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Predictive value of cord blood bilirubins for hyperbilirubinemia in neonates at risk for maternal-fetal blood group incompatibility and hemolytic disease of the newborn

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Abstract

Objective—To determine the predictive ability of cord blood bilirubin (CBB) for hyperbilirubinemia in a population at risk for maternal-fetal blood group incompatibility and hemolytic disease of the newborn.

Study Design—This is a single center retrospective case-control study. Cases received phototherapy; controls did not. Cases were matched 1:3 to controls by gender and treating physician. Inclusion criteria included: 35 weeks gestation, CBB, and one or more total serum bilirubin (TSB) concentrations. The primary outcome was CBB. Secondary outcomes were a TSB > 75th percentile, length of stay, and neonatal intensive care unit admission. The prognostic ability of CBB for phototherapy and TSB > 75th percentile was assessed using area under the receiver operating characteristic (ROC) curve. Logistic regression analyses were performed to determine predictors for phototherapy and TSB > 75th percentile.

Result—When compared to controls (n=142), cases (n=54) were more likely to have a positive Coombs' test (82% vs. 41%, p<0.001) and TSB > 75th percentile (85% vs. 21%, p<0.001). When compared to controls, cases had a higher mean (±SD) CBB (2.5±0.5 vs. 1.8±0.4 mg/dL, p<0.001). The area under the ROC curve (±SEM) for CBB for phototherapy and TSB > 75th percentile was 0.87±0.03 (p<0.001, 95% CI 0.82,0.93) and 0.87±0.03 (p<0.001, 95% CI 0.82,0.92), respectively.

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Disclosure Statement

The authors have nothing to disclose or any conflicts of interest.

This research was conducted in accordance with the ethical standards of all applicable national and institutional committees and the World Association's Helsinki Declaration.

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Conclusion—In this study, the mean CBB concentration was higher in neonates who received phototherapy compared to those who did not. CBB concentrations may help predict severe hyperbilirubinemia and phototherapy in a population at risk for hemolytic disease of the newborn.

Keywords

bilirubin; neonates; phototherapy; hemolytic disease

Introduction

Hyperbilirubinemia (HB) in most healthy newborns is well-tolerated and considered a normal physiological process. However, excessive unconjugated bilirubin concentrations can cross the blood-brain barrier and result in kernicterus—a disease associated with death, choreoathetoid cerebral palsy, sensorineural hearing loss, and developmental delays [1–5]. Many nurseries have adopted the 2004 American Academy of Pediatrics (AAP) Clinical Guidelines for Management of HB in the Newborn Infant, which recommend that newborns be assessed for HB prior to discharge by evaluating total bilirubin concentrations and risk factors [6].

Hemolytic disease of the newborn (HDN) is a well-established risk factor for severe HB. One of the most common causes of HDN is the destruction of red blood cells (RBC) by maternally acquired antibodies [2–7]. RBC destruction leads to elevated total serum bilirubin (TSB) concentrations. As a result, blood group incompatibility with a positive direct antiglobulin test is considered a major risk factor for the development of severe HB, and the AAP recommends starting phototherapy (PT) earlier and at lower TSB concentrations for infants with HDN in comparison to neonates without HDN [6].

Cord blood bilirubin (CBB) concentrations measure in utero hemolysis and represent a possible biomarker for severe HB secondary to HDN. The ability to predict high-risk neonates shortly after birth may help guide clinical management particularly in an era where early discharge from nurseries is promoted and readmission to the hospital for PT continues to be a significant problem [8–12]. Some studies have demonstrated that CBB concentrations may predict severe HB and PT treatment in full-term, healthy neonates. However, some of these studies were performed in homogenous populations outside the United States, excluded neonates at risk for or with HDN, and did not utilize the AAP Clinical Practice Guidelines [13–16]. The objective of this study was to determine CBB's predictive ability for severe HB in a contemporary cohort of neonates who were at risk for HDN secondary to maternal-fetal blood group incompatibility.

Methods

This is a single site retrospective case-control study where CBB testing is routinely performed after neonates are born to mothers with blood types O or Rh negative or who have positive antibody screens. Inclusion criteria included admission to the nursery, one or more TSB measurements prior to discharge, 35 weeks gestational age, and a documented CBB concentration. Exclusion criteria included confirmed liver disease, congenital infections, major congenital anomalies, or a positive maternal hepatitis B screen. Cases

received PT while controls did not. In order to identify potentially eligible cases, billing records were screened for HB by the International Classification of Diagnosis-9 (ICD-9) code during the period February 2012 until December 2012. Cases were matched 1:3 to controls by gender and treating physician within a seven day period. The institutional review board (IRB) at the University of California, Los Angeles approved the study and a waiver of consent was granted.

The primary outcome was CBB concentration. Secondary outcomes included a TSB > 75th percentile using the AAP guidelines [6], length of hospital stay, and admission to the neonatal intensive care unit. Subjects with birth weights < 10th or > 90th percentile were classified as small or large for gestational age, respectively [17]. Breastfeeding (any breast milk intake on the day of discharge), early onset sepsis (confirmed positive blood culture at < 72 hours of age and need for intravenous and/or intramuscular antibiotic treatment for > 5 days), and chorioamnionitis (documented in the medical chart by the medical team) were recorded.

Neonatal TSBs are usually measured between 24–48 hours of life at the same time as the newborn metabolic screen. The medical team generally follows the 2004 AAP Clinical Practice Guidelines for assessing and treating neonatal HB [6]. Ultimately, the medical team dictates when PT should be prescribed.

The research team used the 2004 AAP guidelines and nomograms to retrospectively determine if a subject had a TSB that was > 75th percentile after 12 hours of life and to determine which cases warranted PT [6]. To determine which cases warranted PT, the risk factors, gestational age, sepsis, and positive Coombs' test, were used. According to the AAP Clinical Guidelines, it is recommended that PT be initiated if the TSB concentration exceeds the value indicated by the curve for that patient. The AAP also states that it is an option to begin PT at TSB concentrations 2–3 mg/dL below the guidelines' recommended value particularly for at risk neonates such as premature neonates or those with HDN [6]. In this study, the concept of "threshold" was employed. Threshold was defined as a TSB concentration that was two mg/dL below a case's designated curve on the AAP nomogram for PT for a specific hour of life. A TSB exceeding threshold was classified as within the acceptable threshold range.

Statistical Methods and Analysis

Continuous variables were compared between cases and controls, and those with TSB 75th and > 75th percentile using the Student t- or Wilcoxon rank-sum test. Categorical variables were compared between groups using the chi-square or Fisher's exact test. The overall prognostic ability of CBB for PT and a TSB > 75th percentile was assessed using the area under the receiver operating characteristic (ROC) curve. Accuracy was assessed in terms of sensitivity and specificity for CBB cut-points. The analysis was run on the complete cohort as well as a subgroup where the cases' TSB concentrations plotted within the acceptable threshold range and their matched controls. Cases within the acceptable threshold range and below threshold were compared to determine if there were any significant differences between these subgroups.

Univariate and multivariate logistic regression models were constructed to examine the predictive ability of CBB and well-described characteristics known to influence one's risk for requiring PT or having a TSB > 75th percentile (gestational age, gestational diabetes, male sex, large for gestational age, race, blood group incompatibility, and a positive Coombs' test) [6]. In order to find the best panel of predictor variables for the multivariate analysis, we used forward and backward stepwise selection. The area under the ROC curve and confidence intervals from these models were reported.

A p-value of < 0.05 was considered statistically significant. Statistical analysis was performed with SAS 9.3 (SAS Institute, Cary NC) and SPSS 22 (IBM Corp., Armonk, NY). Continuous data is presented as a mean $\pm$ SD.

Results

A total of 53 cases and 142 matched controls were identified. No subjects were excluded for missing data. When compared to controls, cases were more likely to have maternal fetal blood group incompatibility (66% vs. 29%, $p<0.001$), a positive Coombs' test (82% vs. 41%, $p<0.001$), and be a product of a Cesarean section (40% vs. 20%, $p<0.01$). Of the 66 subjects with maternal fetal blood group incompatibility, 82% had ABO incompatibility, and 18% had Rh incompatibility (Table 1).

Cases had a significantly higher CBB at 2.5 ± 0.5 mg/dL as compared to 1.8 ± 0.4 mg/dL for controls ($p<0.001$). Cases with ABO incompatibility had a higher CBB in comparison to controls with ABO incompatibility (2.6 ± 0.6 vs. 1.8 ± 0.3 mg/dL, $p<0.001$). Likewise, a similar trend was observed with cases with Rh incompatibility when compared to controls with Rh incompatibility (3 ± 0.6 vs. 1.7 ± 0.5 mg/dL, $p<0.004$).

Seventy seven percent (41/53) of the cases' TSB values fell below their designated curve on the AAP nomogram [6], and 54% (22 out of 41) were below threshold. The CBB for cases' whose TSB that were within the acceptable threshold range was significantly higher in comparison to the CBB concentration for cases below threshold (2.6 ± 0.5 vs. 2.3 ± 0.5 mg/dL, $p=0.01$). When these two populations were compared, cases whose TSBs that were categorized as being within the threshold range were more likely to have a positive Coombs' test in comparison to cases whose TSBs were below threshold (89% vs. 11%, $p<0.001$). With regards to other variables, there was no difference between these two subgroups for male sex ($p=0.6$), white race ($p=0.8$), gestational diabetes ($p=0.4$), large for gestational age ($p=0.07$), gestational age > 41 weeks ($p>0.99$), length of stay > three days ($p=0.3$), and positive antibody screen ($p=0.3$). Because there was a small number of neonates with a gestational age < 37 weeks in this study, a statistical comparison could not be performed for this variable.

The area under the ROC curve ($\pm$ SEM) for CBB for PT treatment was 0.87 ± 0.03 ($p<0.001$, 95% CI 0.82, 0.93). A CBB cut-off value of 2.05 mg/dL had 80% sensitivity and 78% specificity for predicting PT prescription. When cases and their controls whose TSB concentrations plotted below threshold were omitted from the analysis, the mean CBB for cases increased to 2.6 ± 0.6 mg/dL in comparison to 1.7 ± 0.3 mg/dL for controls ($p<0.001$).

The area under the curve (AUC) for CBB for PT treatment increased to 0.95 ± 0.2 (95% CI 0.91, 0.99) and the sensitivity and specificity improved to 90% and 84%, respectively for a cut-off value of 2.05 mg/dL (31 cases, 86 controls) (Figure 1 and Table 2).

CBB concentration, blood group incompatibility, positive Coombs' test, and TSB > 75th percentile significantly increased the odds of being prescribed PT ($p < 0.01$ each). CBB had the highest AUC for PT. The AUC increased slightly in the multivariate analysis to 0.93 ± 0.2 (95% CI 0.89, 0.96) when CBB was combined with TSB > 75th and a positive Coombs' test from the stepwise reduced model (Table 3).

Cases were more likely to have a TSB > 75th percentile when compared to controls (85% vs. 21%, $p < 0.001$) (Table 1). Neonates with a TSB > 75th percentile were more likely to have blood group incompatibility (55% vs. 31%, $p < 0.003$) and a positive Coombs' test (74% vs. 46%, $p < 0.02$). The predictive ability of CBB, blood group incompatibility, and Coombs' test for a TSB > 75th percentile was statistically significant with AUCs of 0.87 ± 0.03 (95% CI 0.82, 0.92, $p < 0.001$), 0.62 ± 0.05 (95% CI 0.53, 0.71, $p < 0.01$), 0.64 ± 0.07 (95% CI 0.51, 0.77, $p < 0.04$), respectively. Other risk factors (gestational age, infants of diabetic mothers, sex, large for gestational age, post-term delivery, and race) were not predictive of a TSB > 75th percentile. A CBB cut-off value of 1.95 mg/dL had a sensitivity of 87% and specificity of 66% for predicting a TSB > 75th percentile. Unlike the multivariate analysis for PT, the forward and backward stepwise selection technique determined that no additional variables added any predictive ability above and beyond CBB.

Only one case was admitted to the neonatal intensive care unit for severe HB. This patient did not receive intravenous immunoglobulin or an exchange transfusion. The average number of days spent in the hospital was increased for cases in comparison to controls (2.8 ± 1.1 vs. 1.8 ± 0.8 days, $p < 0.001$). Cases received a mean of 27 ± 17 hours of PT, which was initiated at a mean of 24 ± 19 hours of life (range 2–99 hours). Using the AAP's nomogram for PT treatment [6], 45% (24/53) of cases were classified as lower risk, and the remaining 55% (29/53) were classified as medium risk.

While percent weight loss from birth weight at discharge was increased in cases in comparison to controls ($5.7 \pm 2.9\%$ vs. $4.5 \pm 2.6\%$, $p < 0.001$), percent weight loss on the first ($3.1 \pm 2.1\%$ vs. $2.6 \pm 3.2\%$, $p = 0.3$), second ($5.3 \pm 2.4\%$ vs. $5 \pm 3.5\%$, $p = 0.7$) and third day of life ($7.7 \pm 1.9\%$ vs. $5.7 \pm 5.2\%$, $p = 0.1$) was comparable between the two groups.

Discussion

In this single center retrospective analysis, neonates born to mothers with blood type O or Rh negative or a positive antibody screen that were prescribed PT had a statistically significant higher mean CBB concentration than their matched controls. Additionally, they were more likely to have maternal-fetal blood group incompatibility, a positive Coombs' test, and a TSB > 75th percentile, be delivered by Cesarean section, and require a longer hospital stay when compared to controls (Table 1). One of the important findings of this study was the predictive value of CBB for severe HB and PT in a target population at risk for maternal-fetal blood group incompatibility and HDN. The area under the ROC curves

generated from this data for PT and TSB >75th percentile (0.87 ± 0.03) indicate that CBB may be a relatively accurate test for discriminating which at risk neonates will be prescribed PT and develop severe HB. Considering that most cases of pathologic HB are easily treated with PT and all neonates should be screened prior nursery discharge [6], an additional screening test, such as CBB, used alone or in combination with TSB, could be clinically useful.

One of the advantages of this study is that it is a contemporary investigation examining the predictive value of CBB in neonates at risk for blood group incompatibility and HDN. A 1977 report by Risemberg *et al* described the results of 91 infants who were the product of pregnancies affected by ABO incompatibility. All infants with CBB of 4 mg/dL developed TSB > 16 mg/dL within the first 12–26 hours of life [18]. In a group of Turkish full term neonates, Ipek *et al* found that the mean CBB was significantly higher at 2.1 mg/dL in neonates with ABO incompatibility as compared to 1.6 mg/dL in neonates without ABO incompatibility. In the cohort described by Ipek *et al*, a CBB of 2.1 mg/dL had a much lower sensitivity at 50% as compared to our study, but a similar specificity at 86% for PT [14]. A prospective German study of over 1,000 neonates (none of which had a positive Coombs' test) reported a CBB cut-off value of 1.7 mg/dL having 90% sensitivity for PT in healthy term and near-term neonates [15].

In terms of our study's other findings, the AUC for blood group incompatibility and a positive Coombs' test was lower than the AUC obtained for CBB alone. It should be noted that the CBB was higher in cases with blood group incompatibility (both ABO and Rh) in comparison to controls without blood group incompatibility indicating that these clinical characteristics may increase the accuracy of future prediction models. Because of our study's small size, particularly with regards to subjects with Rh incompatibility ($n=12$), we did not examine the predictive value of these variables individually. However, considering that neonates with Rh disease are at high risk for HDN and severe HB [1,2], we would anticipate that CBB would be useful for discriminating which neonates would require PT from neonates who do not require PT in this subpopulation.

While the AUC did not improve substantially when a positive Coombs' test result was combined with CBB (data not shown), the AUC improved to 0.93 in the multivariate analysis that included TSB > 75th percentile and a positive Coombs' test (Table 3). Previous reports have indicated that infants with ABO incompatibility and a positive Coombs' test have the same risk for HB as infants with a negative Coombs' test [19–21]. As a result, routine Coombs' testing is not universally recommended and may not be useful when used as a sole predictor for severe HB [6].

As expected, the sensitivity and specificity of CBB improved in the sub-group analysis that eliminated cases prescribed PT below threshold (Figure 1). The high rate of PT prescription for cases with TSB concentrations below threshold may limit the interpretation of this study's findings. Because some clinicians may believe a specific CBB concentration indicates an increased risk for severe HB, the primary outcome (PT) may be biased. Other factors (maternal/fetal blood type or a positive Coombs' test) may have also motivated the medical team to prescribe PT. In an ideal world, clinicians would have been masked to the

CBB values. However, at the study's institution, CBBs are routinely performed in a specific population, making this option impossible. In order to overcome this bias, we opted to also investigate whether CBBs can predict TSB concentrations > 75th percentile, a less biased outcome. The AUC for CBB for predicting PT and a TSB > 75th percentile were similar. Lastly, it would be helpful if the research team could have determined if CBB predicts a TSB range at a specific hour of life. Because TSB concentrations were measured at various hours of life for convenience, this was not possible.

The study's definition of an acceptable threshold range may be considered somewhat arbitrary; however this range was defined a priori. In the AAP Clinical Guidelines for Management for HB, the authors state that lower TSB concentrations may be used when specific HB neurotoxicity risk factors (prematurity, HDN, glucose-6-phosphate dehydrogenase deficiency, asphyxia, sepsis, acidosis, and serum albumin < 3 mg/dL) are present [6]. In this study, other than culture proven sepsis, we were unable to determine which subjects had these risk factors. HDN is classically defined by an elevated serum reticulocyte count, anemia and a blood smear suggestive of RBC destruction. These laboratory studies were rarely performed in our study population (data not shown). As a result, the study team relied upon a positive Coombs' test as surrogate for HDN, which is recognized as a major risk factor for severe HB and may more accurately reflect clinical practice [6].

With regards to additional findings in this study, cases' had a higher rate of Cesarean section and a longer hospital stay in comparison to controls (Table 1). A length of stay > 72 hours, however, has been described to decrease one's risk for severe HB [6]. In general, neonates born to mothers who have undergone a Cesarean section are more likely to stay in the hospital longer compared to those born via vaginal delivery. Longer hospital stays in comparison to shorter hospital stays may result in closer observation for HB resulting in a higher PT prescription rate. In addition, neonates prescribed PT may be more likely to stay in the hospital longer than those who do not receive this intervention. As a result, cases may have remained in the hospital longer in comparison to controls because they were a product of a Cesarean section, received PT, and/or other unknown reasons.

Other risk factors associated with an increased risk for severe HB (gestational age, infants of diabetic mothers, sex, large for gestational age, race) did not predict PT or a TSB > 75th percentile (Table 3). The current study may not have detected differences in these variables due to its small sample size and inclusion criteria. To overcome some study design limitations, each case was matched to three controls by gender and attending physician. Gender has been described to influence HB [6]. The attending physician of service was included as a matching criteria since personal practice represents a potential source of bias.

Given the ease in which a CBB can be obtained after birth, the rapid availability of test results, and its low cost, CBB testing may be an ideal option to use alone or in combination with clinical factors or a TSB to determine which neonates are at risk for severe HB secondary to HDN. Earlier disease detection could result in earlier treatment, which, in turn, could drive a more appropriate and timely utilization of healthcare resources and decrease HB associated healthcare costs.

Conclusion

This study supports that CBB may help predict HB in neonates at risk for maternal-fetal blood group incompatibility and HDN. The study is limited by its retrospective design and sample size. Larger prospective studies are warranted before widespread application of CBB testing as a clinical biomarker can be applied to newborn care.

Abbreviations

HB	hyperbilirubinemia
CBB	cord blood bilirubin
TSB	total serum bilirubin
HDN	hemolytic disease of the newborn
PT	phototherapy
ROC	receiver operating characteristic curve
AUC	area under the curve

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Figure 1. Receiver operating characteristic curves for A. the entire study population and B. the subpopulation of cases within threshold and their controls.

Table 1

Maternal and Neonatal Characteristics for Cases and Controls

	Cases (n=53)	Controls (n=142)	p-value
Neonatal Characteristics			
Gestational Age (weeks)	40±1.2	40±1.2	0.4
Birth weight (kg)	3.5±0.5	3.4±0.4	0.2
Vaginal Delivery	60% (32)	80% (112)	0.01
Race			0.3
White	57% (30)	70% (99)	
African-American	4% (2)	1% (2)	
Asian	11% (6)	11% (15)	
Other	28% (15)	18% (26)	
Hispanic	34% (18)	35% (49)	0.9
Small of gestational age	6% (3)	6% (8)	1
Large for gestational age	17% (9)	10% (14)	0.2
1 minute Apgar	8±1.3	8±0.8	1
5 minute Apgar	9±0.4	9±0.4	0.3
Neonatal blood type			<0.001
O	38% (20)	59% (84)	
A	26% (14)	15% (21)	
B	32% (17)	8% (11)	
Other/unknown	4% (2)	18% (26)	
Positive Rh blood type	91% (48)	89% (127)	0.8
Blood group incompatibility*	66% (33/50)	29% (33/114)	<0.001
Positive Coombs' test*	82% (27/33)	41% (15/37)	<0.001
TSB > 75th percentile	85% (45)	21% (30)	<0.001
Breastfeeding	96% (51)	99% (141)	0.2
Early onset sepsis	0%	0%	1
Maternal Characteristics			
Age	32±5	31±6	0.4
Gravida	2±1.4	2±1.5	0.8
Para	2±1.2	2±1.2	0.6
Gestational diabetes	11% (6)	8% (11)	0.4
Chorioamnionitis	9% (5)	3% (4)	0.06
Blood type O	98% (52)	96% (136)	0.7
Rh negative	6% (3/50)	8% (9/115)	>0.99
Antibody positive*	2% (1/50)	1% (1/141)	0.5

Data is presented as a mean±SD or percentage (n).

* Different sample size.

Table 2

Phototherapy Predictors

	p-value	AUC±SEM (95% CI)
Univariate analysis		
Gestational age (weeks)	0.3	0.55±0.05 (0.46,0.64)
Gestational diabetes	0.7	0.52±0.05 (0.43,0.61)
Male	0.9	0.51±0.05 (0.42,0.6)
Large for gestational age	0.5	0.54±0.05 (0.44,0.63)
Gestational age ≥ 41 weeks	0.8	0.51±0.05 (0.42,0.6)
White race	0.2	0.57±0.05 (0.47,0.66)
CBB (mg/dL)	<0.001	0.87±0.03 (0.82,0.93)
Blood group incompatibility	<0.001	0.69±0.05 (0.60, 0.78)
TSB > 75th percentile	<0.001	0.82±0.04 (0.75, 0.89)
Positive Coombs' test	0.003	0.71±0.06 (0.58,0.83)
Multivariate analysis (forward stepwise)		
CBB (mg/dL)		
TSB > 75th percentile	<0.001	0.93±0.02 (0.89, 0.96)
Positive Coombs' test		
Multivariate analysis (backward stepwise)		
CBB (mg/dL)		
TSB > 75th percentile	<0.001	0.93±0.02 (0.89,0.96)
Positive Coombs' test		

Table 3

Sensitivity and specificity for cord blood bilirubin.

Entire Study Population (cases=53, controls=142)		Cases within Threshold and their Controls (cases=31, controls=86)			
Cut-point (mg/dL)	Sensitivity	Specificity	Cut-point (mg/dL)	Sensitivity	Specificity
2.05	0.8	0.78	2.25	0.77	0.98
1.95	0.85	0.7	2.15	0.87	0.94
1.75	0.9	0.49	2.05	0.9	0.84
1.65	0.95	0.35	1.95	0.94	0.72