Original Article

Cord Blood Bilirubin as a Predictor of Neonatal Hyperbilirubinemia

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Abstract

Introduction: In the 1st week of life, hyperbilirubinemia is the most common clinical condition in newborns that has to be evaluated and treated. It is also a prominent cause of readmission to the hospital. Some newborns experience noticeable, potentially dangerous bilirubin levels, which can directly increase the risk of severe brain damage, despite it being a benign, postnatal, transitory phenomenon. The current investigation looked at the relationship between cord blood bilirubin levels and the predictability of pathological jaundice. **Materials and Methods:** Cord blood bilirubin was estimated at birth. Bilirubin estimation was done at 48 h, 72 h, and 5–7 days of life using a trans-bilirubinometer. The study was approved by the Institutional Ethical Committee. **Results:** Significant hyperbilirubinemia was found in 3.7% of the neonates. A statistically significant correlation was found between cord blood bilirubin and the development of significant hyperbilirubinemia at 48 h of life. Gender, gestational age, birth weight, and use of Oxytocin have no correlation with cord bilirubin or the subsequent development of jaundice. A cord blood value of >2 mg/dL has a high negative predictive value (98%), sensitivity (83%), specificity (41%), and positive predictive value (5.3%) in predicting the future development of future pathological jaundice. **Conclusions:** A high negative predictive value in our study suggests that healthy term babies with cord bilirubin ≤2 mg/dL can be discharged early with assurance to parents. Babies with cord blood bilirubin >2 mg/dL should be followed more frequently.

Keywords: Cord blood bilirubin, high negative predictive value, hyperbilirubinemia, trans-bilirubinometer

Introduction

Neonatal hyperbilirubinemia is the seventh most common cause of neonatal mortality in the 1st week of life worldwide, and it can have severe long-term sequelae such as kernicterus spectrum disorder.[1,2]

Jaundice is a common clinical condition of the newborn period encountered in 60% of term and 80% of preterm babies.[3-5] Bilirubin usually rises on the 2nd day of life and shows a peak on days 3 and 5 in term and preterm babies, respectively. Based on the American Academy of Pediatrics guidelines, specific cutoffs for age are defined that warrant the management of hyperbilirubinemia. For term babies, the cutoff values of serum bilirubin are 15.5 mg/dL and 21 mg/dL on days 2 and 5 of life, respectively. For preterm babies, the cutoff values are 11 mg/dL and 15 mg/dL, respectively.[6,7] This calls for a need to observe newborns for at least 5 days for the development of hyperbilirubinemia. Significant hyperbilirubinemia is more likely to develop if a newborn has underlying asphyxia, infection, acidosis, and exaggerated hemolysis.[8]

In India, where healthcare resources are scarce and unevenly distributed and prolonged hospital stays mean lost wages for the parent, an early discharge of the newborn after delivery is often desirable. In such a setting, early recognition, follow-up, and timely treatment of jaundice suffer a setback. A decreased length of stay in the hospital often leads to later readmission due to multiple reasons, the most notable being hyperbilirubinemia.[9-12] Hence, it is important to identify newborns who are at risk of developing hyperbilirubinemia so that their early discharge is discouraged and treatment is instituted. Therefore, we planned a study with the objective

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of evaluating the correlation between the concentration of bilirubin in the cord blood and the occurrence of significant hyperbilirubinemia in healthy newborns.

Materials and Methods

Ethical approval

Ethical clearance was obtained from the Institutional Ethical Committee (Letter Number: D.No. 2247/FM dated February 2, 2016).

Study design

This is a prospective, observational study. A total of 158 healthy newborns ≥35 weeks of age or with a birth weight of more than 2500 g delivered at this hospital fulfilling the inclusion criteria were consecutively enrolled in the study. It was also ensured that newborns belonged to Aligarh, and the family was willing to turn up for follow-up. Newborns with blood group incompatibility, a significant illness requiring admission, or major congenital malformations were excluded from the study. Clinical data on all newborns were collected. After birth, umbilical cord blood bilirubin was obtained, and newborns were evaluated at 48 h, 72 h, and in between days 5 and 7 for hyperbilirubinemia through transcutaneous bilirubinometer measurement using the Drager Jaundice Meter JM-105. If higher values were noted, the serum bilirubin value was measured.

Study setting

This hospital-based study was conducted from October 2015 to September 2017 in the Neonatology Division of the Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, U.P. Informed written consent was obtained from parents before enrollment in the study.

Sample size

The following formula was used to calculate the sample size:

$n = Z^2P\,(1 - P)/d^2$

where

n = sample size

Z = level of confidence

P = expected prevalence or proportion (prevalence is 10%), and

d = precision (=5).

Considering the dropout rate of 10%, the sample size was calculated as 158.

Statistical methods

Statistical analysis was done using the Statistical Package for the Social Sciences (IBM, Statistical Package for the Social Sciences (SPSS), Version 26, Chicago) for Windows software. Pearson's Chi-square test was applied to sets of categorical data to evaluate whether any observed difference between the sets arose by chance. P <0.05 was taken as statistically significant.

Results

A total of 158 healthy full-term and late-preterm newborns delivered at the hospital fulfilling the inclusion criteria were enrolled in the study. The majority of them were females (51%). The mode of delivery of approximately two-thirds of subjects was normal vaginal delivery (65%). The gestational age of 37 weeks and more was found in the majority of subjects (73%). The mean gestational age was 38.3 ± 1.12 weeks [Table 1].

A significant proportion of the mothers (65%) had previously undergone routine antenatal care visits. The use of oxytocin was seen in 86% of mothers [Table 2]. The mean birth weight in babies with significant hyperbilirubinemia was 2.97 ± 0.49 kg [Table 3]. Out of the 158 subjects included in the study, a gestational age of more than 37 weeks was found in the majority of babies (73%) [Table 4]. The incidence of significant hyperbilirubinemia was 3.7% in our study.

The box and whisker plot shows the trend of bilirubin rise during the 1st week of life on follow-up evaluation. At 48 h of life, the mean bilirubin value was 9.06 ± 2.53; at 72 h of life, the mean value was 9.14 ± 2.91; and on days 5–7 of life, the observed value was 4.96 ± 2.38. There was a rise in the levels of bilirubin until 72 h of life, and then, the level fell [Figure 1].

Table 1: Demographic data of the study population

Neonatal factors	Number of newborns (%)
Birth weight (kg)	
2.5–2.99	92 (58)
3.0–3.49	52 (33)
≥3.5	14 (9)
Gender	
Male	77 (49)
Female	81 (51)
Gestational age (weeks)	
≥35–<37	43 (27)
≥37	115 (73)
Mode of delivery	
Vaginal	102 (65)
LSCS	56 (35)

LSCS: Lower segment caesarean section

Table 2: Maternal characteristics of study population

Maternal factors	Number of neonates (%)
ANC visits	
Booked	104 (65)
Unbooked	54 (34)
Gravida	
Primi	60 (38)
Multi	98 (62)
Use of syntocin	
Yes	136 (86)
No	22 (14)

ANC: Antenatal care

All the neonates receiving phototherapy responded well to treatment, and no adverse outcome was reported.

We analyzed the level of cord bilirubin with bilirubin values at 48 h, 72 h, and 5–7 days by means of a linear regression model [Figure 2]. There was a significant association found between cord blood bilirubin and 48 h bilirubin levels, derived from an equation:

Transcutaneous bilirubin (TCB) (48 h) =8.043 + 0.413 × cord bilirubin.

The coefficient of determination is $r^2 = 0.025$; therefore, about 2% of the variation in TCB is explained by cord bilirubin ($P = 0.049$). There was no significant relationship observed between the cord blood bilirubin levels and the bilirubin levels at 72 h and days 5–7 of life.

Using cord blood bilirubin >2 mg/dL, significant hyperbilirubinemia can be predicted with a sensitivity of 83.3%, a specificity of 41.4%, a positive predictive value of 5.37%, and a negative predictive value of 98.4% [Table 5].

Discussion

Hyperbilirubinemia develops in otherwise healthy newborns due to reduced hepatic clearance of bilirubin. In most of such instances, the levels are mildly deranged, whereas in a small proportion, the jaundice requires active intervention through phototherapy, exchange transfusions, and medications. It is imperative to timely diagnose and treat the aforementioned conditions to avoid the prospects of detrimental neurological complications of the kernicterus, choreoathetoid cerebral palsy, and hearing defects. Fortunately, due to augmented medical facilities and ambulatory services, most cases are dealt with favorable outcomes. Nevertheless, a fraction of newborns does fall prey to protracted hyperbilirubinemia notably in developing countries.

In our study, the incidence of significant hyperbilirubinemia requiring phototherapy was found to be 3.7%. An almost similar incidence was seen in the study conducted by Ahire *et al*.[13] (3.5%) and Knüpfer *et al*.[14] (3.4%). The incidence of significant hyperbilirubinemia varies from 3.4% to 19.86%.[14-17]

When gender, gestational age, birth weight, and mode of delivery were evaluated in our study, there was no relationship found between Cord blood bilirubin (CBB) and bilirubin measured until the 5th day of life. Similar findings were noted by Jehangir *et al*.,[18] Rostami and Mehrabi,[19] and Eshwara Chary *et al*.[15]

Table 3: Relationship of significant hyperbilirubinemia with birth weight

Birth weight (kg)	Total	Frequency (%)		P
		Significant hyperbilirubinemia	Insignificant hyperbilirubinemia	
2.5–2.99	92	3 (3.2)	89 (96.7)	0.779
3.0–3.49	52	2 (3.8)	50 (96.1)	
≥3.5	14	1 (7.1)	13 (92.8)	
Total	158	6 (3.7)	152 (96.2)	

Table 4: Association of gestational age with significant hyperbilirubinemia

Gestational age (weeks)	Total	Frequency (%)		P
		Significant hyperbilirubinemia	Insignificant hyperbilirubinemia	
≥35–<37	43	1 (2.3)	42 (97.6)	0.554
≥37	115	5 (4.3)	110 (95.6)	
Total	158	6 (3.7)	152 (96.2)	

Table 5: Diagnostic predictability of cord blood bilirubin >2 mg/dL for significant hyperbilirubinemia

Cord blood bilirubin cutoff point (mg/dL)	Significant hyperbilirubinemia - present	Significant hyperbilirubinemia - absent	Total
>2	5	89	94
≤2	1	63	64
Total	6	152	158

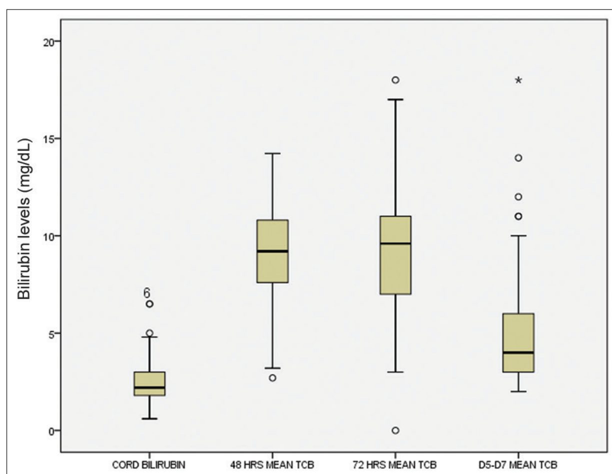

Figure 1: Box and whisker plot showing the trend of bilirubin rise over time. TCB: Transcutaneous bilirubin

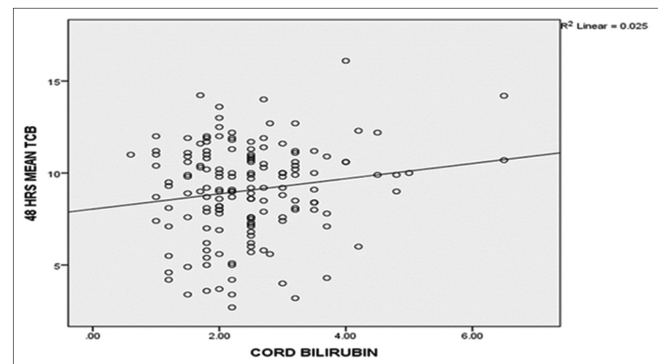

Figure 2: Scatter plot showing the correlation between cord blood bilirubin and 48-h bilirubin level. TCB: Transcutaneous bilirubin

Considering a cutoff value of >2 mg/dL of cord blood bilirubin, significant hyperbilirubinemia can be predicted with a sensitivity of 83%, a specificity of 41%, a positive predictive value of 5.3%, and a negative predictive value of 98% [Table 2]. A similar study was done by Rajpurohit *et al*.,[20] and considering a cord blood bilirubin of >2 mg/dL, significant hyperbilirubinemia can be predicted with a sensitivity of 90%, a specificity of 53.89%, a positive predictive value of 17.8%, and a high negative predictive value of 98%.

Ahire *et al*.[13] utilized a higher cutoff value for cord bilirubin. In their work, cord blood bilirubin values ≥3 mg/dL had a sensitivity of 100%, a specificity of 98.17%, a positive predictive value of 66.67%, and a negative predictive value of 100%. A cutoff level between two and three was also utilized by previous investigators with good negative predictive value.[18,21]

A high negative predictive value has an important implication for planning early discharge. Babies with cord bilirubin <2 may be sent home with fewer chances of developing significant hyperbilirubinemia. It may be desirable if neonates with cord blood bilirubin >2 mg/dL are followed strictly either in the hospital or at an outpatient department until days 5–7, if practicable.

In our study, we conducted continuous monitoring of TCB levels until day 5 of life. The measured value of TCB at 48 h of life has a high correlation with cord blood bilirubin. Whereas Guan H *et al*. found a correlation between TCB and serum bilirubin concentration in the hyperbilirubinemia group at 72 h, the regression equation was obtained: $Y = -158.81 + 19.57X$, correlational coefficient $r = 0.887$.[22]

Study limitations

The study design has certain limitations, as the effect of delayed passage and clearance of meconium was also not ascertained. Administration of a steroid and a specific anesthetic agent (such as bupivacaine) to the mother, which could potentially affect the bilirubin metabolism in the baby, was also not taken into consideration. In addition, we did not measure the direct antigen titer and albumin level in the study subjects, which are likely to affect the bilirubin levels in the babies in the initial days of life.

Conclusions

The use of cord blood bilirubin levels in healthy infants may help identify infants at low risk for hyperbilirubinemia and minimize an unnecessary prolongation of hospitalization. With parents' assurance, babies with cord blood bilirubin levels <2 mg/dL can be discharged early.

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Conflicts of interest

There are no conflicts of interest.

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