Trans-Cutaneous Bilirubinometery versus Serum Bilirubin in Neonatal Jaundice

Manoochehr Mahram[1], Sonia Oveisi[2], and Najmeh Jaberi[3]

[1] *Department of Pediatrics, Children Growth Research Center, Qazvin University of Medical Science, Qazvin, Iran*

[2] *Department of Community of Medicine, Metabolic Diseases Research Center, Qazvin University of Medical Sciences, Qazvin, Iran*

[3] *School of Medicine, Qazvin University of Medical Science, Qazvin, Iran*

Received: 22 Jan. 2014; Accepted: 23 Oct. 2014

Abstract- Hyperbilirubinemia is a common problem in neonates and causes serious complications. Thus, serial measurements of bilirubin should be done. This assessment is done through two methods of laboratory measurement in serum sample and transcutaneous bilirubinometer. This descriptive study compared transcutaneous bilirubin assessment and laboratory serum bilirubin. Bilirubin level was assessed among 256 neonates admitted to the Qods Children's Hospital in Qazvin- Iran, because of neonatal indirect jaundice, through two methods of transcutaneous bilirubinometery from two sites of forehead and sternum and laboratory measurement of bilirubin in serum. The cases were non-hemolytic icteric term neonates weighing 2500 gram or more and had not received phototherapy or other treatments. Neonates with hemolytic forms of jaundice, sepsis and suspicious to metabolic disorders were excluded. Assessments by means of KJ-8000 transcutaneous bilirubinometer from two sites of forehead and sternum and through laboratory measurement of serum bilirubin were registered and analyzed. The results of the current study showed that there was a correlation of 0.82 between serum bilirubin and transcutaneous forehead bilirubin assessment and for the used device sensitivity of 0.844; specificity of 0.842, Youden Index of 0.709 and Shortest of 0.042 for a cut-off of 12.4 in bilirubin of participants. Furthermore, Likelihood Ratio positive and negative (LR) were 5.665 and 0.164, respectively and diagnostic Odds Ratio (LR+/LR-) was 34.56. Transcutaneous bilirubinometery can be considered as a reliable tool to assess bilirubin for the screening of neonatal jaundice in term neonates.

Acta Med Iran 2015;53(12):764-769.

Keywords: Neonatal Jaundice; Transcutaneous bilirubinometery; Bilirubin; Sensitivity; Specificity

Introduction

Hyperbilirubinemia is a common and in most cases benign problem in neonates. Jaundice is observed during the first week of life in approximately 60 percent of term infants and 80 percent of preterm infants. Hyperbilirubinemia itself does not have any harm for the body unless exceeds a level which leads to kernicterus, or bilirubin encephalopathy, that is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs have a grave prognosis; more than 75% of infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Mental retardation, deafness, and spastic quadriplegia are common. The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable and the duration of exposure to high bilirubin levels needed to produce toxic effects is unknown (1).

To prevent this complication and to do appropriate management such as blood exchange or phototherapy as soon as possible, all susceptible neonates with jaundice are checked for serum level of bilirubin. Once this check-up is merely as a screening test and in some cases with near-critical levels, serial measurements should be done. Besides the traditional method of measurement of Total Serum Bilirubin (TSB) level, today, non-invasive techniques for Transcutaneous Measurement of

Corresponding Author: S. Oveisi
Department of Community of Medicine, Metabolic Diseases Research Center, Qazvin University of Medical Sciences, Qazvin, Iran
Tel: +98 912 5042401, Fax: +98 281 3326033, E-mail address: soveisi@razi.tums.ac.ir

Bilirubin (TCB) are used. This is recommended to use TCB just to screen infants, and determination of serum bilirubin level is indicated in patients with elevated age-specific transcutaneous bilirubin measurement, progressing jaundice, or risk for either hemolysis or sepsis (1,2).

Blood sampling for measurement of TSB is a painful procedure, may increase the risk of infection and scar formation, may lead to anemia in the cases of frequent sampling especially in premature newborns and also causes discomfort to infants and anxiety in parents (3,4). On the other hand, TCB is a safe and rapid method to assess the level of bilirubin.

This descriptive study was carried out to compare transcutaneous bilirubin assessment from two sites of forehead and sternum to laboratory measurement of bilirubin in serum.

Materials and Methods

A total of 256 neonates admitted to the Qods Children's Hospital in Qazvin- Iran, because of neonatal indirect jaundice and for receiving phototherapy were studied from March to September 2012. The sample size was calculated by the below-mentioned formula, considering *P*=0.08 and d=0.05:

$$n = \frac{p(1-p)(z_{1-\frac{\alpha}{2}})^2}{d^2}$$

All parents of the children provided written informed consent before enrollment and results were confidential. The ethics review board of the Qazvin University of Medical Sciences approved the study. Bilirubin was evaluated using two methods: The first, serum bilirubin was measured by laboratory, and then bilirubin was assessed by transcutaneous bilirubinometer in two sites (forehead and sternum). The used device was KJ-8000 Transcutaneous Jaundice Meter, made by Xuzhou Kejian High-Tech Co., Ltd. with a registered product standard number of YZB/SU0372/2007.

The used device has an accuracy of ≤6 percent preset value and continuous variable of ≤3 percent. Choosing forehead and sternum for transcutaneous bilirubin assessment was with regard to some previous studies in which the best correlation with TSB had been shown (5-6).

The other background data used for this study included body weight, sex, and gestational age. Body weight was measured by means of a balanced beam scale while wearing only a baby's nappy.

Excluding low birth-weight and/or preterm neonates, neonates with hemolytic forms of jaundice, sepsis and suspicious to metabolic disorders; the cases were selected among non-hemolytic term neonates weighing 2500 gram or more, hospitalized to receive phototherapy. All included neonates in the study had not been under phototherapy, or other types of treatment before hospitalization and also all assessments of TCB and TSB were done at the beginning of entry and before receiving phototherapy in our hospital.

Excel office 2007 and SPSS version 19 were used for descriptive analyzes. Differences between serum bilirubin and transcutaneous one were tested using Pearson correlations in two stages: (a) in all cases (b) in neonates with bilirubin more than 15. The Receiver Operating Characteristic (ROC) curve was used to the classifying beginning of phototherapy in non-hemolytic icteric term neonates with 2500 gram and more. ROC has correctly discriminated subjects developing end points from the others without end points (0.5 and 1.0 are chance and perfect discrimination respectively). Sensitivity and specificity were measured to present the probability of truly identifying diseased and non-diseased individuals, respectively. In addition, the Youden Index as the maximum potential effectiveness of transcutaneous test (sensitivity +specificity -1) and the point of shortest distance value (1-sensitivity) 2 + (1-specificity) 2 were measured. These methods were used to diagnose the optimal bilirubin cut-off in neonatal jaundice as predispose to begin phototherapy (7,8).

Furthermore, to assess the value of performing transcutaneous bilirubinometer as a diagnostic test for treatment, the Likelihood Ratio Positive (LR+) and Likelihood Ratio Negative (LR–) were assessed.

Results

A total of 256 neonates, including 129(50.4%) girls and 127(49.6%) boys, with average gestational age, ranged between 37 to 41 weeks (39.58 ± 0.83) consisted the samples. Data of bilirubin in serum and transcutaneous assessment in forehead and sternum are shown in Table 1.

Furthermore, we have interested to evaluate the correlation between serum bilirubin and transcutaneous bilirubin in neonates in Tables (2,3). (Table 2: in 256

neonates and Table 3: in 123 neonates with serum bilirubin more than 15). Results indicated that ρ Pearson is decreasing from 0.82 to 0.55 when serum bilirubin is rising in neonates.

Table 1. Mean and SD of bilirubin in serum and transcutaneous bilirubin in forehead and sternum

	Min.	Max.	Mean	75th percentile	SD
TCB-forehead	2.00	24.80	12.62	16.40	4.69
TCB-sternum	3.50	24.00	11.99	17.30	5.31
Serum Bilirubin	6.10	27.00	15.02	19.20	4.89

*TCB=Transcutaneous Measurement of Bilirubin

Table 2. Comparing the results of TCB from forehead and sternum and TSB in 256 neonates

		TCB-forehead	TCB-sternum	Serum Bilirubin
TCB-forehead	Pearson Correlation	1		
	Sig. (2-tailed)			
TCB-sternum	Pearson Correlation	.923*	1	
	Sig. (2-tailed)	.001		
Serum Bilirubin	Pearson Correlation	.820*	.830*	1
	Sig. (2-tailed)	.001	.001	
	N	256	256	

*Correlation is significant at the 0.01 level (2-tailed). TCB=Transcutaneous Measurement of Bilirubin

Table 3. Comparing the results of TCB from forehead and sternum and TSB in 123 neonates with TSB>15 mg/dL

		TCB-forehead	TCB-sternum	Serum Bilirubin
TCB-forehead	Pearson Correlation	1		
	Sig. (2-tailed)			
TCB-sternum	Pearson Correlation	.883*	1	
	Sig. (2-tailed)	.001		
Serum Bilirubin	Pearson Correlation	.549*	.583*	1
	Sig. (2-tailed)	.001	.001	
	N	123	123	123

*Correlation is significant at the 0.01 level (2-tailed). TCB=Transcutaneous Measurement of Bilirubin

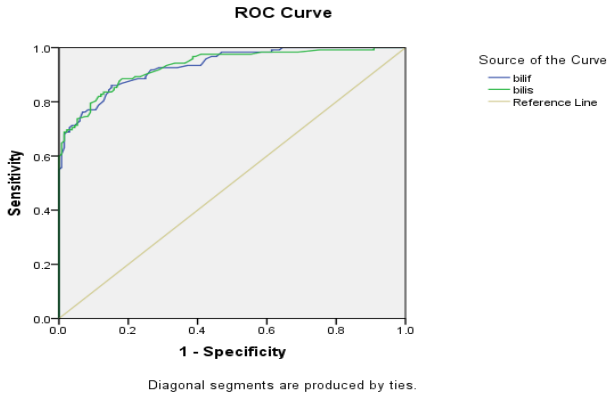

Figure 1. Sensitivity and specificity for trans-coetaneous bilirubin test by ROC analysis

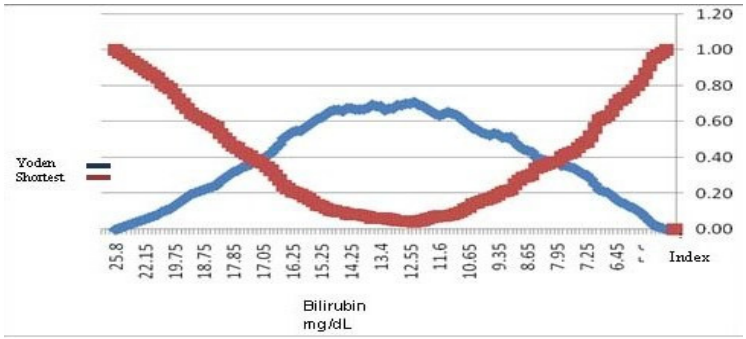

Figure 2. Youden Index and Shortest for cut-off 12.4 in bilirubin of patients with neonate jaundice

Moreover, for the used device in this study regarding bilirubin assessment through the forehead, ROC analysis showed the sensitivity of 0.844 and specificity of 0.842 (Figure 1), Youden Index of 0.709 and Shortest of 0.042 for cut-off 12.4 in serum bilirubin in neonatal jaundice (Figure 2). On the other hand, LR+ and LR-were 5.665 and 0.164, respectively. Diagnostic Odds Ratio (LR+/LR-) was 34.56.

Discussion

Regarding the results of the current study, TCB underestimated measures comparing to TSB. For the used device of percutaneous bilirubinometery from the forehead, there is a sensitivity of 0.844; specificity of 0.842, Youden Index of 0.709 and Shortest of 0.042 for a cut-off of 12.4 in bilirubin of patients with neonatal jaundice. Furthermore, LR+ and LR- were 5.665 and 0.164, respectively and diagnostic Odds Ratio (LR+/LR-) was 34.56.

The Youden index (J), a function of sensitivity (q) and specificity (p), is a commonly used measure of overall diagnostic effectiveness. This index ranges between 0 and 1, with values close to 1 indicating that the biomarker's effectiveness is relatively large and values close to 0 indicating limited effectiveness (10) and for evaluation, the values of 0.55, 0.65, 0.75, and 0.85 indicate that the diagnostic accuracy of the test is at the acceptable, good, very good, or excellent levels, respectively (10).

Therefore, this index as 0.709 indicates the good accuracy of the device. On the other hand, likelihood ratio, a measure derived from the sensitivity and specificity of a test is defined as the ratio between the probability of observing that result in patients with the disease in question, and the probability of that result in patients without the disease. LR+ is defined as the probability of an individual with disease having a positive test divided by the probability of an individual without disease having a positive test and LR− is defined as the probability of an individual with disease having a negative test divided by the probability of an individual without disease having a negative test (11). LR of greater than 1 indicates the test result is associated with the disease and LR less than 1 indicates that the result is associated with the absence of the disease. Tests, where the LR lie close to 1, have little practical significance as the post-test probability (odds) is little different from the pre-test probability, and as such is used primarily for diagnostic purposes, and not screening purposes. When the positive likelihood ratio is greater than 5 or the negative likelihood ratio is less than 0.2 (i.e. 1/5) then they can be applied to the pre-test probability of a patient having the disease tested for to estimate a post-test probability of the disease state existing (12). This shows that the LR+ and LR- measures of the current study, i.e., 5.665 and 0.164, respectively were acceptable.

Rodríguez-Capote *et al*., assessed the association between TCB measurements, performed using Bili-Check or Minolta Air-Shields JM-103, and TSB and evaluated the predictive accuracy of TCB measurements for risk using the nomogram. They found that both devices had a good correlation with the laboratory method, but underestimated the serum bilirubin. In that study, after correcting for the differences using either the bias or the 95% CI the false negative rate was reduced to zero in all cases. They concluded that TCB measurements cannot be directly applied to a TSB nomogram but must be adjusted for any observed biases to avoid misclassifying newborns at risk for hyperbilirubinemia (13). Similarly, Wainer *et al*., and Sajjadian *et al*., found the same underestimation in their study (14,15). Although these studies were in agreement with ours, in the study carried out by Panburana *et al*.,

they found higher levels of bilirubin through TCB than TSB. The result of their study revealed that TCB and TSB values had a linear correlation with a significant correlation coefficient (r 0.81, $P<0.001$). The correlation equation was TSB=0.88 + 0.89 x TCB (r2=0.65). TCB levels tended be higher than TSB with mean difference of 0.44 mg/dL (95% CI: 0.7433-0.1323 mg/dL) and SD:1.64. TSB confirmation was recommended when TCB cut-off values greater than 9, 12, 13, 15 mg/dL at 24 (TSB:8 mg/dL), 36 (TSB: 10 mg/dL), 48 (TSB: 12 mg/dL) and 72 (TSB: 15 mg/dL) hours' postnatal age, respectively. They concluded that the TCB levels can accurately predict TSB with the different cut-off points at various postnatal ages before phototherapy (16). The results of the study by Imani *et al*., despite showing TCB measures higher than TSB indicated a high correlation between two methods of measurement.

As above-mentioned studies showed, some difference could be seen in values of TCB comparing TSB that TCB in some studies was higher and in some others was lower than TSB. The reason may be due to some factors such as difference in devices of transcutaneous bilirubinometery, difference in skin darkness of cases, probably including cases with haemolytic jaundice in some studies (showing TSB levels higher than TCB because the rate of bilirubin production in serum is higher and earlier than the time skin becomes icteric), probably including some cases who had received phototherapy before assessments, and so on (17).

Although some studies have shown the correlation between two methods of TCB and TSB assessment, even in preterm neonates and those with low/very low birth weight (19-21), some other accept it as a reliable tool just for the term and late preterm neonates (22,23). Nearly all studies accept TCB as a good device for screening of hyperbilirubinemia, especially in term neonates and non-hemolytic jaundice. Transcutaneous bilirubinometery with having a good diagnostic accuracy can be considered as a reliable tool to assess bilirubin for the screening of neonatal jaundice to reduce repeated blood sampling. This method is more reliable when is used in term neonates and those with lower levels than blood exchange levels.

Acknowledgement

This study as the thesis of Dr. Najmeh Jaberi for MD degree was approved (No.1021) by Deputy for Research Affairs of Medicine Faculty in Qazvin University of Medical Sciences and Health Services.

References

1. Ambalavanan N, Carlo WA. Jaundice and Hyperbilirubinemia in the Newborn and Kernicterus. In: Kliegman RM, Stanton BF, Schor NF, et al, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier Saunders; 2011: p. 603-4,608.
2. el-Beshbishi SN, Shattuck KE, Mohammad AA, et al. Hyperbilirubinemia and transcutaneous bilirubinometry. Clin Chem 2009;55(7):1280-7.
3. Ebbesen F, Rasmussen LM, Wimberley PD. A new transcutaneous bilirubinometer, BiliCheck™, used in the neonatal intensive care unit and maternity ward. Acta Paediatr 2002;91(2):203-11.
4. Sankaran K. Transcutaneous bilirubinometry in neonates. Paediatr Child Health 2006;11(2):75-6.
5. Tan KL, Dong F. Transcutaneous bilirubinometry during and after phototherapy. Acta Paediatr 2003;92(3):327-31.
6. Rubaltelli FF, Gourley GR, Loskamp N, et al. Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. Paediatr 2001;107(6):1264-71.
7. Perkins NJ, Schisterman EF. The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol 2006;163(7):670-5.
8. Pepe MS, editor. The statistical evaluation of medical tests for classification and prediction. 1st ed. Oxford: Oxford University Press; 2004: 66-129.
9. Schisterman EF, Perkins NJ, Liu A, et al. Optimal Cut-point and Its Corresponding Youden Index to Discriminate Individuals Using Pooled Blood Samples. Epidemiology 2005;16(1):73-81.
10. Zhou H. Statistical Inferences for the Youden Index. Mathematics Dissertations. Georgia State University. (Accessed in May 2015, 4, at Available http://scholarworks.gsu.edu/cgi/viewcontent.cgi?article=1004&context=math_diss).
11. Akobeng AK. Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. Acta Paediatr 2006;96(4):487-91.
12. Beardsell A, Bell S, Robinson S, et al. MCEM Part A: MCQs, Royal Society of Medicine Press Ltd, UK., 2009.
13. Rodríguez-Capote K, Kim K, Paes B, et al. Clinical implication of the difference between transcutaneous bilirubinometry and total serum bilirubin for the classification of newborns at risk of hyperbilirubinemia. Clin Biochem 2009;42(3):176-9.
14. Wainer S, Parmar SM, Allegro D, et al. Impact of a Transcutaneous Bilirubinometry Program on Resource Utilization and Severe Hyperbilirubinemia. Paediatr

2012;129(1):77-86.
15. Sajjadian N, Shirazi H, Saalehi Z, et al. Transcutaneous Bilirubin Measurement in Preterm Neonates. Acta Med Iran 2012;50(11):765-70
16. Panburana J, Boonkasidach S, Rearkyai S. Accuracy of transcutaneous bilirubinometry compare to total serum bilirubin measurement. J Med Assoc Thai 2010;93(Suppl 2):S81-86.
17. Amoozgar H, Rastegar M. Making a transcutaneous icterometer in Neonates. Iran J Pediatr 2007;17(Suppl 12):224-30.
18. De Luca D, Zecca E, de Turris P, et al. Using BiliCheck for preterm neonates in a sub-intensive unit: diagnostic usefulness and suitability. Early Hum Dev 2007;83(5):313-7.
19. Badiee Z, Mohammadizadeh M, Shamee M. Diagnostic usefulness of transcutaneous bilirubinometry in very preterm newborns, Int J Prev Med 2012;3(4):262-5.
20. Schmidt ET, Wheeler CA, Jackson GL, et al. Evaluation of transcutaneous bilirubinometry in preterm neonates. J Perinatol 2009;29(8):564-9.
21. Ahmed M, Mostafa S, Fisher G, et al. Comparison between transcutaneous bilirubinometry and total serum bilirubin measurements in preterm infants <35 weeks gestation. Ann Clin Biochem 2010;47(Pt 1):72-7.
22. Namba F, Kitajima H. Utility of a new transcutaneous jaundice device with two optical paths in premature infants. Pediatr Int 2007;49(4):497-501.
23. Mishra S, Chawla D, Agarwal R, et al. Transcutaneous bilirubinometry reduces the need for blood sampling in neonates with visible jaundice. Acta Paediatr 2009;98(12):1916-19.