



## Validation of Transcutaneous Bilirubin in Comparison with Serum Bilirubin for the Detection of Hyperbilirubinemia in Neonates

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### Abstract

**Background:** Neonatal hyperbilirubinemia is a common and dangerous complication that should be diagnosed as soon as possible. This study aimed to validate transcutaneous bilirubin in comparison with serum bilirubin for the detection of hyperbilirubinemia in neonates.

**Methods:** This cross-sectional study was conducted in 280 infants with jaundice who were referred to Bahar Hospital in Shahroud in 2016. The serum bilirubin was measured by the photometric method. Three measurements of transcutaneous bilirubin were performed (by Bilicheck) for each infant, and their average was recorded. The sensitivity and specificity of transcutaneous bilirubin measurements were assessed in comparison with the measurements using laboratory methods as the gold standard using ROC analysis.

**Results:** Of the 280 neonates, 153 (54.6%) were male. The mean age of the patients was 11.77±4.6 days. The mean bilirubin level was 16.9±10.1 mg/dl measured using the BiliChek method and 15.3±9.5 mg/dl using the laboratory method, and the difference was significant ( $P < 0.04$ ). The sensitivity and specificity of the BiliChek measurements in neonates were 88.3% and 73.6%, respectively. According to the findings from the ROC curve, the cutoff point was determined to be more than 14.7 units (surface area below the curve (AUC)=87.5%).

**Conclusions:** The results of this study showed that the accuracy (sensitivity and specificity) of the BiliChek device was good and can be used to measure the neonatal bilirubin.

**Keywords:** Hyperbilirubinemia, Serum bilirubin, Transcutaneous bilirubin, Neonates.

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## Introduction

Hyperbilirubinemia is one of the most common problems in the neonatal period, which in most cases is not complicated and improves without treatment.<sup>1</sup> However, in some neonates, jaundice is severe and requires treatment. Brain complications and kernicterus are the major adverse consequences of this phenomena.<sup>1-2</sup> Often, the cause of jaundice is unclear, and the underlying causes of jaundice are also different, including the incompatibility of the mother's blood Rh with that of the baby, thyroid deficiency in the infant, red blood cell enzyme deficiency such as favism disease, jaundice due to lack of breast milk, and other reasons.<sup>3</sup> The risk of jaundice depends on

the weight and age of the baby and usually occurs in low birth weight and premature infants with lower bilirubin levels.<sup>1</sup>

Neonatal jaundice is a common complaint, but few babies need medical treatment. Regardless of the cause, total serum bilirubin (TSB) is above the standard for that weight and age, and phototherapy is used to prevent serious complications, such as kernicterus.<sup>4-5</sup>

It is necessary to know the amount of bilirubin to treat neonatal jaundice appropriately, which is usually done in three ways: ocular, dermatological, and laboratory method evaluation.<sup>6</sup>

The most common goal of neonatal screening is to detect jaundice. The serum bilirubin measurement is not an ideal method because of the need for taking blood samples from the infant which leads to an increased risk of infection, anemia, pain, and stress. Also, this method is problematic, stressful, time-consuming, and costly.<sup>7-8</sup>

Although the eye evaluation method is simple, it has two major problems. One is that it relies on the individual's experience and is not a precise and reliable criterion; second, the probable estimation of jaundice in this method is based on skin color and its dependent factors that can change in different conditions.<sup>8</sup> This method is useful only in the early stages of the onset of jaundice and is not reliable in infants who have undergone photodynamic therapy. Also, the color of the skin, the color of clothing, and the light of the examination environment can completely overshadow the visual acuity.<sup>9</sup>

Therefore, in recent years, noninvasive methods of bilirubin assessment have been proposed to reduce the need for blood sampling and reduce patient stress and laboratory costs. One of these non-invasive methods is jaundice transcutaneous bilirubinometry (TCB).<sup>8-9</sup>

Bilicheck devices measure the severity of jaundice based on the light reflected from the skin of the patient. BiliChek is based on the reflection of the white light waves that leak on the baby's skin.<sup>10-12</sup> The optical radiation reflected from the infant's skin is analyzed in a BiliChek program, and the serum bilirubin is measured based on pre-defined patterns.<sup>10</sup> The manufacturers of the BiliChek device claim that the accuracy of the device is optimal, and factors such as the maturity of the skin and the amount of melanin and hemoglobin do not affect its accuracy. It is also claimed that the accuracy of the BiliChek apparatus is very suitable for measuring bilirubin in different ethnicities and term and near-term neonates.<sup>12-13</sup> According to the results of some studies that have reported the accuracy of the BiliChek

apparatus to be optimal, it may be possible to replace the laboratory measurement of bilirubin with it.<sup>14</sup> Because the accuracy of the BiliChek is not yet exactly determined, this study aimed to validate the TCB for the detection of hyperbilirubinemia in comparison with serum bilirubin measurement in neonates at Bahar Hospital in Shahroud in 2016.

## Materials and Methods

This cross-sectional study was conducted at Bahar Hospital in Shahroud. The study was conducted over a period of 18 months (October 2015 to March 2016). This study included 280 infants with jaundice. Inclusion criteria: All infants at 36–39 weeks' gestational age, weighing between 2500 and 3500 grams, physically healthy, and with parental consent to participate in the research were included.

Infants with any blood, liver, or metabolic illness, admission to the Neonatal Intensive Care Unit (NICU), requiring exchange transfusion, and parental dissatisfaction were excluded.

Ethics approval: This study has an ethics code number (IR.SHMU.REC.1394.143) from the Research Deputy of Shahroud University of Medical Sciences. The essential information and the objectives of the study were explained to the parents of the infants, and written consent was obtained for participation in the study.

In this study, simultaneously with the measurement of serum bilirubin, the skin bilirubin level was measured using the BiliChek apparatus. The BiliChek device was approved by the US Food and Drug Administration in 2001. Also, it has gained standards for medical equipment.<sup>11</sup> Serum bilirubin was measured in a laboratory in a standard manner (with the help of the Olympus Diagnostic Kit, UK). Immediately after the serum bilirubin testing, neonatal bilirubin measurements were performed using a BiliChek set (through the baby's forearm in the lying condition). The probe of the BiliChek was calibrated before each measurement, according to the manufacturer's instructions. Then, with the help of a button, a light was projected on the baby's skin, and BiliChek automatically analyzed the reflected waves in less than 5-minute and read the average of the calculated number in either  $\mu\text{mol/L}$  or  $\text{mg/dL}$ . The forehead area used for the TCB was not exposed to direct sunlight and/or phototherapy. All phototherapy lights were turned off while the BiliChek measurement was taken. Care was taken to avoid skin areas with bruising, birthmarks, hematomas, or excessive hairiness. The gestational age, birth weight, postnatal age, and ethnicity were recorded.

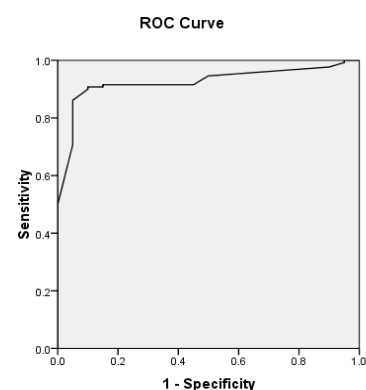
All the collected data from the skin and lab measurements of bilirubin were recorded on a computer and analyzed. The relationship between the TCB values and TSB measurements was investigated by evaluating the sensitivity, specificity, positive predictive value, and negative predictive value. In this situation, the laboratory bilirubin measurement was considered to be the 'gold standard' that determined treatment ( $\text{TSB} \leq 13 \text{ mg/dl}$  was considered normal, and  $\text{TSB} > 13 \text{ mg/dl}$  was considered hyperbilirubinemia).<sup>9</sup> A ROC curve was constructed to investigate the relationship between the bilirubin measurements. The data were analyzed using SPSS software.

## Results

Of the 280 neonates, 153 (54.6%) were male; 31.8% were in the age group of 11–15 days. Breastfeeding was achieved in 69.6%, and the remaining infants were fed with synthetic milk. The main demographic characteristics of the study population are presented in table 1. The mean bilirubin level was  $16.9 \pm 10.1 \text{ mg/dl}$  using the BiliChek device and  $15.3 \pm 9.5 \text{ mg/dl}$  using the laboratory method, and the difference was significant ( $P < 0.04$ ). The sensitivity of the BiliChek apparatus in neonates was 88.3% (95% CI: 85.5–94.0), specificity 73.6% (95% CI: 71.6–77.4), positive predictive value 85.5% (95% CI: 79.4–89.5%), and negative predictive value was 57.8% (95% CI: 53.5–61.4). The ROC curve was used to determine the best cutting point and to compare the diagnostic value. In this method the bilirubin values of the BiliChek were compared with standard laboratory method in healthy infants by measuring the area under curve. In this way, the ROC curve was obtained, with the area under the curve representing the test detection power. According to the findings from the ROC curve, the cutoff point was more than 14.7 units with a surface area below the curve (AUC) of 87.5% (95% CI: 85.2–90.7). In other words, values higher than 14.7  $\text{mg/dl}$  in the standard laboratory method with a sensitivity of 90.7% and specificity of 72.8% were considered as positive tests, and lower values were considered as negative tests. At this point, the test has the most sensitivity and specificity (figure 1).

**Table 1. Demographic characteristics of the study population**

Variables	Frequency (%)	Mean $\pm$ SD
Sex		
- Boy	153(54.6)	-
- Girl	127(45.4)	-
Age (days)	-	11.77 $\pm$ 4.6
Weight (gram)	-	3464.64 $\pm$ 353.64



**Figure 1. ROC curve for transcutaneous bilirubinometry (TCB)**

## Discussion

In the present study, the sensitivity and specificity of the BiliChek device were found to be appropriate and acceptable.

The diagnosis and timely treatment of jaundice in the first few days of life can prevent serious complications.<sup>15-16</sup> Problems with admission and hospitalization are one of the barriers to timely action in these patients. The basis of proper treatment in all these cases is the rapid and reliable detection of jaundice, which can be controlled by timely action. Also, it is necessary to ensure that the use of the new bilirubin measurement tool is safe and free of side effects for infants.<sup>17</sup> There is no need for the alternative methods of measuring bilirubin to be as accurate as the standard laboratory method to the extent that high bilirubin is reported because the concentration of bilirubin is not absolute, and there are several factors affecting it. The decisions on therapeutic proceedings such as phototherapy are based on clinical judgment.<sup>18-20</sup> The current methods of measuring bilirubin are dependent on venous blood sampling and are always accompanied by resistance and dissatisfaction of the families and severe crying of the newborns.<sup>21</sup> The BiliChek device can be very useful due to its functional nature, which does not require blood sampling and does not cause any pain or stress to the baby and its parents. Regarding the accuracy of the results obtained using this device, comprehensive studies have not been carried out, and the number of studies carried out has had different results.<sup>22-24</sup> The skin bilirubin measurements are significantly less than that obtained using the laboratory methods, but because of the lower complications and risks of neonatal sampling, most pediatricians prefer this method.<sup>25</sup> Use of BiliChek for repeated measurements of bilirubin in infants cause less concern regarding the incidence of sampling complications.<sup>26-27</sup> Therefore, repeated measurements of neonatal bilirubin can be done with this method without the fear of blood sampling complications.<sup>28</sup>

This finding was somewhat similar to the study by Knüpfer et al. However, they stated that the TCB measurement devices could only be used in specific and limited situations.<sup>29</sup> One of the most important findings of this research was the cutoff-point on the ROC curve. Using the results of the ROC curve, the difference between the two methods of skin and serum bilirubin measurement can be corrected as, in the BiliChek method, the amount of abnormal bilirubin was found to be 14.7 mg/dl instead of 13 mg/dL as determined using the TSB method.<sup>30</sup> Also, the lack of need for frequent blood sampling from infants is an important advantage of the BiliChek device because it reduces blood sampling complications and also prevents anemia.<sup>28</sup>

To conclude, the results of the present study showed that the BiliChek device is a simple, reliable, and acceptable alternative to laboratory measurement of bilirubin. Using BiliChek reduces unnecessary blood sampling in newborns, with subsequent clinical benefits.

The limitation of the present study was that the parents did not have sufficient information about the BiliChek method, which sometimes provoked resistance in this experiment. This problem was resolved by explaining about the method and ensuring cooperation from the parents.

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## Conflict of Interest

The authors declared that they have no conflict of interest.

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