Sixth hour transcutaneous bilirubin predicting significant hyperbilirubinemia in ABO incompatible neonates

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Original article

Background: **Neonates with ABO hemolytic disease are at greater risk for developing significant hyperbilirubinemia. We aimed to determine whether sixth hour transcutaneous bilirubin (TcB) could predict such a risk.**

Methods: **TcB measurements were obtained at the 6th hour of life in blood group A or B neonates born to blood group O, rhesus factor compatible mothers. Subsequent hyperbilirubinemia was monitored and considered significant if a neonate required phototherapy/exchange transfusion. The predictive role of sixth hour TcB was estimated.**

Results: **Of 144 ABO incompatible neonates, 41(O-A, 24; O-B, 17) had significant hyperbilirubinemia. Mean sixth hour TcB was significantly higher among neonates who developed significant hyperbilirubinemia than those who did not (5.83±1.35 mg/dL *vs.* 3.65±0.96 mg/dL, *P*<0.001). Sixth hour TcB value >4 mg/dL had the highest sensitivity of 93.5% and >6 mg/dL had the highest specificity of 99%. Area under receiver operating characteristic curve was 0.898.**

Conclusion: **Sixth hour TcB predicts subsequent significant hyperbilirubinemia in ABO incompatible neonates.**

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Key words: **ABO incompatibility;**
neonate;
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Introduction

Neonatal hyperbilirubinemia is the most common cause for readmissions within days after initial discharge.[1-4] Hemolytic jaundice accounts for 20% of all significant jaundice in newborns, and ABO and Rh incompatibility comprise two thirds of the total.[2] Currently, ABO hemolytic disease (ABO-HD) is the most common cause of neonatal jaundice because of blood group incompatibility.[1-5]

Early postnatal discharge of newborns is complicated by subsequent significant hyperbilirubinemia.[1,2,4] Such a risk is greater in newborns with ABO incompatibility.[4] The clinical course of ABO-HD has been studied along with the reticulocyte count, Coombs positivity and/or a strongly positive elution test and the presence of a sibling with neonatal jaundice as predictors.[5-7] However, other studies did not support the use of any routine screening tests in the management of ABO-HD and reported that such tests are not cost effective.[8,9]

Early serum bilirubin and reliable transcutaneous bilirubin (TcB) measurements predicting subsequent severe hyperbilirubinemia among term and near term infants have been well documented.[10,11] Sarici et al[4] reported a sixth hour serum bilirubin level predicting nearly all newborns developing subsequent significant hyperbilirubinemia and severe hemolytic disease among ABO incompatible newborns. However, estimation of serum bilirubin is invasive and painful. We aimed to study whether the sixth hour TcB could predict subsequent significant hyperbilirubinemia in term and late preterm newborns with ABO incompatibility.

Methods

All inborn neonates with blood groups A or B born to blood group O mothers were enrolled prospectively for the study at Kasturba Hospital between November 2008 and July 2009. The institutional ethical committee approved the study, and informed consents were obtained from the parents. Neonates with simultaneous Rhesus blood factor incompatibility, group A or B who were born to heterospecific A or B mothers, outborn neonates and those less than 34 weeks of gestation were

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excluded. Blood grouping, Rhesus factor study and direct Coomb's test were performed on the cord blood. TcB measurements were obtained on the sternum at the 6th hour of life (between 6-8 hours) using JM-103 (Minolta, Airshields). Onset and progression of jaundice was monitored subsequently by visual assessment and TcB at 6-12 hour intervals. Serum bilirubin levels were obtained when TcB values were between 9-15 mg/dL depending on the gestational age, birth weight and postnatal age to decide the interventions. Phototherapy or exchange transfusions were based on Cockington's chart.[12] Neonates receiving these interventions were considered to have significant hyperbilirubinemia. In these neonates, peripheral smear, reticulocyte count and hematocrit values were obtained. Evidence of hemolysis included reticulocytosis and/or presence of spherocytes in the peripheral smear. Glucose-6-phosphate dehydrogenase (G-6PD) enzymes were estimated only in neonates with evidence of hemolysis.

Demographic characteristics like gender, birth weight, gestational age and mode of delivery were noted in all neonates along with history of jaundice in the sibling, presence of cephalhematoma, bruising and hepatomegaly/splenomegaly. The critical TcB levels at the sixth hour with different sensitivity and specificity were determined. Statistical data were analyzed with independent sample *t* test. Predictive role of the sixth hour TcB was evaluated using the receiver operating characteristic curve (ROC) analysis.

Results

During the study period, 151 (17.2%) newborns out of 878 live births were ABO incompatible with their mothers. Seven neonates less than 34 weeks of gestational age were excluded. O-A group constituted 52.1%, and O-B group, 47.9% in the remaining 144 neonates.

Table 1 shows the characteristics of the neonates. Forty-one (28.5%) neonates had significant hyperbilirubinemia and required phototherapy. None required exchange transfusion. The mean bilirubin value was 14.5±2.3 mg/dL. O-A and O-B groups represented 58.5% and 41.5%, respectively. Twenty-two of 41 (53.7%) neonates had evidence of hemolysis (14 in OA group, 8 in OB group). Among these 22 neonates, 5 had hepatosplenomegaly. Three neonates in the O-A group had positive direct Coomb's test, and they all had significant hyperbilirubinemia. All infants were exclusively breastfed. The gender, birth weight, gestational age and mode of delivery were not significantly different between newborns with or without significant hyperbilirubinemia. The bilirubin level rose to intervention level in four neonates with cephalhematoma during the initial 24-36 hours. There

Table 1. Characteristics of study neonates (*n*=144)

Variables	*n*	%
Male sex	71	49.3
O/A incompatibility	75	52.1
Birth weight <2499 g	35	24.3
Gestational age <37 wk	20	13.9
Vaginal delivery	85	59.0
Multipara mothers	61	42.4
Sibling treated for jaundice	5	3.5
Cephalhematoma	4	2.8
Significant hyperbilirubinemia	41	28.5
Evidence of hemolysis	22	15.3

Table 2. Comparison of six-hour TcB values among ABO incompatible neonates with or without subsequent significant hyperbilirubinemia

Neonates	TcB value at 6th hour of life (mg/dL)			
	Range	Mean	SD	*P* value
Neonates with significant hyperbilirubinemia	3.1-8.5	5.83	1.35	<0.001
Neonates without significant hyperbilirubinemia	1.7-5.6	3.65	0.96	

SD: standard deviation; TcB: transcutaneous bilirubin.

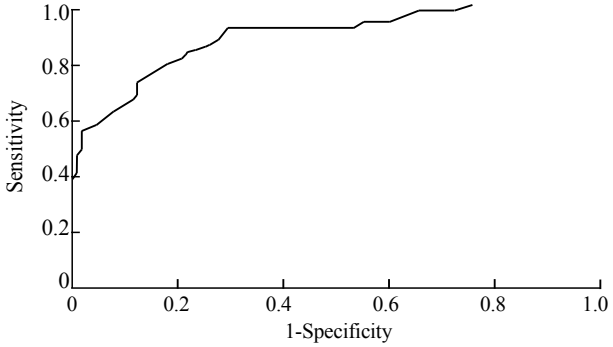

Fig. The receiver operating characteristic curve with performance of transcutaneous bilirubin values at the sixth hour of life in predicting significant hyperbilirubinemia.

Table 3. Predictive characteristics of TcB values at six hour life for the development of significant hyperbilirubinemia

TcB value at sixth hour (mg/dL)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
>4	93.5	70.5	58.1	96.1
>5	69.6	87.6	71.1	86.8
>6	47.8	99.0	95.7	81.2

TcB: transcutaneous bilirubin.

was no case of G-6PD deficiency. There was no weight loss beyond physiological range (7% of birth weight) in neonates requiring phototherapy. History of sibling treated for jaundice was reported in 5, but the exact etiology for intervention in all of them could not be identified.

The mean sixth hour TcB value was significantly higher in neonates who developed significant hyperbilirubinemia than those who did not (P<0.001) (Table 2). The sixth hour TcB value of >4 mg/dL had the highest sensitivity (93.5%) and >6 mg/dL had the highest specificity (99%) (Table. 3). The ROC curve demonstrated discriminative performance of sixth hour TcB. Area under curve of 0.898 indicated good predictive ability (Fig.).

Discussion

About 8%-11% of well neonates require interventions for hyperbilirubinemia and about 30% require continued monitoring.[2] Early postnatal discharge faces the risk of subsequent significant hyperbilirubinemia. The risk of unmonitored jaundice is not known and rapidly raising bilirubin reaching a high level may lead to bilirubin encephalopathy and related complications. Kernicterus has never completely disappeared even in North America.[13] Predischarge risk assessment and appropriate follow-up are the key elements to prevent kernicterus.[13-15] The risk identification by first day serum bilirubin levels has been well studied in term and late preterm newborns.[2,10,11,15,16] Randev and Grover[16] reported that first day serum bilirubin level of less than 6.4 mg/dL had a minimum risk for subsequent hyperbilirubinemia.

Although most cases of jaundice due to ABO incompatibility are mild, significant hyperbilirubinemia of 9%-21.3% requiring phototherapy and severe hyperbilirubinemia of 4% requiring exchange transfusion have been reported.[4,17,18] The exchange transfusion rate was 40% in another study.[19] The slightly higher rate of significant hyperbilirubinemia of 28.5% in the present study may be due to Asian race.[20] Racial difference in ABO-HD with higher jaundice level in Asian and African races has been recognized.[19-21] Cephalhematoma typically contribute to hyperbilirubinemia at 48-72 hours of life.[20] Kaplan et al[22] reported a higher rate (51.8%) of overall hyperbilirubinemia in direct antiglobulin test positive neonates.

The routine screening for neonatal ABO-HD by several tests was found to have no role.[8,9] Sarici et al[4] reported the sixth hour serum bilirubin levels of 4 mg/dL and 6 mg/dL predicting nearly all newborns developing significant hyperbilirubinemia and severe hemolytic disease, respectively. Schutzman et al[23] in their retrospective study using serum bilirubin estimations demonstrated reliable applicability of the Bhutani's nomogram[10] in direct Coombs-positive, ABO incompatible infants. Serum bilirubin estimation, however, is painful and one needs to wait for reports. TcB, on the other hand, is non-invasive, pain free, handy and provides rapid reports. Lease and Whalen[24] suggested predischarge systematic assessment for risk of developing severe hyperbilirubinemia in all newborns. In this context, we evaluated the predictive role of sixth hour TcB for hyperbilirubinemia in a defined subgroup.

Sixth hour TcB >4 mg/dL detected 93.5% neonates at risk of developing subsequent significant hyperbilirubinemia with a specificity of 70.5%. Sarici et al[4] found serum bilirubin of 4 mg/dL having the highest sensitivity of 86.2%. The TcB value of >6 mg/dL at 6 hours in the present study had the highest specificity of 99%. Optimum cut off value was 4.6 mg/dL with a sensitivity of 80.4% and a specificity of 82%. The area under ROC curve of 0.898 (predictive point: 89.8%) is closer to 0.862 (predictive point: 86.2%) for the sixth hour serum bilirubin in a study by Sarici et al.[4] Stoniene et al[25] found the sixth hour TcB level ≥98 μmol/ L (5.7 mg/dL) having a sensitivity of 100% and a specificity of 98% for the diagnosis of ABO-HD.

The limitations of the present study include using the older, Cockington's chart for deciding the interventions for hyperbilirubinemia instead of the newer, American Academy of Pediatrics (AAP) 2004 Guidelines.[26] However, the cutoff values for phototherapy at different postnatal age do not differ much among these two references. The AAP 2004 nomogram has an added advantage of 12th hourly reference points compared to only 24 hourly cutoff values in the Cockington's chart. We also limited G-6PD enzyme estimations to neonates with evidence of hemolysis. This selective screening was adopted because a large number of neonates screened for G-6PD deficiency in the center earlier showed normal values.

Early identification of neonates at risk for severe hyperbilirubinemia reduces morbidity.[14] A favorable association between initiation of screening and decrease in rates of hyperbilirubinemia, treatment and readmissions for hyperbilirubinemia compared with the baseline of no screening was found in a review by Trikalinos et al.[27] Early identification and therapy of significant hyperbilirubinemia avoided invasive exchange transfusion in the present study.

In conclusion, neonates ABO incompatible with their mothers are at increased risk of significant hyperbilirubinemia. Sixth hour TcB was significantly

higher in neonates who developed subsequent significant hyperbilirubinemia than who did not. The sixth hour TcB value >4 mg/dL had the highest sensitivity (93.5%) and >6 mg/dL had the highest specificity of 99%. This predictive characteristic of the sixth hour TcB could guide clinicians for early discharge of ABO incompatible term and late preterm neonates.

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