value.

Keywords:
Newborn;
Bilirubin;
Neonatal Jaundice
Hyperbilirubinemia;
Jaundice

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Edited by:
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How to cite this article: Andes pediatr. 2024;95(1):34-40. DOI: 10.32641/andespediatr.v95i1.4851

EDITORIAL IKU

Introduction

Hyperbilirubinemia is a biochemical concept that indicates a plasma bilirubin level above normal caused by a combination of increased heme catabolism and hepatic physiological immaturity to conjugate and excrete bilirubin. It is a common morbidity in newborns and, among its causes, are hemolytic disorders (ABO or Rh incompatibility and enzymatic or corpuscular defects), polycythemia, birth trauma, infections, and prematurity, among others[1,2].

Clinical follow-up and thorough monitoring of bilirubin in the neonatal stage are essential to prevent toxicity to the central nervous system, which can lead to acute bilirubin encephalopathy, particularly Kernicterus spectrum disorders and their sequelae (cerebral palsy, choreoathetosis, sensorineural hearing loss). There is a series of curves to determine its pathological potential and the need for treatment[1-3].

Different diagnostic techniques for jaundice have been used:

1. Visual inspection: it is a subjective evaluation and is used as a criterion to indicate more precise complementary tests. Kramer's rule of cephalocaudal progression allows an estimation of total serum bilirubin (TSB) levels[4].
2. Non-invasive measurement: these are transcutaneous bilirubin (TBC) analyzers, which are portable and provide an easy, fast, non-invasive, and, therefore, painless result. These devices determine the yellowish color of subcutaneous tissue by measuring the difference in optical densities of light in the blue (450 nm) and green (550 nm) wavelength regions. The denser the transcutaneous bilirubin, the weaker the reflected blue light.
3. Invasive measurement: it reliably quantifies bilirubin levels, but it requires venous, capillary, or arterial puncture and involves risks such as pain, edema, and bleeding. In our hospital, it is performed using the azo coupling or colorimetric technique. This is based on the reaction of bilirubin with the diazo reagent to form the colored azobilirubin compound. Through the TSB, the AAP has created a nomogram that allows determining, according to hours of life, whether the bilirubin level presented should be considered significant and indicative of follow-up and/or treatment. It is classified into 4 groups: high risk (> p95), intermediate-high, intermediate-low, and low; allowing to predict the possibility of reaching a bilirubin level > p95 with the consequent risk of complications[4-6].

The gold standard test is TSB, which is an invasive test. An alternative measurement is TcB, as it is a non-invasive method that could be very useful for screening. There are studies with varying results on the correlation between TcB and TSB[1,2,4,6].

The objective of this study is to determine the correlation between TcB measured with the jaundice meter and TSB measured by the azo coupling technique in newborns ≥ 35 weeks.

Patients and Method

Observational, cross-sectional, analytical, and retrospective study that included 90 newborns born at the *Hospital Universitario de Fuenlabrada*, between June 1, 2022, and January 31, 2023. Newborns with gestational age ≥ 35 weeks and significant jaundice who underwent simultaneous TcB and TSB were selected. Newborns with severe illness and those who had previously received phototherapy were excluded.

According to the Neonatal Unit protocol, TcB measurement was performed on newborns with significant clinical jaundice, considered as mucocutaneous coloration at levels 3-4 of Kramer's cephalocaudal progression. Depending on the risk zone in which the newborn was classified based on the AAP nomogram[6], TSB was requested if TcB was < 2 mg/dl in relation to the nomogram for gestational age and risk factors.

TcB measurement was performed with the Dräger jaundice meter JM-105, which determines the mean of 3 serial readings measured in the sternal area. TSB was obtained from a capillary sample by heel or venipuncture and was collected within 45 minutes after TcB measurement and then measured by colorimetric assay.

14 variables were recorded: gestational age, prematurity (35-36 weeks), birth weight, sex, skin tone, type of delivery, type of feeding at the time of TcB/TSB measurement, etiology of hyperbilirubinemia, hours of life at TcB measurement, TSB value, TSB in low-risk, low-intermediate, intermediate-high, or high-risk zone, TcB value, TcB in low-risk, low-intermediate, intermediate-high, or high-risk zone, and whether or not they received phototherapy.

Clinical data were collected from electronic records using the SELENE® software. Excel and SPSS Statistics version 25 software were used for statistical analysis. Quantitative variables had a normal distribution and were expressed as mean and 95% confidence interval. Qualitative variables were expressed as percentages. To determine the statistical relationship between two continuous variables, Pearson's correlation coefficient was used, and the differences between the two variables were compared through the Bland-Altman plot. The validity indicators were used to determine the diagnostic value of the test: sensitivity, specificity, and positive and negative predictive values.

The study was accepted and approved by the *Hospital Universitario de Fuenlabrada* Drug Research Ethics Committee (22/106).

Results

During the study period, 786 children were born. Of those born with a gestational age equal to or greater than 35 weeks (769), 90 newborns who met inclusion criteria and underwent simultaneous TcB and TSB measurements were included.

Table 1 describes the characteristics of the study population. Regarding the hours of life for TcB and subsequently TSB measurement, the mean was 60.3 ± 21.1 hours.

Regarding the nomogram and TcB, 91.1% (n = 82) were in the intermediate-high or high-risk zone, and 8.9% (n = 8) were in the low-intermediate or low-risk zone. Of the samples in the intermediate-high or high-risk zones (82), 69.5% (57 cases) were confirmed with TSB, with 30.5%[25] false positives. Among the samples in low-intermediate or low-risk zones[8], all were confirmed in those zones by TSB, with no false negatives. Likewise, validity indicators were analyzed obtaining a sensitivity and negative predictive value of 100% (Table 2).

Table 1. Study population characteristics

Variables	Values(n = 90)
Average gestational age (weeks)	37.45 ± 1.94
- Term % (n)	57.8 (52)
- Preterm (35-36 weeks % (n)	42.2 (38)
Average birth weight ± DE	3021.6 ± 577.9
Gender % (n)	
- Male	66.7 (60)
- Female	33.3 (30)
Skin color % (n)	
- Light brown	72.2 (65)
- Medium brown	21.1 (19)
- Dark Brown	6.7 (6)
Mode of delivery % (n)	
- Normal vaginal delivery	60 (54)
- Instrumental delivery	26.7 (24)
- Caesarean section	13.3 (12)
Feeding mode % (n)	
- Exclusive breast milk	70 (63)
- Mixed feeding	12.2 (11)
- Formula only	17.8 (16)
Presumed cause of hyperbilirrubinemia % (n)	
- ABO/Rh incompatibility	26.7 (24)
- Suboptimal intake	22.2 (20)
- Polycythemia	10 (9)
- Small for gestational age	7.8 (7)
- Cephalohematoma	3.3 (3)
- Unclassified	30 (27)
Photoherapy % (n)	
- Yes	42.2 (38)
- No	57.8 (52)

RNPT: recién nacido pretérmino. RNT: recién nacido a término. LM: lactancia materna. FA: fórmula artificial. CIR: crecimiento intrauterino retardado.

TcB values had a mean of 14.84 mg/dl ± 2.27 and TSB values of 13.1 mg/dl ± 2.39. The Pearson correlation coefficient between the values obtained by TcB and TSB was 0.78 (95% CI 0.71-0.85), indicating a high positive correlation of these variables. In addition, for our sample, the TSB prediction equation was $y = 0.881x + 0.4327$, showing an appropriate correlation between TcB and TSB values (Figure 1).

Regarding the timing of bilirubin sampling, the Pearson correlation coefficient between 0-48 hours of life was 0.82, and between 49-120 hours of life was 0.70. Through the Bland-Altman plot, it was determined that TcB overestimated TSB in 95.6% of cases (86 measurements) and underestimated it in 4.4% (4 measurements) without any common characteristics among these latter (Figure 2). In these 4 patients, there was no risk, and the greatest difference between TcB and TSB was 1.7 mg/dl. Simultaneous TcB and TSB measurements were different in all measurements with a mean difference of 1.72 ± 1.48.

For TcB values in low-intermediate or low-risk zones according to the nomogram (n = 8), the mean difference between TcB and TSB values was 0.84 ± 0.78, with the jaundice meter overestimating TSB in 100% of the samples. The Pearson correlation coefficient between TcB and TSB figures in these values was 0.88 (95% CI 0.78-0.98).

For TcB values in the intermediate-high or high-risk zone (n = 82), the mean difference was 1.56 ± 1.34, with the jaundice meter overestimating TSB in 95.1% (78) of the samples. The correlation coefficient between TcB and TSB figures in these values was 0.74 (95% CI 0.64-0.84). In cases where TcB was underestimated, the difference values between TcB and TSB showed a mean of 1.86 ± 1.35, and in cases where it was overestimated, the mean was 1.29 ± 0.4.

Finally, the correlation coefficient between TcB and TSB was also calculated for a series of variables (Table 3).

Discussion

The recommendations of the American Academy of Pediatrics (AAP) indicate that the use of TcB analyzers is valid and reliable, with an adequate correlation between TcB and TSB measurements (generally TcB < 3 mg/dl and TSB < 15 mg/dl)6. The mean difference between TcB measurements and TSB may

depend on skin melanin concentration and the instrument used to measure TcB[6]. For example, the *BiliChek* device may overestimate TSB at higher levels (predominantly if >15 mg/dL) in newborns with higher cutaneous melanin concentration with a mean of 1 to 2 mg/dL, and the Dräger JM-103 and JM-105 devices may overestimate TSB with a mean of 0.7 to 2.5 mg/dl[6]. In our sample, the mean difference of TcB and TSB measurements was 1.72 ± 1.48. For TcB values in low-intermediate or low-risk zone, the mean difference was 0.84 ± 0.78, and in intermediate-high or high-risk zone was 1.56 ± 1.34, therefore, the difference was greater in high values (usually with TSB > 15 mg/dl), which was also consistent with AAP and other studies[4,7-10].

In our study, the Pearson correlation coefficient between TcB and TSB values was 0.78, indicating a high positive correlation between the variables, and it can be inferred that it is a clustered and upward-trending sample, similar to other published studies using the same device[7-9]. Also, the correlation coefficient for TcB and TSB values in the intermediate-high or high-risk zone was 0.74 and in the low-intermediate or low-risk zone was 0.88, indicating that the correlation is worse at higher values, similar to the conclusions of other reviews using the same analyzer[7-9]. We show a comparative table with the results described in several articles regarding the Pearson correlation coefficient for TcB and TSB values. Comparing the results with our study, the correlation coefficient is similar to papers that use Dräger JM-105 and Kejian KJ-8000 devices but better than the Dräger JM-103 analyzer.

Through the Bland-Altman plot, it is established

Table 2. Table sensitivity and specificity

		TSB	
TCB	High/intermediate-high	Low/intermediate-low	Total
High/ intermediate-high	57 (VP)	25 (FP)	82
Low/ intermediate-low	0 (FN)	8 (VN)	8
Total	57	33	90

TCB: transcutaneous bilirubin. TSB: total serum bilirubin

- Sensitivity (S): 100% (CI 95%: 93,7-100)
- Specificity (E): 24,2% (CI 95%: 12,8-41)
- Positive predictive value (PPV): 69,5% (CI 95%: 58,9-78,4)
- Negative predictive value (NPV): 100% (CI 95%: 67,6-100)

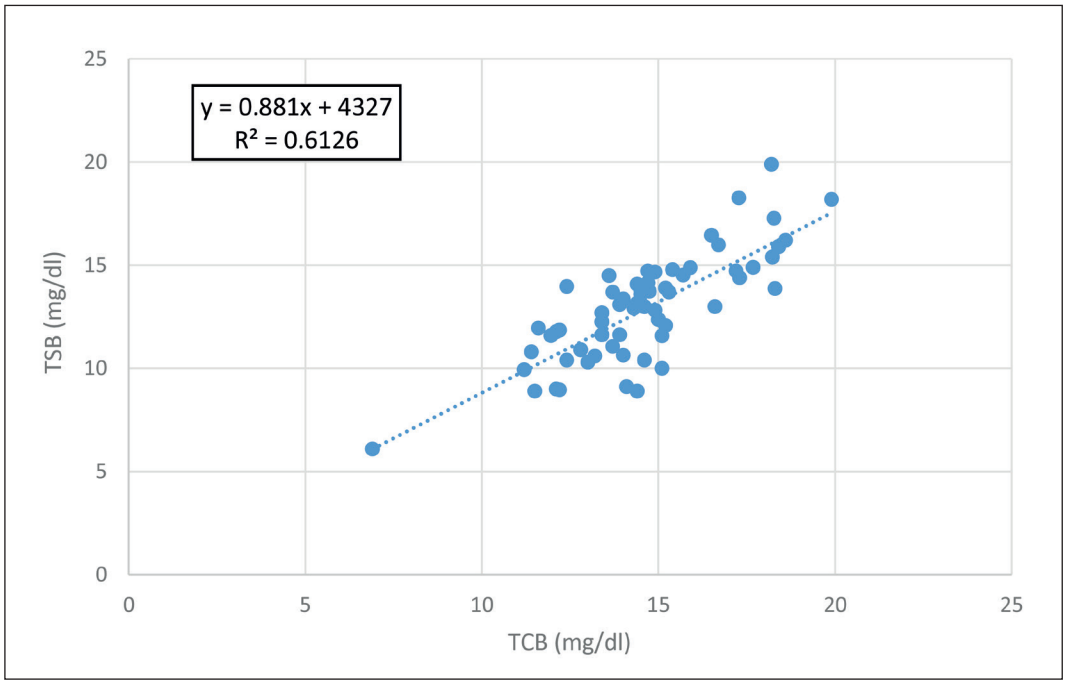

Figure 1. Scatter plot of TSB (total serum bilirubin) versus TCB (transcutaneous bilirubin).

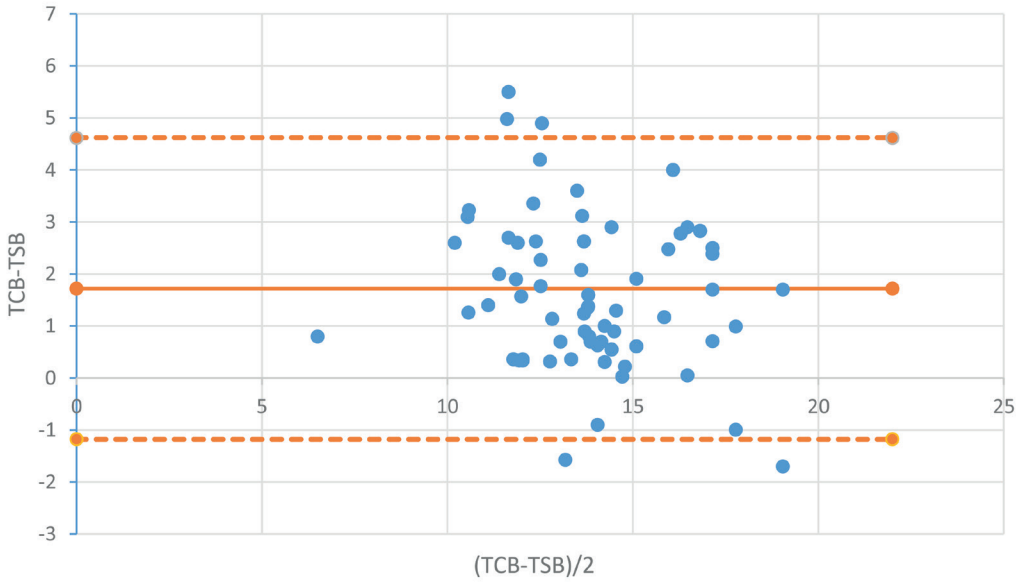

Figure 2. Bland-Altman plot. TSB: total serum bilirubin. TCB: transcutaneous bilirubin..

that in our sample, there is good agreement, similar to other reviews[7-9,11]. Mohamed et al. showed through a Bland-Altman plot analysis a good agreement between TcB (measured with the Dräger JM-105 device) and TSB, with only 8/130 (6.2%) of samples outside the established limits[8]. In our study, good agreement is also observed with 5.55% (5/90) of measurements outside the established limits, implying a very homogeneous sample.

Table 3. Variable analysis

Variables	Pearson Correlation Coefficient	Confidence Interval (95%)
Average gestational age		
- Preterm (35-36 weeks)	0.72	0.43-0.93
- Term	0.84	0.74-0.91
Skin color		
- Light brown	0.92	0.80-0.99
- Medium brown	0.76	0.45-0.94
- Dark Brown	0.52	-0.30-0.92
Feeding mode		
- Exclusive breast milk	0.79	0.4-0.94
- Mixed feeding	0.89	0.78-0.95
- Formula only	0.70	0.42-0.85
Presumed cause of hyperbilirrubinemia	0.78	0.42-0.93
- ABO/Rh incompatibility	0.85	0.76-0.94
- Suboptimal intake	0.86	0.70-0.89
- Polycythemia	0.92	0.81-0.98
- Small for gestational age	-1	-
- Cephalohematoma	0.72	0.41-0.88
- Unclassified		

RNPT: recién nacido pretérmino. RNT: recién nacido a término. LM: lactancia materna. FA: fórmula artificial. CIR: crecimiento intrauterino retardado.

Regarding the timing of bilirubin sampling, the correlation coefficient between 0-48 hours of life was 0.82, and between 49-120 hours of life was 0.70. These results are similar to those described by Olusanya using the *BiliChek* and Dräger JM-103 devices, and it is because with more hours of life, bilirubin levels are higher and, therefore, the discrepancy is greater[12].

In the analysis of the possible influence of some variables on the concordance between TcB and TSB values, in our study, it was found that regarding gestational age, the correlation coefficient in preterm and full-term newborns was 0.72 and 0.84, respectively. However, the reviewed articles show a better correlation in preterm newborns compared with full-term newborns, probably due to the higher levels they present[9-11]. In our result, the different sample sizes of 38 preterm newborns and 52 full-term newborns are possibly influencing.

Regarding skin tone, it has a lower correlation coefficient in those with light and dark brown skin compared with those with fair skin. This finding does not coincide with published articles using the same device, where skin tone does not seem to interfere, but it does with the study by Esquea-Guerrero et al. using the Kejian KJ-8000 analyzer and concluding that fair-skinned newborns have less discrepancy than mulatto-skinned ones[8-10].

Regarding the type of feeding in our sample, a very similar correlation coefficient was observed[7].

Table 4. Comparative table of published studies

Article	Bilirubinometer	Pearson Correlation Coefficient
Our studio	*JM-105 Dräger*	0.78
Ohishi et al.[7]	*JM-105 Dräger*	0.85
Mohamed et al.[8]	*JM-105 Dräger*	Forehead: 0.82. Sternum: 0.80
Kumar et al.[9]	*JM-105 Dräger*	Forehead: 0.80. Sternum: 0.82
Chimhini et al.[4]	*JM-103 Dräger*	Forehead: 0.70. Sternum: 0.76
[E]squea-Guerrero et al.[10]	*Kejian KJ-800*	Forehead: 0.91. Sternum: 0.78

Finally, regarding the etiology, the correlation coefficient is very similar in all of them, except in the diagnosis of cephalohematoma whose result is -1 (perfect negative correlation), but since it only includes 2 newborns, this result should not be considered. It can be concluded that the etiology of hyperbilirubinemia does not generate differences in the correlation coefficient.

In our review, TcB measurement was performed in the sternal area. In the published literature, similar studies have been conducted, whose TcB measurements were made in the sternal and forehead areas. Kumar et al. and Esquea-Guerrero et al. observed a positive and significant linear correlation between TcB and TSB values in the sternum, as well as between TcB and TSB in the forehead, considering both locations (sternum and forehead) valid for TcB sampling[9-10].

In similar studies, the TcB measurement as a screening test shows data consistent with our results: sensitivity 100%, specificity 24.2%, PPV 69.5%, and NPV 100%. Therefore, sensitivity and NPV are excellent, so it is unlikely that a newborn with a significant level of hyperbilirubinemia will not be correctly detected. Besides, it is concluded that TcB cannot be considered a reliable method for making therapeutic decisions (such as phototherapy, immunoglobulin, and exchange transfusion) since it presents low specificity and low PPV.

The limitations of our study are that it is a retrospective study and that our data cannot be applied to the population of preterm newborns of less than 35 weeks as they have not been studied.

Conclusions

Our study concludes that this non-invasive method can be used as an initial screening tool for the neonatal population ≥ 35 weeks, highlighting the excellent sensitivity and negative predictive value, thus avoiding the pain, edema, bleeding, and infection risk of invasive techniques.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent6 of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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