



Original article

Early predictive value of cord blood bilirubin and dynamic monitoring of transcutaneous bilirubin for hyperbilirubinemia of newborns

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ABSTRACT

Objective: To study the early predictive value of cord blood bilirubin and dynamic monitoring of transcutaneous bilirubin for hyperbilirubinemia of newborns.

Methods: 389 newborns delivered from June 2014 to December 2015 were enrolled as the research subjects; detailed records were made about the general data of newborns and mothers, and after cord blood bilirubin being graded, the incidence of hyperbilirubinemia was counted, and the prediction efficiency of cord blood bilirubin was analyzed by receiver operator characteristic (ROC) curve. At the same time, the transcutaneous bilirubin was detected continuously when the neonate was born and 24 h, 48 h and 72 h after birth, and the relativity between transcutaneous bilirubin at 72 h and serum bilirubin was analyzed.

Results: No significant difference was found in the hyperbilirubinemia group and the non-hyperbilirubinemia group concerning general data of the newborns and their mothers. With the concentration of cord blood bilirubin increased, the incidence of hyperbilirubinemia also increased; separate prediction of hyperbilirubinemia by cord blood bilirubin showed a sensitivity and specificity of 71.4% and 65.6% respectively, and they need further dynamic monitoring. The daily mean of transcutaneous bilirubin in hyperbilirubinemia group was significantly higher than that in non-hyperbilirubinemia group at 24 h, 48 h and 72 h, and the measurement value of transcutaneous bilirubin at 72 h had a high correlation with serum bilirubin. When transcutaneous bilirubin value is higher than 18, the incidence of hyperbilirubinemia should be considered.

Conclusions: The increase of cord blood bilirubin effectively predict the occurrence of neonatal hyperbilirubinemia. There is a good correlation between levels of transcutaneous bilirubin and serum bilirubin. Moreover, combined detection of transcutaneous bilirubin and cord blood bilirubin can significantly improve the prediction accuracy of hyperbilirubinemia.

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1. Introduction

Neonatal hyperbilirubinemia is one of the common symptoms available during neonatal period. Bilirubin metabolism in adults and newborns is not the same, and the golden standard to evaluate neonatal hyperbilirubinemia is the concentration of total serum bilirubin (TSB). If the concentration of serum bilirubin in adults was higher than 2 mg/dL, there would be yellowish pigmentation

of skin and sclera; in case the newborns had a wealth of capillaries, when the concentration of serum bilirubin was higher than 5 mg/dL, their skin would show visible yellow (Huang and Guan, 2012). With the development of bilirubin measurement instrument, coupled with the advantages of simple operation and being painless, transcutaneous bilirubin is becoming widely used. Whereas for the measurement of serum bilirubin, venous or heel blood collection is necessary, which will bring stress and pain, even infection to the newborns, and repeated blood tests may also cause iatrogenic blood loss. Currently, transcutaneous bilirubin is more extensively used in the stepwise screen of hyperbilirubinemia, while TSB is less widely used (Nagar et al., 2013). In 1980, Yamanouchi et al. (1980) developed a light and portable device for the determination of hemoglobin. Transcutaneous bilirubin measurement can monitor neonatal jaundice continuously and dynamically, perform large-scale screening of neonatal hyperbilirubinemia and avoid measurement of serum bilirubin by skin

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puncture, which can not only reduce the newborns' pain, but also lessen the risk of infection without trauma, convenience, efficacy or simplicity. Affected by race, skin color and instrument error, however, clinical studies have shown there are certain limitations of Transcutaneous bilirubin measurement. As reported in literature (Persson et al., 2013) that the cord blood bilirubin (CBB) can predict hyperbilirubinemia early, which makes it earlier for doctors in terms of diagnosis and treatment. Through continuous study on neonatal hyperbilirubinemia, people have more in-depth understanding on the disease. Although partial causes of hyperbilirubinemia have not yet been clear, research has never been ceased and various methods will be used for early diagnosis and treatment of hyperbilirubinemia; furthermore, combined use of different treatment methods and emergence of new treatments will lead to rapid, safe and reliable treatment for neonatal hyperbilirubinemia (Li et al., 2005).

389 newborns were included as the research subjects and detailed records were made about the general data of the newborns and their mothers; moreover, the cord blood bilirubin, the transcutaneous bilirubin and the serum bilirubin were detected, and hyperbilirubinemia incidence in cord blood bilirubin and transcutaneous bilirubin with different concentrations were analyzed as well; furthermore, the diagnostic value of separate and combined detection of hyperbilirubinemia was evaluated through ROC curve. The study aimed at providing diagnostic basis for clinicians.

2. Materials and methods

2.1. Data source

389 newborns which were delivered during June 2014 and December 2015 were considered as the research subjects, and then detailed records were made about the characteristics of newborns and their mothers, which were listed in Tables 1 and 2. Inclusion criteria: newborns without diseases in heart, liver, kidney and other important organs; mothers without hepatobiliary diseases; Apgar scored higher than 8 points; informed consents were signed before this study was conducted.

2.2. Methods

2.2.1. Detection of the total cord blood bilirubin

When the neonatal umbilicus was cut after delivery, 2 mL umbilical venous blood was extracted immediately from the placental umbilical cord stump and was taken for examination. In order to avoid hemolysis, after the sample was sent to clinical laboratory, it should be promptly placed in water bath under the condition of 37 °C for 30 min; when the blood was fully solidified, it was placed in a centrifugal machine whose speed was 2000 turn/min to separate serum for 5 min, and then the serum was detected through Japanese Hitachi 7170A automatic biochemical analyzer.

Table 1
Neonatal characteristics.

Features	Type	Hyperbilirubinemia group (N(%))	Non-hyperbilirubinemia group (N(%))	χ^2	<i>p</i>
Gender	Male	50 (59.52)	160 (52.46)	1.32	0.25
	Female	34 (40.48)	145 (47.54)		
Gestational age/week	Preterm delivery (<35)	22 (26.19)	80 (26.23)	0.32	0.82
	Late preterm delivery (35–<37)	25 (29.76)	81 (26.56)		
	Full-term (≥ 37)	37 (44.05)	144 (47.21)		
Birth weight/g	<2500	7 (8.33)	25 (8.20)	0.14	0.93
	2500–<3000	19 (22.62)	75 (24.59)		
	≥ 3000	58 (69.05)	205 (67.21)		
Delivery mode	Natural birth	49 (58.34)	183 (60.00)	0.4	0.82
	Delivery through vaginas	7 (8.33)	30 (9.84)		
	Cesarean delivery	28 (33.33)	92 (30.16)		
Twins/triplets		9 (10.71)	25 (8.20)	0.52	0.47
Feeding/nutrition	Exclusive breast-feeding	25 (29.76)	69 (22.62)	5.32	0.15
	Artificial feeding	5 (5.95)	7 (2.30)		
	Breast-feeding and artificial feeding	53 (63.10)	224 (73.44)		
	Parenteral nutrition	1 (1.19)	5 (1.64)		
Blood type	A	27 (32.14)	113 (37.05)	3.15	0.37
	B	29 (34.52)	110 (36.07)		
	AB	7 (8.33)	31 (10.16)		
	O	21 (25.00)	51 (16.72)		
	Rh+	71 (84.52)	275 (90.16)		

Table 2
Maternal characteristics.

Features	Type	Hyperbilirubinemia group (N(%))	Non-hyperbilirubinemia group (N(%))	χ^2	<i>p</i>
Age (during the period of delivery)/ years old	<25	25 (29.76)	75 (24.59)	0.95	0.62
	25~<35	49 (58.34)	193 (63.28)		
	≥ 35	10 (11.90)	37 (12.13)		
Firstborn (parity)		53 (63.10)	176 (57.70)	0.79	0.37
Blood type	A	29 (34.53)	118 (38.69)	4.93	0.18
	B	24 (28.57)	106 (34.75)		
	AB	5 (5.95)	21 (6.89)		
	O	26 (30.95)	60 (19.67)		
	Rh+	73 (86.90)	280 (91.80)		

2.2.2. Detection of transcutaneous bilirubin

In reference to the study of Stoniene et al. (2009), through 101 type transcutaneous bilirubin measurement instrument (TcBM) produced by Japanese Minolta company, transcutaneous bilirubin in the neonatal forehead (area between two eyebrows) and 2 parts of the neonatal chest were detected respectively when the neonatal was born and 24 h, 48 h and 72 h after birth.

2.2.3. Detection of serum bilirubin and judgement criteria of hyperbilirubinemia

The venous blood of 72-h-old newborn was taken for measurement by the same method of detecting total bilirubin in cord blood. According to the diagnostic criteria for neonatal jaundice of Chinese Pediatric Society, Chinese Medical Association, the judgement criteria for hyperbilirubinemia is 12 mg/dL.

2.3. Statistical methods

According to the serum bilirubin value 1 mg/dL = 17.1 $\mu\text{mol/L}$, the data were converted into a unified unit and were then analyzed through SPSS 23.0 software. χ^2 test was used to count data and t-test was used to calculate data. $P < .05$ indicates the difference is statistically significant. ROC curve was adopted to analyze the diagnostic efficiency of cord blood bilirubin, and, the concentrations of TRANSCUTANEOUS BILIRUBIN and serum bilirubin in 72 h were compared to analyze the correlation.

3. Results

3.1. Neonatal and maternal characteristics

Detailed data of neonate sex, gestational age, birth weight, delivery mode, multiple births, feeding patterns, blood type (Table 1) and maternal age, parity, blood type (Table 2) were collected. Whether it belonged to hyperbilirubinemia was judged according to the golden standard and the data; then the data were performed chi square test which indicated that no significant difference can be found ($P > .05$).

3.2. Relationship between the cord blood bilirubin and the incidence of hyperbilirubinemia and ROC analysis

After the measured cord blood bilirubin and transcutaneous bilirubin concentration having been graded, the incidence of neonatal hyperbilirubinemia was counted up. If the concentration of cord serum bilirubin was lower than 29.92 $\mu\text{mol/L}$, the hyperbilirubinemia incidence was 14.81%; if the concentration was within 29.92–40.18 $\mu\text{mol/L}$, the incidence was 15.59%; if the concentration was higher than 40.18 $\mu\text{mol/L}$, the hyperbilirubinemia incidence rose to 57.14%. And then the data was made chi square test, the difference was significant, $P < .05$ (Table 3).

The ROC curve of separate detection of cord blood bilirubin for hyperbilirubinemia is shown in Fig. 1. AUC was 0.732, with

Table 3

The relationship between bilirubin concentration and hyperbilirubinemia incidence.

Bilirubin concentration ($\mu\text{mol/L}$)	Hyperbilirubinemia (case)	Non-hyperbilirubinemia (case)	Incidence (%)	χ^2	p
<i>Cord blood bilirubin</i>					
<29.92	12	69	14.81	29.88	0.00
29.92–<40.18	29	157	15.59		
40.18–<51.3	27	67	28.72		
≥ 51.3	16	12	57.14		
Total (case)	84	305			

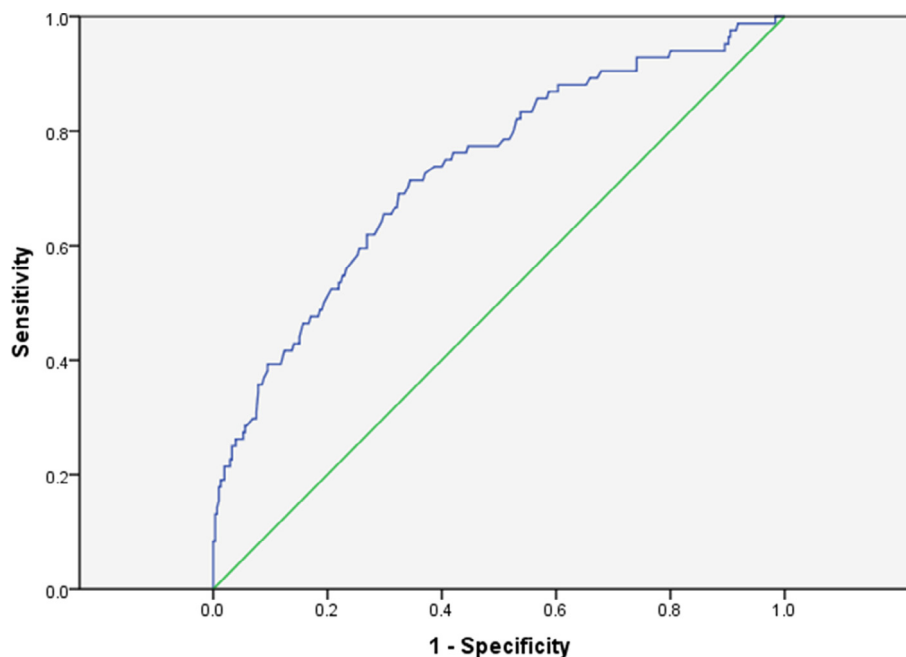


Fig. 1. The ROC curve of separate detection of cord blood bilirubin for hyperbilirubinemia group.

Table 4

The comparison of cord blood bilirubin concentration and mean daily value of transcutaneous bilirubin within three days.

Group	Case	Cord blood bilirubin concentration ($\mu\text{mol/L}$)	Transcutaneous bilirubin			
			At birth	24 h after birth	48 h after birth	72 h after birth
Hyperbilirubinemia	84	39.05 \pm 9.34	11.15 \pm 2.33	13.57 \pm 1.35	17.48 \pm 1.29	19.75 \pm 2.11
Non-hyoerbilirubinemia	305	30.61 \pm 7.15	11.03 \pm 2.48	12.74 \pm 1.21	14.32 \pm 1.16	16.84 \pm 1.94
t		2.764	1.679	7.324	21.720	12.240
P		0.007	0.094	0.000	0.000	0.000

$P = .000$. According to the results of ROC curve, the cut-off value of bilirubin in the diagnosis of hyperbilirubinemia was 32.1 $\mu\text{mol/L}$, and its sensitivity and specificity were 71.4% and 65.6%.

3.3. Comparison of cord blood bilirubin and transcutaneous bilirubin concentrations in hyperbilirubinemia group and non-hyperbilirubinemia group

Statistical method was employed to analyze the difference of cord blood bilirubin as well as daily mean values of transcutaneous bilirubin within 3 days in hyperbilirubinemia group and non-hyperbilirubinemia group, as shown in Table 4.

3.4. Correlation analysis of transcutaneous bilirubin and serum bilirubin

Through the statistical analysis of transcutaneous bilirubin and serum bilirubin concentration in hyperbilirubinemia group at 72 h, the regression equation was obtained: $Y = -158.81 + 19.57X$, correlation coefficient $r = 0.887$. Y was the dependent variable, referring to the serum bilirubin concentration ($\mu\text{mol/L}$), X was the independent variable, referring to the transcutaneous bilirubin readings. If the serum bilirubin concentration was 205.2 $\mu\text{mol/L}$ (12 mg/dL), the transcutaneous bilirubin value was 18.6, namely, when transcutaneous bilirubin value is higher than 18, the incidence of hyperbilirubinemia should be considered.

4. Discussion

Jaundice is a common problem in neonatal period and severe hyperbilirubinemia will cause nervous system of the neonatal damage. Newborns generally exhibit jaundice 3 days after delivery, and most of them will fade after 7–10 days, which is a normal physiological phenomenon. The conditions of some newborns don't demand treatment and their jaundice may fade naturally; in case the conditions of some newborns get worsen rapidly, they require hospitalization and their jaundices even develop into nuclear jaundice. The unconjugated bilirubin in blood increases and goes into the central nervous system, which thus causes lesions in basal ganglia, subthalamic nucleus, globus pallidus or other parts. As early as in 2004, American Academy of Pediatrics formulated surveillance, prediction and treatment guidelines for neonatal jaundice (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004) to guide clinical intervention in time to avoid the occurrence of nuclear jaundice. In China, bilirubin encephalopathy still occurred now and then, 28 hospitals in China reported totally 348 cases of bilirubin encephalopathy (Yu et al., 2014) in 2009, and this disease will cause severe consequences to the society and family; therefore, early diagnosis can timely intervene with hyperbilirubinemia so as to prevent pathological jaundice. Some researches (Li, 2015) showed that if umbilical cord blood was extracted immediately after delivery to determine the concentration of bilirubin, accompanied with daily continuous determination of transcutaneous

jaundice, the incidence of neonatal hyperbilirubinemia can be effectively predicted in advance. Some researches (Maisels, 2012) also showed that through transcutaneous bilirubin, we can get instant information of the neonatal jaundice level, which generally had more advantages than observation through naked eyes, thus it can be used as a screening method of general neonatal jaundice (Wainer et al., 2009). Although the results of transcutaneous bilirubin measured by different instruments were less consistent, many researches (Akahira-Azuma et al., 2013; Schmidt et al., 2009; Sajjadian et al., 2012; Chawla et al., 2014) have confirmed transcutaneous bilirubin determination with high accuracy, high safety and correlation in newborns including full-term infants and over 28 weeks premature without considering the influence of gestational age and skin color, and the correlation coefficient was between 0.68 and 0.96, which was a desirable method to painlessly evaluate neonatal jaundice.

In this research, after the measured cord blood bilirubin being graded, the incidence of neonatal hyperbilirubinemia was counted. Results showed that with the increase of cord blood bilirubin concentration, the incidence of hyperbilirubinemia also increased with significant differences; therefore, the higher the concentration of cord blood bilirubin was, the more vigilant people should be to the occurrence of hyperbilirubinemia so as to leave no room for omission which may finally result in severe conditions. According to ROC curve, the diagnostic effect of cord blood bilirubin for hyperbilirubinemia had a sensitivity of 71.4%, a specificity of 65.6% and an AUC of 0.732. The results indicated that cord blood bilirubin has a value for predicting the hyperbilirubinemia, but monitoring of other indicators is also needed to get reliable results. This study conduct a continuous monitoring of transcutaneous bilirubin concentration of newborns within three days, the daily mean of transcutaneous bilirubin at 24 h, 48 h and 72 h in hyperbilirubinemia group was significantly higher than that in non-hyperbilirubinemia group. What's more, the measured value of transcutaneous bilirubin at 72 h has a high correlation with serum bilirubin, and when transcutaneous bilirubin value is higher than 18, the incidence of hyperbilirubinemia should be considered. Different transcutaneous bilirubin measurement instrument has different conversion relation of serum bilirubin. As for the 101 type transcutaneous bilirubin measurement instrument produced by Japanese Minolta company, there was a research showing that when transcutaneous bilirubin value is higher than 20, the incidence of hyperbilirubinemia should be considered. Therefore, the precondition of applying the transcutaneous bilirubin measurement instrument is to make a correlation curve between cord blood bilirubin and transcutaneous bilirubin value of the specific type, and to calculate the critical value of transcutaneous bilirubin.

The affections of hyperbilirubinemia are particularly abounded, and there are also many relevant recommendations for its prevention. For example, foreign researches show (Zhang et al., 2011; Gao et al., 2017a, 2017b; Clark, 2013) that early-onset jaundice is related to insufficient breastfeeding, while persisting jaundice is related to breast milk itself; therefore, unscheduled breastfeeding helps prevent early-onset jaundice; but the key point is to take early diagnosis in newborns. In this research, combined detection

of cord blood bilirubin and dynamic monitoring of transcutaneous bilirubin has clinical significance in predicting the neonatal hyperbilirubinemia incidence, which can effectively predict pathological jaundice and provide a basis for clinical diagnosis of hyperbilirubinemia in a simple and easy way; therefore, we say it is suitable for clinical application. Early diagnosis of hyperbilirubinemia can effectively improve the birth population quality and reduce the economic burden of families; in this sense, it has certain social benefits.

5. Conclusion

Based on detection of the cord blood bilirubin, the transcutaneous bilirubin and the serum bilirubin, this study determined the relationship between hyperbilirubinemia and non hyperbilirubinemia, and further detection found that detection of the cord blood bilirubin and dynamic monitoring of transcutaneous bilirubin had certain diagnostic value for hyperbilirubinemia.

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