Predictive value of cord blood bilirubin in development of neonatal hyperbilirubinemia

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ABSTRACT

Introduction: The early detection of neonatal hyperbilirubinemia (NNH) can be done by various methods; however, the most reliable is cord blood bilirubin (CBB). **Objective:** The objective of this study is to evaluate the predictive value of the CBB levels for the subsequent hyperbilirubinemia in healthy term newborns and its association with various maternal and neonatal factors. **Materials and Methods:** Two hundred healthy term-neonates between 37 and 42 weeks of gestation were included in the study. A thorough antenatal, perinatal, and natal history was obtained. Cord blood was collected from all newborns, and the samples were sent for the estimation of serum bilirubin, blood grouping, and Rh typing. **Results:** Various risk factors such as gender difference ($p<0.05$), development of jaundice ($p=0.00$), extent of jaundice ($p=0.00$), number of cases requiring referral ($p<0.05$), and jaundice in siblings ($p=0.01$) were found statistically significant. Several maternal and neonatal factors such as maternal history of jaundice ($p=0.009$), gestational hypertension ($p=0.01$), antepartum hemorrhage ($p<0.05$), obstructed labor ($p=0.009$), use of oxytocin ($p=0.008$), ABO, and Rh incompatibility ($p<0.001$) were also found statistically significant in relation to CBB >2.5 mg/dl. At a cutoff of 2.5 mg/dl, sensitivity and specificity came out to be 33.33% and 96.25%, respectively. **Conclusion:** NNH and CBB level were found to be associated with several maternal and neonatal risk factors. Hence, total serum bilirubin in cord blood was indicative of the jaundice severity among neonates.

Key words: *Bilirubin, Neonatal hyperbilirubinemia, Term neonates*

Neonatal hyperbilirubinemia (NNH) or jaundice is one of the most common conditions that demand medical attention in newborns [1]. It is observed in the 1st week of life in approximately 60% of term and 80% of preterm infants [2]. According to the American Academy of Pediatrics (AAP), it was estimated that every newborn develops an unconjugated serum bilirubin level of >30 μmol/L (1.8 mg/dL) during the 1st week of life [3]. After delivery, newborns are early discharged from the hospital because of medical, social, and economic reasons. However, after some time, readmission occurs because of NNH. The AAP recommends that newborns discharged within 48 h should have a follow-up visit after 2–3 days to detect significant jaundice and other problems [3]. This recommendation is not always possible in our country due to limited follow-up facilities in the community.

NNH needs appropriate and timely intervention because if left untreated, it may lead to serious complications such as the development of neurologic dysfunction which includes, acute and chronic (kernicterus) bilirubin-induced encephalopathy [4]. Prevention of these complications depends on the time of detection and effective early treatment. In the recent years, many efforts have been made to identify those infants, which are likely to develop neonatal jaundice. One of the most common measures used for the identification of jaundice is the clinical examination; however, it is not a reliable measure for the estimation of serum bilirubin. Hence, alternative strategies should be developed to predict the risk of significant jaundice as they can reduce hospital stay for normal babies and identify significant NNH that may happen in the future.

There are some reliable strategies to identify jaundiced neonates after delivery. These are universal follow-up within 1–2 days of early discharge, umbilical cord bilirubin concentration at birth, routine predischarge serum bilirubin, transcutaneous bilirubin measurement, and the universal clinical assessment of risk factors of developing jaundice [5]. Among these methods, estimation of cord bilirubin levels at delivery is the most commonly used as it is cheap, practical, an easy to perform and may offer an attractive predictive marker for hyperbilirubinemia occurring later on. Hence, it would be convenient to be able to predict the risk of jaundice to implement safe, cost-effective, and early treatment and thereby minimize the risk of bilirubin dependent brain damage. Hence, the present study was undertaken to evaluate the predictive ability of cord bilirubin levels for the subsequent development of significant NNH in healthy term neonates.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Paediatrics and Obstetrics and Gynaecology of a tertiary care

teaching hospital of central India during 1 year period from March 2015 to February 2016. Ethical clearance was obtained from the Institutional Ethical Committee. Written informed consent was taken from the parents/caregivers of the neonates. In this study, 200 healthy, full-term neonates between gestational age 37–42 weeks, born consecutively at the obstetrics department were included in the study. The babies admitted to neonatal intensive care unit and showing any signs of complication or congenital anomaly were excluded from the study.

A thorough antenatal, perinatal, and natal history was obtained and recorded in a predesigned pro forma. Cord blood was collected from all newborns, fulfilling the inclusion criteria, and the samples were sent to the ward-side laboratory for the estimation of serum bilirubin and to the blood bank for blood grouping and Rh typing.

Cord Blood Sampling

After birth, the cord was clamped and then cut. The blood was collected in a serum separator vial following all aseptic precautions and then centrifuged in a machine at a speed of 200 rpm for 5 min. The centrifuged serum was sent to laboratory for total serum bilirubin and unconjugated bilirubin estimation. The noncentrifuged, ethylene diamine tetra acetate sample was sent for blood grouping and Rh typing. All neonates were assessed clinically following the birth for up to 7 postnatal days for the development of jaundice. They were also assessed for the presence of risk factors, related to the development of neonatal jaundice.

Total Serum Bilirubin Estimation

It was done within 12 h of collection of the sample by the diazotized sulfanilic test. This method for bilirubin estimation is based on the principle that bilirubin in the sample reacts with the diazotized sulfanilic acid in acidic medium to form a pink colored complex that can be measured by spectrophotometry. The color of the complex is directly proportional to bilirubin concentration of the sample. There are two methods for the measurement of serum bilirubin: Direct and indirect. Direct Bilirubin, reacts directly in acidic medium because of water-soluble nature, whereas indirect or unconjugated bilirubin being water insoluble is solubilized using a surfactant and then it reacts similarly to direct bilirubin. The "direct" and "indirect" bilirubin is only approximately equivalent to the conjugated and unconjugated fractions [6].

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago, version 22.0). Continuous variables were presented as mean for parametric data and median for non-parametric data. Student's t-test and Mann–Whitney were applied to calculate the statistical significance of normative data and non-normative data, respectively. Categorical variables were expressed as frequencies and percentages. Nominal-categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. The $p<0.05$ were considered statistically significant. Minitab version 17 is used for computation of statistics.

RESULTS

A total of 200 mothers and neonates were included in the study. Out of 200 mothers, 78.5% were between 20 and 30 years, and 55.5% belonged to urban area. Cord blood bilirubin (CBB) was measured, and a cutoff of 2.5 mg/dl was set. Among 200 neonates, 157 have CBB <2.5 mg/dl and the rest 43 have CBB >2.5 mg/dl. Several risk factors were assessed for the signs of jaundice and statistical significance with CBB was estimated. Among 200 neonates, 55% were male babies, and 77% babies have >2.5 kg birth weight. Among 200 neonates, 120 developed jaundice. Among 120 neonates, 47% have developed jaundice between 48 and 72 h, 42% have extent till legs. Nearly 75.5% neonates did not require referral and 91% neonates have jaundice in their siblings. Among the above variables, gender difference ($p<0.05$), development of jaundice ($p=0.00$), extent of jaundice ($p=0.00$), number of cases requiring referral ($p<0.05$), and jaundice development in siblings ($p=0.01$) were found statistically significant in relation to CBB >2.5 mg/dl (Table 1).

Several maternal and neonatal factors that can affect CBB were assessed. Among maternal factors, maternal history of jaundice ($p=0.009$), gestational hypertension ($p=0.01$), antepartum hemorrhage (APH) ($p<0.05$), obstructed labor ($p=0.009$), and use of oxytocin ($p=0.008$) during labor were found to be significantly and statistically associated with CBB >2.5 mg/dl. Among neonatal factors, ABO incompatibility and Rh incompatibility, both were significantly associated with CBB >2.5 mg/dl ($p=0.001$) (Table 2).

In the above study, at CBB cutoff of 2.5 mg/dl, sensitivity was 33.33%, specificity was 96.25%, positive likelihood ratio was 8.89, negative likelihood ratio was 0.69, positive predictive value was 93.02% and negative predictive value was 49.04% (Table 3).

Logistic regression was calculated for clinical jaundice based on CBB and regression coefficient of 0.6638 was obtained ($p=0.011$), (Table 4).

Fig. 1 showing the probability of development of clinical jaundice. It was shown in line graph: As the CBB increases, probability of occurrence of clinical jaundice also increases.

DISCUSSION

Jaundice or hyperbilirubinemia is a clinical condition that is caused due to the elevated serum concentration of bilirubin. In neonates, it is one of the major causes of concern. Its early detection is very difficult as neonatal jaundice may not appear until serum bilirubin exceeds 5 to 7 mg/dl [7]. In the present study, there were 110 males and 90 female neonates, and the occurrence of NNH was significantly more among female neonates. These findings were consistent with the study done by Garosi *et al.* [8], Maisels and Kring [9], Satrya *et al.* [10], whereas Boskabadi

Table 1: Risk factors and their association with CBB level

Variable	CBB<2.5 (n=157)	CBB>2.5 (n=43)	Total (%)	p value (Chi-square test)
Gender				
Female	59	31	90 (45)	*<0.05
Male	98	12 (11%)	110 (55)	
Birth weight				
1.8–2.0 kg	8	0	8 (4)	♦0.37
2.0–2.5 kg	30	8	38 (19)	
>2.5 kg	119	35	154 (77)	
Development of jaundice (120 neonates)				
<24 h	0	7	7 (5.8)	*0.00
24–48 h	21	21	42 (35)	
48–72 h	46	10	56 (46.6)	
>72 h	13	2	15 (12.6)	
Extent of jaundice				
Up to face	13	3	16 (13.3)	*0.00
Up to chest	13	7	20 (16.7)	
Up to abdomen	2	10	12 (10)	
Up to legs	42	8	50 (42)	
Up to sole	10	12	22 (18)	
Referral required				
No	139	12	151 (75.5)	*<0.05
Yes	18	31	49 (24.5)	
Jaundice in siblings				
No	147	35	182 (91)	*0.014
Yes	10	8	18 (9)	

CBB: Cord blood bilirubin, *denotes statistical significance (p<0.05), ♦: Fisher exact test applied

Table 2: Maternal and neonatal factors affecting CBB

Factors	Variables	CBB (<2.5) n=157	CBB>2.5 n=43	p value
Maternal factors	History of jaundice	1	3	*0.009
	Gestational hypertension	22	10	*0.0143
	Eclampsia	5	3	0.373
	Preeclampsia	11	5	0.344
	APH	7	10	*<0.05
	PROM	7	3	0.451
	Obstructed labor	20	0	*0.009
	Oligohydriamnios	6	0	0.344
	Oxytocin	4	6	*0.008
	Fetal distress	34	10	0.975
Neonatal factors	ABO incompatibility	27	18	*0.001
	Rh incompatibility	1	4	*0.001

PROM: Premature rupture of membranes, *denotes statistical significance (p<0.05). CBB: Cord blood bilirubin, APH: Antepartum hemorrhage

et al. [11] found that bilirubin level was higher among male newborns. Taksande *et al.* [12], Rostami and Mehrabi [5] and Rajpurohit *et al.* [13] found no correlation. Veni concluded that male newborns are always more susceptible to NNH because of higher metabolic rate. This theory is enforced by the fact that XY blastocysts and embryos grow at an accelerated rate when compared with XX chromosome bearers [14].

In our study, birth weight was not associated with NNH. This finding was in concordance with the many previous studies where they found no correlation between the NNH and the birth weight of the newborn [14-17]. The appearance of clinical jaundice and the extent of jaundice were significantly correlated with CBB. In addition, higher CBB was significantly associated with the number of cases required referral for the management of NNH. This finding was consistent with studies done by Nahar *et al.* [18], Zeitoun *et al.* [7], Ipek *et al.* [19], Farhat *et al.* [20], Trivedi *et al.* [21], Chary *et al.* [22], Dwarampudi and Ramakrishna [23], and Ahire *et al.* [24]. This suggests that higher the CBB, more

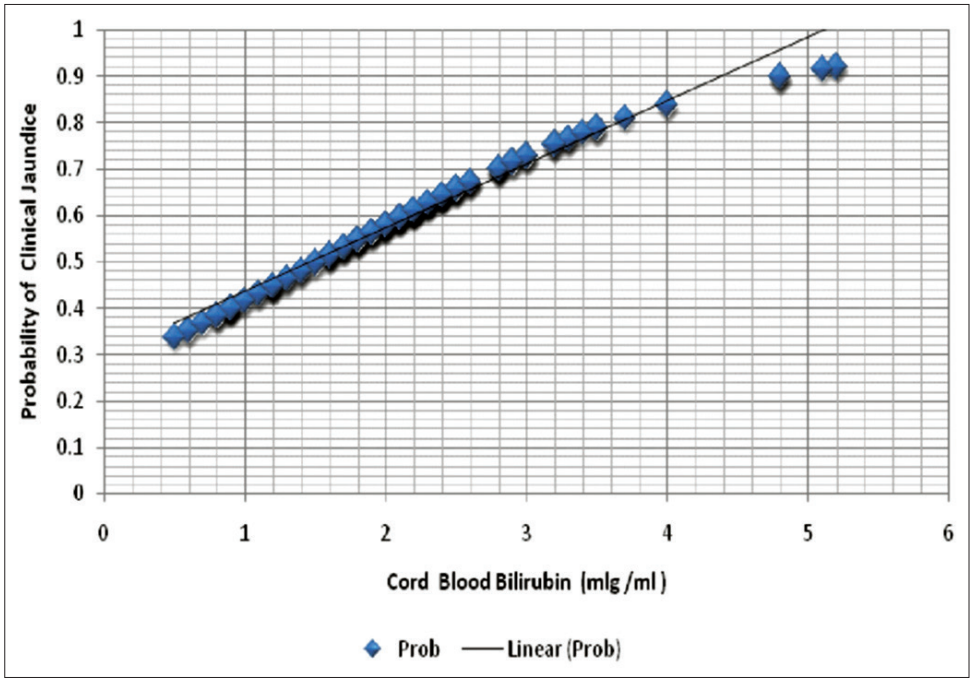

Figure 1: Probability of development of clinical jaundice

Table 3: Sensitivity and specificity of CBB (at 2.5 mg/dl)

Statistic	Value	95% CI
Sensitivity	33.33%	24.99–42.52%
Specificity	96.25%	89.43–99.22%
Positive likelihood ratio	8.89	2.85–27.76
Negative likelihood ratio	0.69	0.61–0.79
Positive predictive value	93.02%	80.94–98.54%
Negative predictive value	49.04%	40.99–57.14%

CBB: Cord blood bilirubin, CI: Confidence interval

Table 4: Logistic regression of development of clinical jaundice

Statistic	Intercept	CBB
Regression coefficient	−1.0103	0.6638
Standard error	0.4419	0.2028
OR	-	1.9422
OR low	-	1.3053
OR high	-	2.8900
p value	0.0222	*0.0011

***Denotes statistical significance (p<0.05). CBB: Cord blood bilirubin, OR: Odds ratio**

likely and earlier the child will develop jaundice and will require referral for intervention for its management.

We found a significant association between the maternal history of jaundice, gestational hypertension, induction of labor with oxytocin, APH, obstructed labor with the development of NNH ($p<0.05$). In a case of obstructed labor, there are high chances of injury to the baby and hence bleeding, which makes a newborn susceptible to develop NNH. CBB and subsequent development of NNH were not found to be associated with the maternal history of eclampsia and preeclampsia. The contradictory results were observed in a study done by Taskande *et al.*, where they found no significant differences between the development of significant NNH with maternal oxytocin use, as well as PIH in mother, feeding pattern, and hematocrit level [12]. Induction of labor with use of oxytocin was found significant in previous studies also [8,12-16,25-27]. This can be explained by the fact that oxytocin has anti-diuretic and saluretic effects, which causes maternal hypo-osmolality and hyponatremia. These biochemical changes are aggravated by the infusion of oxytocin with electrolyte free dextrose solution. This hypo-osmolality gets transferred transplacentally in the fetal blood and causes osmotic fragility of the red blood cells. These swollen, hyper-fragile erythrocytes get easily destroyed in spleen and result in increased bilirubin production [26].

In our study, CBB, at a cutoff value of 2.5 mg/dl, had a sensitivity of 33.33%, specificity of 96.25%, positive predictive value was 93.02%, and negative predictive value of 49.04%. This finding was consistent with the previous studies [7,19-24]. Taksande *et al.* [12] showed that the CBB >2 mg/dl has a sensitivity of 89.5%, specificity of 85%, negative predictive value of 98.7%, and positive predictive value of 38.8%. Nahar *et al.* [7] showed that the cord bilirubin level ≥2.5 mg/dl has a sensitivity 77%, specificity 98.6%, with negative predictive value of 96%.

There were few limitations our study such as we could not do a long-term follow-up which is necessary in these neonates. In addition, we have enrolled only term neonates; therefore, the results of this study cannot be generalized to preterm neonates. Hence, a trial that enrolls both term and preterm neonates in a sufficient number should be conducted in future.

CONCLUSION

NNH and CBB level were found to be associated with, several maternal and neonatal risk factors like ABO Incompatibility, Rh incompatibility, sibling's history of jaundice, and maternal history of jaundice, Gestational hypertension, antepartum hemorrhage,

and maternal oxytocin use. Estimation of CBB should be considered as a strategy for early identification of those at risk of neonatal jaundice, which in turn could drive a more appropriate and timely utilization of healthcare resources.

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