Role of Cord Blood Albumin and Bilirubin for Prediction of Significant Neonatal Jaundice

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ABSTRACT

Introduction: Nearly 60-80% of the term and preterm neonates are affected due to rise in bilirubin levels during early postnatal days, and causes readmission of the neonate sometimes with severe jaundice, which can be reduced if neonatal hyperbilirubinemia can be predicted early. The study was conducted to evaluate the predictive values of cord blood albumin and bilirubin for neonatal hyperbilirubinemia and to evaluate the better predictor between them.

Method: In this hospital based observational study, 152 healthy term newborns with birth weight more than 2.5 kg were included. Assessment of cord blood haemoglobin, blood group, albumin and bilirubin levels was done. Follow-up for first consecutive five days after birth was done and assessed daily to look for evidence of jaundice, sepsis or any other illness. Serum bilirubin was evaluated at 72-96 hours of life in all neonates and was done early, if clinically indicated. Receiver's Operating Characteristics curves were used for calculating the cut-off values of cord blood albumin and bilirubin in relation to hyperbilirubinemia.

Result: The cut-off values obtained for albumin and bilirubin of cord blood was < 2.56 mg/dL and >2.33 mg/dL respectively at optimum sensitivity and specificity. Cord blood bilirubin was found to be highly sensitive for early recognition of significant neonatal hyperbilirubinemia as compared to cord blood albumin and can be used for screening purpose.

Conclusion: Cord blood albumin and bilirubin can be used for negating the development of NNHB, but for screening purpose, cord blood bilirubin is more predictive of neonatal hyperbilirubinemia.

Keywords: cord blood albumin; cord blood bilirubin; neonatal hyperbilirubinemia

INTRODUCTION

Jaundice is one of the most common problems encountered in the newborns.[1] Most of the times, it is physiological as the liver maturity has not been complete. There is inability of neonatal liver to take care of high bilirubin levels which is a result of higher circulating volume of erythrocyte and with a smaller erythrocyte life-span, usually called "bilirubin peak." During this time, there is also ongoing transition of metabolism of bilirubin from foetal to adult stage.[2] This is generally a benign condition, but sometimes this bilirubin peak can go up to harmful level. At times, untreated high level of serum bilirubin in newborn can lead to bilirubin encephalopathy, which can result in kernicterus and have long term consequences. Hence, early detection of hyperbilirubinemia and needful treatment is the need of the hour.

The synthesis of albumin is done in the liver and it helps in transportation of unconjugated bilirubin. Cord blood bilirubin and albumin level may be able to predict significant hyperbilirubinemia in the babies. Studies have shown good diagnostic accuracy of cord blood albumin and bilirubin in prediction of neonatal hyperbilirubinemia.[3] In recent times, few studies have been conducted on prediction of neonatal hyperbilirubinemia using cord blood albumin and bilirubin. Both being non-invasive procedure and minimal cost, parents will give their consent easily for conducting these tests. These studies have recommended undertaking further research to find out the ethnic and geographical impact and to formulate guidelines as per requirement.

Hence, we undertook this study to evaluate the diagnostic accuracy of cord blood albumin and bilirubin to evaluate the predictive value for neonatal hyperbilirubinemia and formulate customised guidelines for "early prediction of neonatal hyperbilirubinemia" in our institution.

METHODS

The present study is a hospital based prospective observational study carried out in the Department of Paediatrics of a tertiary care teaching institute in central India from January 2017 to June 2018. One hundred and fifty two full term healthy neonates delivered during this period, fulfilling the inclusion criteria were included. A voluntary consent was obtained from the parents of the neonate for allowing participation.

The healthy term baby (Gestational age > 37 weeks) (based on last menstrual period or by first trimester USG) with birth weight > 2.5 kg (weighed on electronic weighing scale, accurate up to 10 grams) were included in the study. Newborns with development of jaundice in the first 24 hours of life, ABO and Rh incompatibility, preterm, direct hyperbilirubinemia, cord blood bilirubin > 4 mg/dL and co-morbidities requiring NICU admission (sepsis, asphyxia, respiratory distress etc) were excluded from the study.

A detailed maternal and newborn history was obtained. All babies were carefully examined on first day of life. Complete physical examination including weight, temperature, gestational age, heart rate, capillary refilling time, colour of skin, edema, cyanosis, birth trauma, any sign suggestive of sepsis, was carried out till next five postnatal days.

Daily physical assessment of hyperbilirubinemia was done in accordance with Kramer's Dermal Zone. Peripheral venous blood was collected and serum bilirubin was assessed at 72 - 96 hours of age or earlier if required, which was based on physical examination. Significant hyperbilirubinemia was defined as: Serum bilirubin > 12 mg/dL between 24 - 48 hours of age, serum bilirubin > 15 mg/dL between 48 - 72 hours of age or serum bilirubin > 17 mg/dL after 72 hours of age.

Neonates with significant hyperbilirubinemia were treated with phototherapy or exchange transfusion, as indicated. Serum bilirubin and serum albumin estimation was done using VITROS BuBc and VITROS ALB slide method. The sample size basis was a previous study which had reported prevalence of significant hyperbilirubinemia to be 10%. Based on this fact, sample size obtained was 144 at a confidence interval of 95% and 80% power of the study. Accordingly 152 neonates were enrolled.

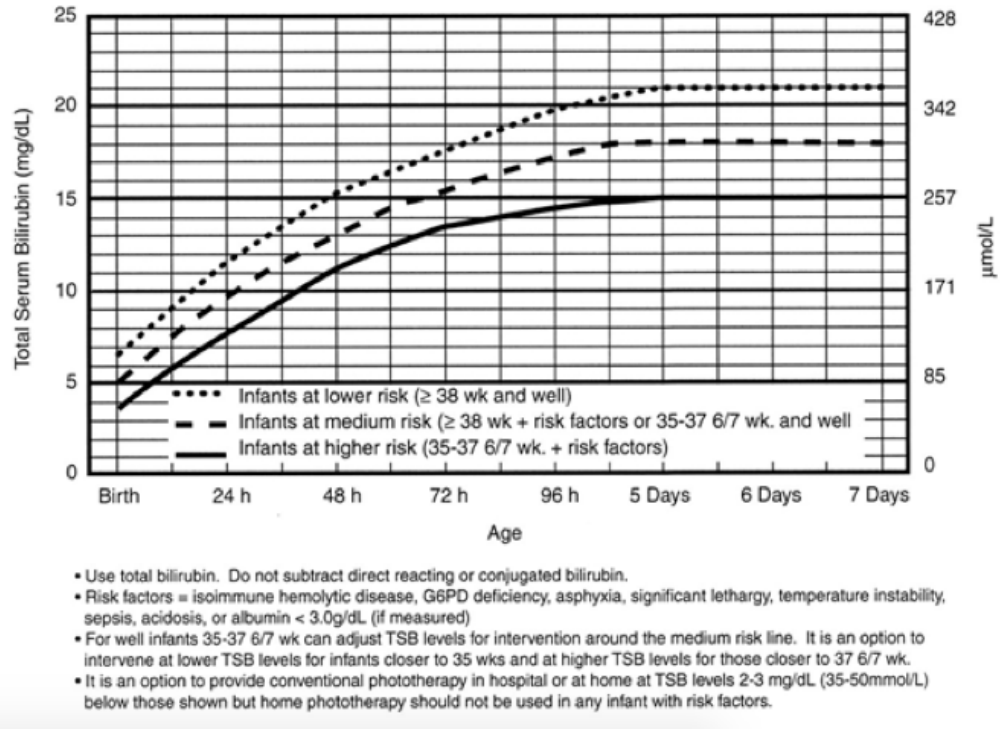

Figure 1. Guidelines for phototherapy in hospitalised infant of 35 or more weeks of gestation

P values were calculated using statistical software like GraphPad, MedCalc. Receiver operating characteristics was used for calculating cut-off values. Association between two non-parametric variables was seen using Pearson Chi-square test. Comparison between means of two groups was done using Unpaired 't' test. Correlation between two parametric variables was done using Pearson correlation coefficient. A p value of < 0.05 was taken as statistically significant.

All ethical considerations were kept while conducting the research. Approval from institutional ethics committee was taken for the study.

RESULTS

The mean age of 152 neonates was 2.88 days with a range of 2.50 to 3.81 days. Of these 152, 103 (67.7%) neonates were exclusively breastfed and 49 (32.2%) neonates were on mixed feeds. Eighty six (56.6%) were males and 66 (43.4%) females, showing a male preponderance. The mean birth weight was comparable between neonates with and without significant hyperbilirubinemia (2.88 ± 0.19 kg vs. 2.88 ± 0.32 kg respectively), p = 0.995.

There were 55.3% primigravidae and 44.7% multigravidae mothers. Sixty one (40.1%) neonates were born through Caesarean section and 91 (59.9%) neonates were delivered vaginally. Significant neonatal hyperbilirubinemia was seen in 17 (11.2%) neonates and in rest it was absent. (Table 1) .

12.8% males and 9.1% females were having significant neonatal hyperbilirubinemia. Of the 103 neonates who were exclusively breastfed, 15.5% neonates had significant neonatal hyperbilirubinemia and 2.0% of the neonates who were on mixed feeding had high bilirubin level. The mean cord blood bilirubin in exclusively breastfed newborns was 2.05 ± 0.57 mg/dL and in mixed fed newborns was 1.94 ± 0.53 mg/dL. The mean cord blood bilirubin among the exclusive breastfed and mixed fed was not significant (p = 0.239). But the mean cord blood albumin was significantly higher in the mixed fed in comparison to the exclusively breastfed infants (p = 0.001). (Table 2)

The mean cord blood bilirubin was significantly higher in significant neonatal jaundice group in comparison to the non-significant neonatal jaundice

Table 1. Distribution of NNHB (Neonatal Hyperbilirubinemia) in newborns

SN	Neonatal hyperbilirubinemia (NNHB)	Frequency	Percent
1	Neonatal Hyperbilirubinemia present	17	11.2
2	Neonatal Hyperbilirubinemia absent	135	88.8
	Total	152	100.0

group (p = 0.001). The mean cord blood albumin was significantly lower in significant neonatal jaundice group in comparison to the non-significant neonatal jaundice group (p = 0.001) (Table-3).

The resulting AUC was 0.768, suggesting a "fair" diagnostic test for predicting severe neonatal hyperbilirubinemia. The cut-off value obtained was ≤ 2.56 gm/dL. A cord blood albumin value of less than or equal to 2.56 gm/dL was predictive of neonatal hyperbilirubinemia. At this cut-off the sensitivity of the test was found to be 70.59%, specificity was 83.70%, positive predictive value was 35.29%, negative predictive value was 95.76% and diagnostic accuracy was 82.24%. The specificity, negative predictive value and diagnostic accuracy of cord blood serum albumin is very high, but sensitivity and positive predictive value is poor. Hence, this test cannot be used for screening for neonatal hyperbilirubinemia, but can be definitely used for negating (absence) neonatal hyperbilirubinemia development later on.

Table 2. Comparison of mean cord blood bilirubin and albumin between the exclusively breastfed and mixed fed newborns

Parameter	Group	No	Mean ± SD	't' value	P value
Cord blood bilirubin	Exclusively breastfed	103	2.05 ± 0.57	1.183, df = 150	0.239, NS
	Mixed fed	49	1.94 ± 0.53		
Cord blood albumin	Exclusively breastfed	103	2.83 ± 0.51	-4.856, df = 150	0.001 *
	Mixed fed	49	3.24 ± 0.42		

Unpaired 't' test applied. P value < 0.05 was taken as statistically significant.

The resulting AUC was 0.948, suggesting an "excellent" diagnostic test to predict severe neonatal jaundice. The cut-off value obtained was > 2.33 mg/dL. A cord blood bilirubin value of greater than 2.33 mg/dL was predictive of neonatal hyperbilirubinemia. At this cut-off the sensitivity of the test was found to be 94.12%, specificity was 86.67%, positive predictive value was 47.06%, negative predictive value was 99.15% and diagnostic accuracy was 87.50%. The sensitivity, specificity, negative predictive value and diagnostic accuracy of cord blood serum bilirubin is very high, but positive predictive value is poor. Hence, this test can be used for predicting Neonatal hyperbilirubinemia but caution should be taken as it has a poor positive predictive value tending to give higher false positive. On the basis of very high negative predictive value, but can be definitely used for negating (absence) the development of neonatal hyperbilirubinemia.

Table 3. Comparison of mean cord blood bilirubin and albumin between the significant neonatal jaundice and non-significant neonatal jaundice groups

Parameter	Group	No.	Mean ± SD	t' value	P value
Cord blood bilirubin	Significant neonatal jaundice	17	2.90 ± 0.44	8.455, df = 150	0.001*
	Non-significant neonatal jaundice	135	1.90 ± 0.46		
Cord blood albumin	Significant neonatal jaundice	17	2.53 ± 0.67	-3.823, df = 150	0.001*
	Non-significant neonatal jaundice	135	3.02 ± 0.47		

Unpaired 't' test applied. P value < 0.05 was taken as statistically significant.

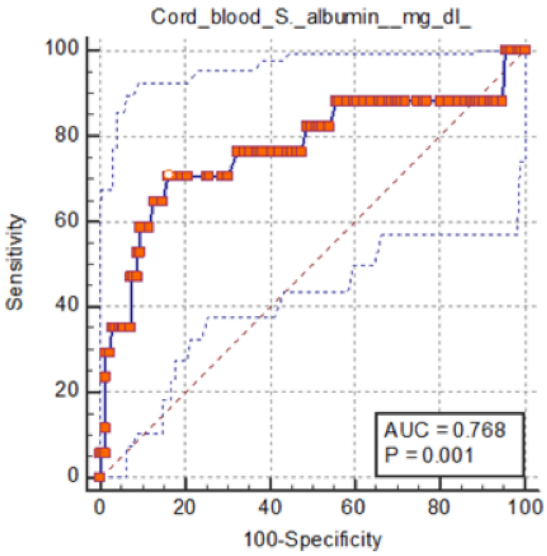

Figure 2. ROC between cord blood albumin and clinical NNHB

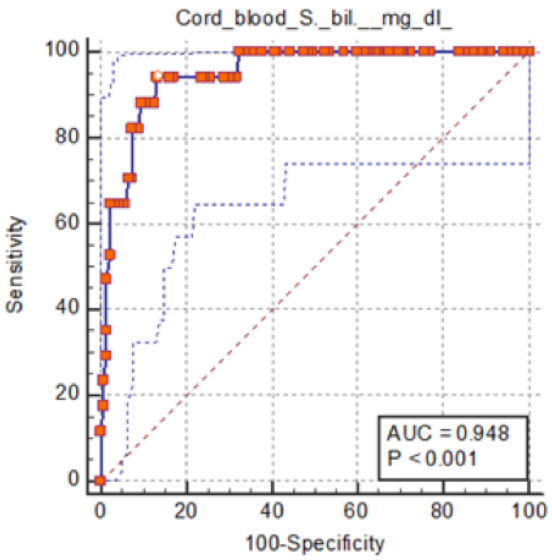

Figure 3. ROC between cord blood bilirubin and clinical NNHB

The correlation coefficient 'r' obtained was -0.213 with a p value of 0.004 between albumin in cord blood and serum bilirubin at 72 - 96 hours, which showed that there is an inverse relationship between albumin level in cord blood and serum bilirubin at 72 - 96 hours. This correlation is very weak, but statistically significant. (Table 4)

The correlation coefficient 'r' obtained was 0.504 with a p value of 0.001 between bilirubin level in cord blood and serum bilirubin at 72 - 96 hours, which showed that there is a positive relationship between bilirubin level in cord blood and serum bilirubin at 72 - 96 hours. This correlation is good and statistically significant. (Table 4)

Table 4. Correlation between cord blood albumin and bilirubin with serum bilirubin at 72 - 96 hours

Pair	'r' value	P value	Significance
Cord blood albumin to Serum bilirubin level at 72 - 96 hours	-0.213	0.004*	Very weak, negative statistically significant correlation
Cord blood bilirubin to Serum bilirubin level at 72 - 96 hours	0.504	0.001	Strong, positive statistically significant correlation

DISCUSSION

It has always been a subject of discussion about the length of stay of the newborn mother dyad in the institution, safety and danger of before time hospital discharge (jaundice, feeding problem, screening, anomaly detection) and designing a follow-up plan for each nation considering its economic constraint, community attitude, health infrastructure etc.

Neonatal hyperbilirubinemia has been found to be the most prevalent reason for readmission of the newborns.[5] The most recent guideline of AAP - 2004 states that infants discharged before 24 hours of age should be seen at 72 hours of age, discharged between 24 - 48 hours of age at 96 hours of age, and those discharged between 48 and 72 hours of age should be seen at 5th day of life.[4] However in our country a complete follow up is not always possible because of non compliance and lack of medical facilities in peripheral areas. Thus there is utmost need for framing up our own discharge policy and follow up program, since neonatal hyperbilirubinemia can be treated easily. Identifying high risk newborn and ensuring their follow up or delaying discharge is very important.

In this study, we aimed to determine the future risk of neonatal hyperbilirubinemia by predictive ability of cord blood bilirubin and cord blood albumin

level in term newborn without any risk factor for subsequent significant neonatal hyperbilirubinemia development. In our study, out of 152 newborns 17 (11.2%) newborns developed significant neonatal hyperbilirubinemia requiring phototherapy. Studies done by other authors reported a variation from 8.3 to 12.8% in the incidence of significant neonatal hyperbilirubinemia depending upon region, ethnic constitution of the population, laboratory standard variability in the bilirubin measurement.[6]

Exclusive breast feeding was found to be significantly associated with the increased risk of NNHB in our study. Maisels et al. (2009) in their study suggests exclusive breast feeding and gestational age being the two most important clinical factors for significant neonatal hyperbilirubinemia development.[7] In our study, a positive statistically significant correlation between cord blood bilirubin and serum bilirubin level was observed (p value = 0.001).

The relationship between the clinical sensitivity and specificity with respect to every possible cut-off value of cord blood bilirubin was constructed using ROC curve. The point with maximum sensitivity (94.12%) and specificity (86.67%) was found at value of more than 2.33 mg/dl, with area under curve 0.948. Positive predictive value and negative predictive value at this point were found to be 47.06% and 99.15% respectively. In another prospective study conducted by Bernaldo et al. in 2004, in which they had included 380 full term newborns, few had blood group incompatibility while others were without any complications. They concluded 53% of their newborns with higher levels of cord blood unconjugated bilirubin (> 2.0 mg/dl) required phototherapy at third day after birth.[8] Higher percentage of significant jaundice in this study as compared to ours may be because they have taken high risk cases also. In another study, 84 stable newborns were followed-up for initial five days. Study of ROC found that the bilirubin level in cord blood > 2.5 mg/dL had a sensitivity of 77% (high) and precision of 98.6% (high) to predict occurrence of severe jaundice.[9] Likewise a study by Khare et al. provides an overview of the ROC curve. A cut-off value for cord blood bilirubin level > 1.875 mg/dl indicates sensitivity, precision, positive predictive value, and the negative predictive value of 76.8%, 61.3%, 81.5%, and 54.3%.[10]

We constructed ROC in our study also for albumin of the cord blood. Albumin level of less than or equal to 2.56 gm/dl seems best as predictive value with sensitivity 70.59% and specificity 83.7%. Positive and negative predictive value at this point was found to be 35.29% and 95.76% respectively.

In a study carried out by Rashed et al. on 150 term and preterm newborns, there was significant relationship between albumin of cord blood and neonatal hyperbilirubinemia (p = 0.001) in both categories.[10] In term group 61.2% newborns with cord serum albumin < 2.8 gm/dL developed neonatal hyperbilirubinemia. 32.3% newborns had albumin level in cord blood between 2.9 - 3.3 gm/dl, and only 6.5% of the newborns with cord serum albumin level ≥ 3.4 gm/dL developed significant hyperbilirubinemia.[11]

A hospital based study conducted by Aiyappa et al. on 165 healthy term neonates showed cord serum albumin ≤ 2.8 gm/dL had sensitivity 71.8%, specificity 65.1%, positive predictive value 38.9% and negative predictive value 88.2%, with ROC curve showing area under curve (AUC) = 0.684. Our study results are parallel to this study too with AUC 0.735.[12] In the research conducted by Rajpurohit et al., the albumin level cut-off of 2.6 gm/dL in cord blood with a high sensitivity (80 per cent), specificity (86.67 per cent) was selected. The positive and negative predictive value were 40 per cent and 97.5 per cent respectively, at this point.[13] This study also favours more negative predictive value of test.

Haridas et al. in their study on 500 healthy neonate found that umbilical cord blood bilirubin level > 1.78 gm/dL was 90% sensitive and 87% specific with a PPV of 75% and NPV of 92% in predicting significant neonatal hyperbilirubinemia.[14] The results are different from our study as in our study positive predictive value is quite low and bilirubin level 2.33 is significant. Similarly Bhat et al. on their study on 300 newborns found that 11% of them developed significant jaundice and cord blood

bilirubin > 3 mg/dL and albumin less than 2.4 gm/dL are predictors of significant jaundice requiring treatment.[15] In our study, the predictive value of cord blood bilirubin was found to be greater than the predictive value of albumin in cord blood, with higher sensitivity and specificity being obtained on the ROC curve analysis at the cut-off point and larger area under curve.

Our study population consisted of healthy term babies not in high risk group. This is most important point of our study. And we also found these two tests to be more important for ruling out risk of jaundice. We believe that data from this study could be applied to low risk and especially will help to screen babies who develop NNHB despite ruling out other risk factors. Though different studies are stating slightly different level of cord blood bilirubin and albumin for predicting severe jaundice, may be due to difference in study population structure, but all found significant results. Small sample size was the only limitation of our study.

CONCLUSIONS

In this study we found that bilirubin level more than 2.33 mg/dL and albumin level less than or equal to 2.56 gm/dL of the cord blood can be used as a predictive index for development of significant NNHB, with cord blood bilirubin being more sensitive and specific marker than cord blood albumin. Both the tests have greater negative predictive value. Classifying newborns at low risk for hyperbilirubinemia minimise unnecessary prolongation of hospitalisation as it will provide more confidence to neonatologists in decision of early discharge. Babies with high-risk category can be asked for early follow-up or parents can be counselled for need of delayed discharge if timely follow up cannot be ensured. So that simple, safe and economic phototherapy as a treatment option can be provided to reduce neonatal morbidity and mortality.

Based on the results obtained, the authors of the study recommend for large sized studies to be carried out so that an in-depth information regarding the relationship between raised cord blood bilirubin and lower cord blood albumin; with neonatal jaundice could be established.

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