Original Article

Comparison of cord bilirubin and bilirubin albumin ratio to predict significant hyperbilirubinemia in healthy full-term neonates

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ABSTRACT

Background: Early prediction and identification of severe hyperbilirubinemia for that age and appropriate treatment are must to prevent kernicterus. **Objective:** The objective is to study the predictive value of bilirubin albumin ratio (BAR) and to compare it with cord bilirubin alone for early identification of significant neonatal hyperbilirubinemia in healthy term neonates. **Materials and Methods:** This prospective cross-sectional study was done in a tertiary care center located in Central India on 543 healthy term neonates. Cord blood of 2 ml was collected during the delivery from the placental end and sent for BAR and cord bilirubin analysis. All the neonates had undergone total serum bilirubin estimation and neonates with serum bilirubin ≥17 mg/dl at ≥72 h of age were defined to have significant hyperbilirubinemia. **Results:** Among the study population, 44 neonates developed significant hyperbilirubinemia. Sensitivity and specificity of cord BAR were 95.45% and 89.78%. Sensitivity and specificity of cord blood bilirubin were 95.65% and 95.57%. Positive predictive value (PPV) and negative predictive value (NPV) of cord BAR were 45.16% and 99.55%. PPV and NPV of cord blood bilirubin were 64.70% and 99.58%. Considering mean as the cutoff value, cutoff value for cord BAR was 0.89 and it was 2.95 for cord blood bilirubin. Diagnostic accuracy of cord BAR and cord blood bilirubin in predicting the hyperbilirubinemia was 90.79% and 96.31%, respectively. **Conclusion:** Both cord BAR and cord blood bilirubin are the early predictors of neonatal significant hyperbilirubinemia, but cord blood bilirubin is the better diagnostic tool than the former in early detection of neonatal jaundice.

Key words: *Cord bilirubin albumin ratio, Cord blood bilirubin, Neonatal hyperbilirubinemia*

Jaundice occurs in approximately 85% of all term newborns and most of the preterms. Most of such cases are benign in nature; however, due to the potential toxicity of bilirubin, newborn infants must be monitored to identify those who might develop severe neonatal hyperbilirubinemia (NNH) resulting in neurotoxicity [1]. Pathological jaundice occurs in 5–25% of them. In most cases, it is benign and no intervention is required [2]. Approximately 5–10% of them have clinically significant NNH mandating intervention in the form of phototherapy or exchange transfusion. Unconjugated hyperbilirubinemia is potentially harmful for central nervous system and may result in kernicterus causing severe and permanent neurological sequelae [3].

Early prediction and identification of severe NNH for that age and appropriate treatment are must to prevent kernicterus, avoidance of aggressive managements, maternal anxiety, and unnecessary expenditures [4] and to reduce the duration of hospital stay [5]. Early discharge of healthy term newborns after delivery has become a common practice because of medical, social, and economical reasons. The most common cause for readmission during the early neonatal period is hyperbilirubinemia [6]. However, although early discharge from hospital may seem to be safe, the risk of severe NNH is an issue that still needs to be resolved and requires specific strategies to prevent a high morbidity rate [7]. There is currently little agreement about what constitutes safe bilirubin level because it is unclear at what level neurotoxicity develops and the condition under which toxicity develops, remains incompletely defined [8]. The bilirubin albumin ratio (BAR) is a surrogate parameter for free bilirubin and an interesting additional parameter in the management of NNH. Hence, we did this study to predict severe hyperbilirubinemia in healthy full-term neonates by comparing cord blood bilirubin and BAR.

MATERIALS AND METHODS

This prospective cross-sectional cohort study was conducted after obtaining clearance from the Institutional Ethical Committee, in a tertiary care center of Central India, over a period of 1 year. Written consent was obtained from parents of all the recruited neonates. The sample size was calculated using formula: $n = t^2 \times P(1 - P)/m^2$.

The study population comprised of healthy term newborns (gestational age >37 weeks and weight >2.5 kg) of both genders. The exclusion criteria were preterm, low birth weight, and any

complication arising during the hospital stay that could aggravate the hyperbilirubinemia in these newborns (e.g., neonatal sepsis, ABO, Rh incompability, instrumental/traumatic delivery, and birth asphyxia), neonates with antenatal risk factors (meconium stained liquor), gestational hypertension, premature rupture of membrane, preeclampsia, anemia, malaria, maternal fever, chorioamnionitis, any other maternal illness, twins, gross congenital malformations, and/or comorbid illness, and neonates who developed jaundice within 24 h of life. Demographic profile and relevant maternal information were collected by interviewing the mothers and from mother's case sheets. Gestational age was assessed by new Ballard scoring [9].

Sample (2 ml blood) was collected during the delivery from placental end of the cord in a clean, plain vial. Serum was separated by centrifuging at 3000 rpm; serum was stored in refrigerator at 4°C and tested for bilirubin and albumin, within 2 days after collection. Serum albumin was estimated using bromocresol green method and serum bilirubin by modified J and G Method. After this, BAR was calculated. All the babies were followed up daily for first 4 postnatal days and babies were daily assessed for jaundice and its severity. All neonates had undergone total serum bilirubin estimation at 72–96 h of age. The pathologist, who estimated serum bilirubin after 72 h, was unaware about the cord blood bilirubin level.

The main outcome of the study was inferred in terms of significant hyperbilirubinemia. Neonates with serum bilirubin ≥17 mg/dl at ≥72 h of age were defined to have significant NNH and treatment was advised, as per the American Academy of Pediatrics [10]. All cases were recorded on a predefined pro forma which included gender, birth weight, gestational age, mode of delivery, and history of maternal use of oxytocin during labor, and history of neonatal jaundice in sibling was also obtained. All neonates were breastfed.

Statistical Analysis

The data of the present study were recorded, and after its proper validation, checked for error, coding and decoding were compiled and analyzed using the software SPSS 19 for windows. Appropriate univariate and bivariate analysis was carried out using the Student's t-test for the continuous variable (age) and two-tailed Fisher exact test or Chi-square (χ^2) test for categorical variables. All means were expressed as a mean±standard deviation. The critical levels of significance of the results were considered at 0.05 levels, i.e., $p<0.05$ was considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPVs), and diagnostic accuracy were calculated for both cord BAR and cord bilirubin alone. The comparison between three groups was done using ANOVA followed by Bonferroni test for multiple comparisons. All means are expressed as a mean ± standard deviation.

RESULTS

During the study period, a total of 1154 neonates were screened as shown in study flowchart in Fig. 1, and finally, 543 neonates were recruited. Demographic profile of the study population is presented in Table 1. Most of the neonates were of 1st birth order. Of 543 neonates, 44 (8.1%) neonates developed significant NNH. 81% of the neonates, whose mothers had received oxytocin, developed significant NNH and 4 neonates, whose previous sibling had jaundice, also developed significant NNH (Table 2). Of 44 neonates who developed significant NNH, 13 received phototherapy and 31 underwent exchange transfusion. Of those neonates who developed significant NNH, 87.5% had cord BAR above the median value of 0.89 and 75% had cord blood bilirubin above the median value of 2.95 as summarized in Table 3.

Table 1: Demographic profile of the study population

Variables	Number of patients (%)
Sex	
Male	307 (56.5)
Female	236 (43.5)
Birth order	
I	326 (60.0)
II	149 (27.5)
III or more	68 (12.5)
Birth weight (kg)	
2.5–3	285 (52.5)
>3	258 (47.5)
Mode of delivery	
Vaginal	380 (70)
Cesarean section	163 (30)

Table 2: Analysis of neonates with significant NNH

Parameters	Total cases (%)	Non-significant (%)	Significant (%)	p value	Odds ratio
Oxytocin use					
Yes	293 (51.6)	257 (81.3)	36 (54)	0.022	0.1669 (0.0760–0.3663)
No	250 (48.4)	242 (18.7)	8 (46)		
H/o jaundice in previous sibling					
Yes	16 (8)	12 (6.5)	4 (25.0)	0.022	4.778 (1.3365–17.0803)
No	184 (92)	172 (93.5)	12 (75.0)		
Treatment given					
Phototherapy	31 (97)				
Exchange transfusion	13 (3)				

NNH: Neonatal hyperbilirubinemia

Table 4 presents the predictive values of cord BAR and cord blood bilirubin to detect NNH. Sensitivity and specificity of cord BAR were 95.45% and 89.78%. Sensitivity and specificity of cord blood bilirubin were 95.65% and 95.57%. PPV and NPV of cord BAR were 45.16% and 99.55%. PPV and NPV of cord blood bilirubin were 64.70% and 99.58%. Fig. 2 shows the sensitivity and specificity of bilirubin and albumin Ratio and Fig. 3 shows the sensitivity and specificity of Cord Bilirubin. All neonates included in the study were breastfed.

DISCUSSION

Higher cord blood bilirubin levels among infants who later become jaundiced compared to cord blood bilirubin levels in non-jaundiced infants indicate that some mechanisms for the subsequent jaundice are already active in late fetal life [11]. In the present study, 543 healthy neonates were included. Of these, 44 (8%) developed significant NNH. A cord bilirubin level of >2.95 mg/dl predicts the development of significant jaundice (defined as bilirubin ≥17 mg/dl) with sensitivity and specificity: 95.65% and 95.57% and PPV and NPV: 64.70% and 99.58%. Similar observation was noted by Taksande *et al*. in 2005 [12] with the cutoff value of 2.0 mg/dl, with sensitivity of 89.5% and NPV of 98.7%. Hover, at the cutoff value of 2.0 mg/dl, 53% sensitivity was observed by Bernaldo and Segre in 2004 [6], and at 2.5 mg/dl, sensitivity of 71% and specificity of 96% were noted by Agarwal and Deorari in 2002 [1]. Rostami and Mehrabi in 2005 [13] noted that cord blood bilirubin level of 3 mg/dl (51.3 micromol/L) is not a useful predictor of neonatal jaundice. Venkatamurthy *et al*. [14] found that, at cord blood bilirubin level ≥2.1, sensitivity was 100, specificity 61.04, PPV 25, and NPV was 100.

Cord blood bilirubin level ≥2.5mg/dl appeared as high-risk indicator toward predicting NNH which was observed by Trivedi *et a*l. [15] Rajpurohit *et al*. [16] noted that at cord blood bilirubin level of >2 mg/dl had a sensitivity of 90%, specificity of 53.89%, PPV 17.8%, and NPV of 98% in predicting the risk of NNH (p<0.001). The sensitivity of cord BAR in predicting future significant hyperbilirubinemia is 95.45%. Considering a cutoff point of cord BAR 0.89, if the cord BAR is above 0.89, 95.5% of patients can develop future significant NNH.

It was observed in the present study that history of jaundice in the previous sibling was found in 25% of cases in significant group, while it was observed only in 6.5% of non-significant NNH group. This was statistically (p=0.022) significant. This is in accordance with the American Academy of Pediatric guidelines; history of previous sibling with NNH occupies the major and minor risk factor to develop severe NNH. In the present study, it was observed that incidence of significant NNH was higher in those neonates in whom mother received intrapartum oxytocin (p=0.022). The incidence of significant NNH was 81.3% in them as compared to 51.6% in non-significant NNH group.

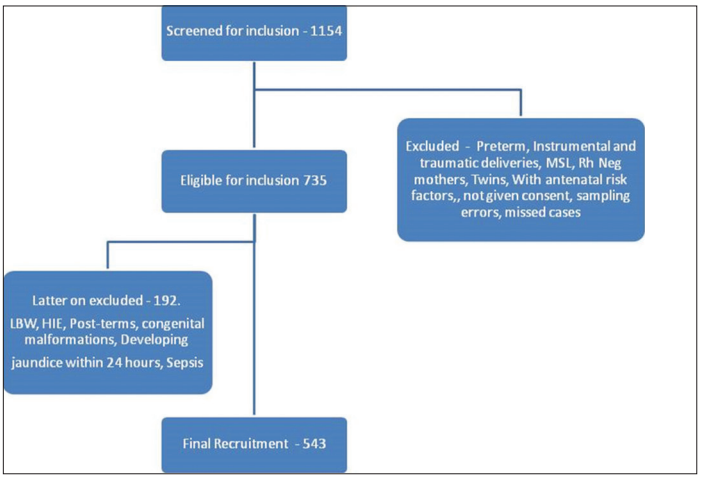

Figure 1: Study flowchart

Table 3: Distribution of cases according to BAR and cord bilirubin

Value	Significant NNH (%)	Non-significant NNH (%)	Total (%)	P value
Cord BAR (median value - 0.89)				
>0.89	39 (87.5)	249 (50)	288 (53)	<0.01
<0.89	5 (12.5)	250 (50)	255 (47)	
Cord bilirubin (median value - 2.95)				
>2.95	33 (75)	228 (45.7)	261 (48.5)	<0.05
<2.95	11 (25)	271 (54.3)	282 (51.5)	
Total	44 (100)	499 (100)	543 (100)	

NNH: Neonatal hyperbilirubinemia, BAR: Bilirubin albumin ratio

Table 4: Statistical values of cord BAR and cord bilirubin

Tests	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR_	DOR
Bilirubin	95.45	89.78	45.16	99.55	9.340	0.051	184.4
Albumin ratio	(84.87–98.74)	(86.81–92.14)			(7.144–12.209)	(0.013–0.196)	(43.367–784.682)
Cord	95.65	95.57	64.70	99.58	21.609	0.045	475.00
Bilirubin level	(85.47–98.80)	(93.39–97.06)			(14.926–32.663)	(0.012–0.176)	(108.116–2086.885)

BAR: Bilirubin albumin ratio, NPV: Negative predictive value, PPV: Positive predictive value

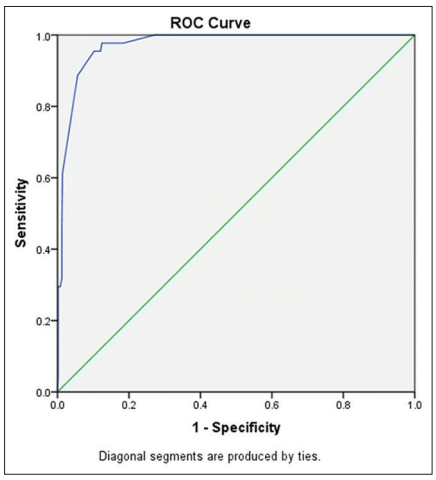

Figure 2: Receiver operating characteristic showing sensitivity and specificity of bilirubin albumin ratio

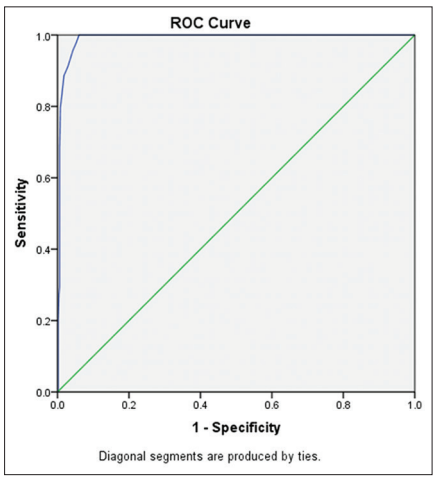

Figure 3: Receiver operating characteristic showing sensitivity and specificity of cord bilirubin

CONCLUSION

We conclude that, at the cutoff value of 0.89, cord BAR had good sensitivity and NPV, and at the cutoff value of 2.59, cord total bilirubin alone has more specificity and diagnostic accuracy. Both, the cord BAR and cord blood bilirubin, are early predictors of significant NNH; however, cord blood bilirubin was found to be a better tool.

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