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Original Article

Relationship among Bilirubin Levels Measured Using Three Methods of Transcutaneous, Serum, and Kramer's Scale in Term Neonates

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ABSTRACT

Background: The measurement of total serum bilirubin is a stressful diagnostic method; therefore, it is necessary to measure bilirubin levels using non-invasive ways. The present study aimed to assess the relationship between bilirubin levels measured using three methods of transcutaneous, serum, and Kramer's scale in term neonates with jaundice.

Methods: This descriptive-analytical study was conducted on 180 full-term neonates admitted to Imam Ali Hospital in Alborz province, Iran. Bilirubin level was measured by three methods of serum, transcutaneous (using MBJ20, B&M Technology Co., China), and Kramer's scale (based on the appearance) before phototherapy. Thereafter, the relationship between serum bilirubin levels using transcutaneous and Kramer's scale was determined by the Pearson and Spearman correlation coefficients.

Results: The correlation coefficient between serum bilirubin and transcutaneous bilirubin (TCB) was obtained at 0.915 before phototherapy. Furthermore, the correlation coefficients between serum bilirubin and TCB were calculated at 0.881 and 0.77 in the covered and uncovered areas after phototherapy, respectively. The correlation coefficient between TCB in the covered and uncovered areas was 0.81. The mean difference between serum bilirubin and TCB was 0.42±1.25 before phototherapy. Moreover, the mean difference values between serum bilirubin and TCB were reported as 1.36±1.37 and 83.1±63.4 in the covered and uncovered areas after phototherapy, respectively.

Conclusion: As evidenced by the obtained results, there was a significant correlation between TCB and serum bilirubin before the initiation of phototherapy. Therefore, it is recommended to use TCB instead of repeated blood sampling to follow and monitor neonates.

Keywords: Serum bilirubin, Term neonate, Transcutaneous bilirubin

Introduction

Jaundice is one of the most common problems in infancy affecting 60% of full-term neonates and 80% of preterm neonates (1). Breast milk jaundice occurs within 2-5 days after birth in 0.5%-2.4% of neonates due to increased enterohepatic cycle. There is benign hyperbilirubinemia in the majority of cases. In a percentage of neonates, jaundice may be severe and progress to bilirubin encephalopathy or kernicterus, with a high risk of neonatal mortality (2). Autopsy findings in newborns with a history of neurotoxic complications due to jaundice demonstrated that bilirubin toxicity is significantly high in Asian neonates. Based on previously conducted studies, low- and middle-income countries have a high burden of severe hyperbilirubinemia (3, 4).

The measurement of total serum bilirubin

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(TSB) is a stressful diagnostic method which enhances the risk of infection in neonates. The heel prick test is one of the most common and painful methods for the measurement of TSB; nonetheless, in this study, intravenous (IV) blood samples were taken, which apart from pain, can lead to osteomyelitis in neonates and needle stick injury in health care providers.

Therefore, the recent technology has advanced to the point where bilirubin levels can be non-invasively measured through the skin. Transcutaneous bilirubinometry is a simple, non-invasive, painless, and safe technique to rapidly estimate bilirubin levels. Despite the widespread use of transcutaneous bilirubinometry as a valid method in bilirubin screening, there is still controversy over the accuracy of the results (5).

Some studies pointed to a correlation between serum bilirubin and transcutaneous bilirubin (TCB) in term and preterm neonates after phototherapy, and other studies suggested that this correlation is very strong in term neonates. Nevertheless, the measurement of serum bilirubin is still a gold standard for the diagnosis of hyperbilirubinemia. Furthermore, depending on the conditions of laboratories and hospitals, the test result may be prepared very late and more time may be lost (6).

Studies indicated a linear relationship between the serum and transcutaneous bilirubinometry methods (7-9). In addition, monitoring bilirubin levels and changes in the skin is suitable for neonatal screening (7). Some studies suggested that transcutaneous bilirubinometry is only sensitive in some races and geographical areas; however, various studies suggested that this method can be used for all races. Therefore, the intermittent monitoring of blood bilirubin levels in high-risk neonates is necessary due to the need to take timely actions against the bilirubin increase (10).

Furthermore, due to the difficulty in blood sampling in neonates and its painful process, the use of transcutaneous bilirubinometry seems reasonable. Nevertheless, since various climatic conditions and demographic characteristics of each region affect the efficiency and accuracy of the transcutaneous method, it seems essential to make a comparison among serum, transcutaneous, and clinical methods of bilirubin measurement (11). In light of the aforementioned issues, the present study aimed to assess the relationship among bilirubin levels measured using three methods of transcutaneous, serum, and Kramer's scale in term neonates with jaundice.

Methods

The present cross-sectional study was conducted on 180 neonates with jaundice who were clinically indicated for bilirubinometry and phototherapy. This study was performed in Imam Ali Hospital, Alborz province, Iran, which is a neonatal referral center, from October 2018 to September 2019. The inclusion criteria were as follows: neonates with indirect hyperbilirubinemia (>15) who were admitted to the hospital to control jaundice and received phototherapy based on the diagnosis of a pediatrician, gestational age over 37 weeks, and postpartum age up to 28 days. On the other hand, the exclusion criteria were direct hyperbilirubinemia, sepsis, congenital anomalies, edema, hemangioma or ecchymosis of the skin, previous history of phototherapy, blood transfusion, and maternal dissatisfaction. The convenience sampling method was performed until the completion of the sample size.

The consent form was obtained from the parents after presenting the study aims and in case of willingness to participate in the study; thereafter, eligible neonates entered the study. Firstly, the demographic information form, including the neonate's age on admission, weight at referral, weight at birth, gestational age, and gender, was completed.

Transcutaneous bilirubinometry was performed in two places (i.e., the upper part of the forehead and glabella that are not covered during phototherapy) using MBJ20 (B&M Technology Co., China) by a trained individual in this field and based on the manufacturer's instructions. Finally, the relevant values were recorded.

Regarding the use of MBJ20, the optical head was placed gently and tangentially on the neonate's skin and mildly pressed. Following that, the measurement was over after 3 to 4 sec, and the bilirubin level appeared in mg/dl on a liquid-crystal display screen and was recorded. Serum bilirubin levels were obtained by IV blood sampling of neonates and sent to the laboratory of Imam Ali Hospital. Individuals working in the laboratory who measured serum bilirubin were completely unaware of the bilirubin levels illustrated by Bilicheck. Regarding identical testing and removal of confounding factors, all the samples were sent to the laboratory of Imam Ali Hospital.

The TCB was first measured upon admission, before phototherapy, and 12-40 h after phototherapy to evaluate the effect of phototherapy on the accuracy of Bilicheck. After serum sampling, TCB was measured and recorded according to the aforementioned method. The maximum time between TCB and serum bilirubin after phototherapy was 10 min. The clinical evaluation was carried out by a physician or nurse before phototherapy while the neonate was naked. Based on Kramer's law, the area of the neonate's body which was yellow was recorded in the relevant questionnaire.

G*Power software (version 3.1.9.4) was used to determine the sample size. The sample size was estimated at 176 subjects based on α=5% (type I error rate), β= 20% (Type II error rate), and a 21% expected correlation coefficient. Finally, a total of 180 newborns entered the study.

Data Analysis

Regarding statistical analysis, the data were entered in SPSS software (version 22). Mean and standard deviation were calculated for quantitative variables. Furthermore, frequency and percentage were used for qualitative variables. The Pearson and Spearman correlation coefficients were applied to determine the relationship among three methods of clinical evaluation, TCB, and serum bilirubin.

Ethical Considerations

The present study was a proposal approved by the Ethics Committee of Alborz University of Medical Sciences (code: IR.ABZUMS.REC.1397.157). The researcher explained the study aims to all the participants and obtained informed consent. The participants were assured of information confidentiality in all stages of the study, and all rights of the participants were reserved.

Results

The demographic characteristics of the neonates, as well as blood group and RH of neonate and their mothers, are presented in tables 1 and 2.

The results of the Pearson correlation test illustrated a significant relationship between TCB and serum bilirubin levels before and after phototherapy (Table 3).

Kramer's law (Figure1) was used to determine bilirubin levels based on clinical signs. The Spearman correlation coefficient between serum bilirubin and clinical examination before phototherapy was calculated to be 0.649, indicating a correlation between clinical examination and serum bilirubin (Table 3).

The accuracy of clinical examination before the initiation of phototherapy was 43.8% (Table 4 and Figure 2).

Table 1. Baseline characteristics of neonates in the study

Gender	n (%)
Male	104 (57.8)
Female	76 (42.2)
Type of birth	
Normal vaginal delivery	91 (50.6)
Cesarean section	89 (49.4)
Phototherapy type	
Single	14 (7.8)
Double	19 (10.6)
Intensive	147 (81.7)
Glucose-6-phosphate dehydrogenase	
Sufficient	168 (93.3)
Insufficient	12 (6.6)
Mean±Standard deviation	
Weight of hospitalization (g)	3182.2±473.8
Weight of birth (g)	3238±460.8
Gestational age of birth (week)	38±0.93
Gestational age of hospitalization (day)	4.7±1.6

Table 2. Blood group and Rh of neonates and their mothers

		Mothers' blood groups								Total
		O+	O-	A+	A-	B+	B-	AB+	AB-	
Neonate blood group	O+	26(14.4)	2(1.1)	8(4.4)	0	6(3.3)	0	1(0.5)	0	43(23.8)
	O-	3(1.6)	3(1.6)	1(0.5)	0	1(0.5)	0	0	0	8(4.4)
	A+	25(13.8)	1(0.5)	30(16.6)	2(1.1)	3(1.6)	0	5	0	66(36.6)
	A-	2(1.1)		1(0.5)	1(0.5)	0	0	0	0	5(2.7)
	B+	25(13.8)	0	4(2.2)	0	7(3.8)	5(2.7)	2(1.1)	0	43(23.8)
	B-	0	0	0	0	1(0.5)	1(0.5)	0	0	2(1.1)
	AB+	0	0	6(3.3)	0	3(1.6)	0	2(1.1)	0	11(6.1)
	AB-	0	0	1(0.5)	0	1(0.5)	0	0	0	2(1.1)
	Total	81(45)	7(3.8)	51(28.3)	3(1.6)	22(12.2)	6(3.3)	10(5.5)	0	180(100)

Table 3. Correlation of transcutaneous bilirubin and serum bilirubin before and after phototherapy

	Mean±Standard deviation				
	Transcutaneous bilirubin	Serum bilirubin	Mean difference	P-value	r
Before phototherapy	16.7±2.8	17.14±3.1	0.42±1.25	0.001	0.91
After phototherapy (covered area)	10.9±2.8	12.3±2.7	1.36±1.37	0.001	0.88
After phototherapy (uncovered area)	7.6±2.6	12.3±2.7	4.63±1.83	0.001	0.77

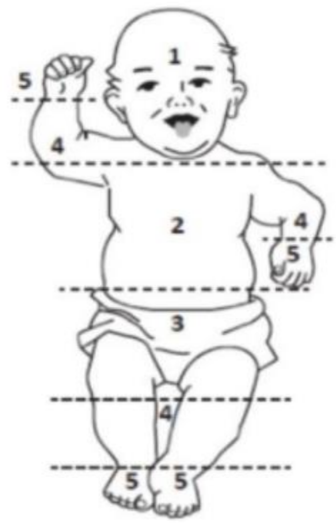

Figure 1. Kramer's law

Table 4. Clinical estimation of bilirubin and relationship between serum bilirubin level and apparent diagnosis of bilirubin

Total N (%)	Incorrect	Correct	Kramer's references
5 (2.7)	4	1	Head and neck: 4-8
38 (21.1)	32	6	Upper body: 5-12
65 (36.1)	32	33	Lower body: 8-16
63 (35)	33	30	Forearm and foot: 11-18
9 (5)	0	9	Palms and soles: Higher than 18
180 (100)	101 (56.1)	79 (43.8)	Total
		0.004	P-value*
		0.649	r

*Spearman correlation coefficient

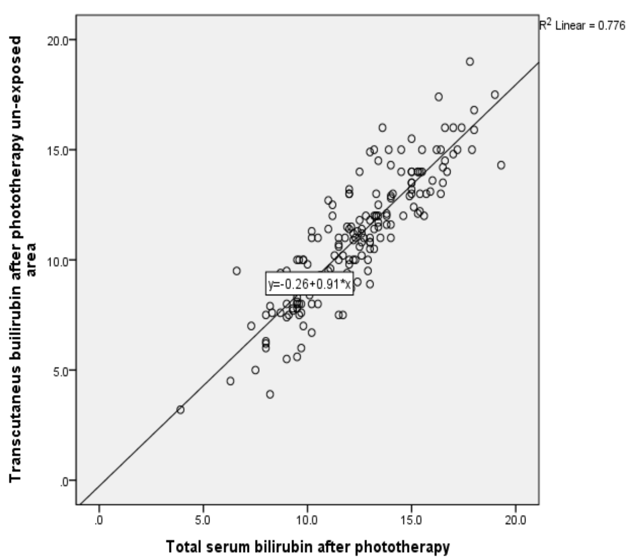

Figure 2. Scatter Diagram of correlation between transcutaneous bilirubin and serum bilirubin in un-covered region

Discussion

In agreement with the results of most studies, in this research, 57.8% of neonates with jaundice were male. In a study performed by Yang et al., 58% of neonates with jaundice were male (12). This contradiction may be due to the higher prevalence of glucose-6-phosphate dehydrogenase (G6PD) in male newborns and the fact that the male gender is a major risk factor for jaundice. In a study performed in Shiraz, 27.5% of participants had a cesarean section (CS), and the rest had a normal vaginal delivery (2). In the present study, the prevalence of G6PD deficiency was 6.6%. Nonetheless, it was reported to be 25% in a study carried out in Shiraz. In the present study, 49.4% of deliveries were CS. However, in the study conducted by Young et al., 70% of neonates were born through CS.

Based on the results, there was a correlation between TCB in the covered area and serum bilirubin before and during phototherapy in term neonates with jaundice. The correlation coefficient was affected after phototherapy and was slightly decreased.

A study carried out by Radfer et al. at Shahid Beheshti University, Tehran, Iran, on 134 full-term neonates and 36 preterm neonates demonstrated a strong correlation (r=0.929) between the serum bilirubin and Bilicheck. The correlation coefficients after phototherapy in the covered areas among term and preterm neonates were 0.921 and 0.88, respectively. These correlation coefficients in the uncovered areas were 0.666 and 0.75 in term and preterm neonates, respectively (13). The results of the aforementioned study are in agreement with those obtained in the present research in terms of the correlation between serum bilirubin and TCB.

Yang et al. in Taiwan assessed TCB and serum bilirubin levels in 52 full-term neonates and 56 near-term neonates receiving phototherapy. The correlation coefficient between serum bilirubin and TCB during 1-6 days since the start of phototherapy was still reasonably high and within 0.9-0.75. It was suggested to reduce blood sampling and use transcutaneous bilirubinometry as a viable method for term and preterm neonates undergoing phototherapy (12).

Raba et al. (2020) observed a strong correlation between TCB and serum bilirubin before phototherapy which exists after at least 24 h of phototherapy. Nevertheless, this correlation is much weaker in the area exposed to phototherapy, as compared to that in the covered area (14).

A study by Arman et al. was performed on 99 neonates with a gestational age of fewer than 34 weeks. They measured serum bilirubin and TCB simultaneously before phototherapy, during phototherapy, and 24 h after the discontinuation of phototherapy. The TSB had a significant relationship with TCB before, during, and after phototherapy (15).

Yu Zhang et al. in a review article and a meta-analysis of 14 studies compared TCB and serum bilirubin in term or near-term neonates during or after phototherapy. In the stated study, the correlation coefficients were 0.71, 0.65, 0.70, and 0.64 in the covered areas, uncovered areas, forehead, and sternum, respectively. As evidenced by the results, there was a moderate correlation between TCB and serum bilirubin levels during phototherapy and short recovery after the discontinuation of phototherapy. The referred study indicated that TCB has a similar predictive value, in comparison with serum bilirubin, and both of them can be used to detect hyperbilirubinemia (16).

Reacher et al. (2014) evaluated the association between TCB and serum bilirubin in neonates with jaundice before and after phototherapy. The correlation coefficient between TCB and serum bilirubin was 0.72. Furthermore, this correlation was low during the first 8 h of phototherapy; nonetheless, after that, the correlation reached 0.65-0.8. The results of the stated study pointed to a good correlation between TCB and TSB at 8 h after phototherapy (17).

Some studies do not allow the use of transcutaneous bilirubinometry during phototherapy. A study by Morley et al. was conducted on neonates born at 34-41 weeks gestation with jaundice under phototherapy. A small area of sternal skin was covered by common light-resistant patches. Serum bilirubin levels were measured four times in the covered area. Receiving phototherapy lasted for 25.3±4.4 h. Bland-Altman plots displayed a weak correlation between serum bilirubin and TCB and did not recommend the use of TCB (18).

One study reported that the level of TCB is higher than serum bilirubin, and these differences were due to the type of Bilicheck used in the study, being term and preterm, and the interval between blood sampling for serum bilirubin and TCB. The bilirubin in the transcutaneous method is estimated to be higher than that of the serum method and will expose preterm neonates to excessive phototherapy (19).

The results of the present study also pointed to a correlation coefficient of 0.64 between serum bilirubin and Kramer's law. Apriliaz et al. (2017) reported a sensitivity of 92.76%, specificity of 89.47%, and accuracy of 86.27% for Kramer's law in the assessment of neonatal jaundice (20). In this study, the accuracy of Kramer's law before the initiation of phototherapy was 43.8%. Varughese PM (2019) carried out a study on 450 newborns over 34 weeks of gestation to compare Kramer's law and transcutaneous bilirubinometry and determine their associations with serum bilirubin. The results of the referred study demonstrated that TCB levels were closer to serum bilirubin levels than Kramer's law (21).

Study Limitations

Among the notable limitations of this study, we can refer to the measurement of TCB upon admission and the long interval between sending the results of initial serum tests which was unavoidable.

Conclusion

As evidenced by the results of the present study, there was a strong correlation between TCB in the forehead and serum bilirubin before the initiation of phototherapy. Nevertheless, this correlation decreased after phototherapy and was low in the covered area. Therefore, due to the appropriate correlation between TCB in the forehead and serum bilirubin before starting phototherapy, transcutaneous bilirubinometry can be used instead of repeated blood sampling to follow and monitor neonates. However, the final decision to discontinue phototherapy should be made using accurate serum bilirubin due to the lower estimate of serum bilirubin.

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Conflicts of interest

The authors declare that they have no competing interests.

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