Predictive value of cord blood bilirubin in neonatal hyperbilirubinemia: A prospective study

Mohd. Ubaid Ur Rahman Mohd. Azam[1], Kishor Gyanoba Rathod[2], Neeta Kaluram Hatkar[3], Nagesh Hanmantrao Lonikar[4]

From [1]Assistant Professor, Department of Pediatrics, Government Medical College, Aurangabad, Maharashtra, [2]Associate Professor, [4]Assistant Professor, Department of Pediatrics, Dr. Shankarrao Chavan Government Medical College, Nanded, Maharashtra, [3]Professor, Department of Pediatrics, Shri Bhausaheb Hire Government Medical College, Dhule, Maharashtra, India

Correspondence to: Dr. Kishor Gyanoba Rathod, Department of Pediatrics, Dr. Shankarrao Chavan Government Medical College, Vishnupuri, Nanded, Maharashtra, India. E-mail: kishorgrathod@gmail.com

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ABSTRACT

Background: As there is a tendency for early discharge from a hospital, some babies may develop significant neonatal jaundice at home, which may go unrecognized and cause subclinical damage to the growing brain. If such babies could be identified early, their discharge can be postponed for timely and better management. **Objectives:** The objectives of the study were to evaluate the umbilical cord bilirubin (UCB) levels as a predictor for hyperbilirubinemia in full-term and near-term newborns up to the 3rd day of life. **Materials and Methods:** A prospective cohort study was carried out in a tertiary care hospital in South India. Data were collected from the enrolled cases by a pre-designed proforma. Statistical analysis was carried out with the help of statistical measures, such as percentages and proportions and the sensitivity, specificity, and negative and positive predictive values (NPV and PPV). **Results:** A total of 301 newborns were enrolled. A cutoff UCB 2 mg/dl had 94% sensitivity, 93% specificity, 61% PPV, and 99% NPV. A total of 61% of neonates who had UCB levels ≥2 mg/dL required phototherapy by the 3rd day of life. However, 99% of neonates who had UCB <2 mg/dL did not require phototherapy, and these infants with low risk of hyperbilirubinemia could be discharged early from the hospital. **Conclusion:** The cutoff value of 2 mg/dL of UCB with 94% sensitivity and 93% specificity can be used as a predictor for developing subsequent hyperbilirubinemia.

Key words: *Bilirubin, Cord blood, Hyperbilirubinemia, Neonatal hyperbilirubinemia, Neonatal jaundice*

Neonatal hyperbilirubinemia (NNH) is a common clinical condition which can occur physiologically or pathologically. Although 60% of term neonates are clinically jaundiced in the first 7 days of life, most of them are physiological. NNH is the most common cause for readmission of the healthy neonates when they are discharged early. The early discharge of the mother-infant dyad will reduce the cost and facilitate mother-infant bonding. However, there are more chances of missing the early diagnosis of babies which are more prone to develop subsequent hyperbilirubinemia, which results in kernicterus and subsequently choreoathetoid cerebral palsy.

The American Academy of Pediatrics recommends that the neonates discharged in 48 h should be followed-up for 2–3 days for the detection of significant NNH. These serious morbidities can be prevented if there is a good predictive test about developing subsequent hyperbilirubinemia. At present, there are no recommended guidelines to detect NNH using umbilical cord blood (UCB) bilirubin [1]. Total serum bilirubin (TSB) is considered the gold standard to diagnose and quantify the risk of developing severe NNH. The strength of UCB lies in its high specificity and high negative predictive value (NPV). The present study was conducted to evaluate the predictability of UCB for subsequent NNH.

MATERIALS AND METHODS

A hospital-based prospective cohort study was carried out in Southern Railway Hospital, from November 2012 to August 2013 in infants born after 34 weeks of gestation. A written informed consent was obtained from the parents for enrollment in the study. All deliveries with Apgar scores >7 at 1 and 5 min were included in the study. Infants with problems such as birth asphyxia, respiratory distress, infection, metabolic diseases, preterm babies, meconium aspiration syndrome, congenital anomalies, and babies born outside the railway hospital and parents who did not agree for the follow-up till the 5th day were excluded from the study.

The study was approved by the institutional ethics committee. The sample size was calculated considering the incidence of hyperbilirubinemia in healthy full-term babies as 4–6%. With an alpha value of 0.05 and a beta value of 80%, the calculated sample size was 75. To account for dropouts, sequentially born 301 neonates were enrolled.

All neonates received 1 mg of Vitamin K by intramuscular route after birth. Around 3–5 ml of cord blood was collected after clamping the umbilical cord with two clamps. UCB, blood groups of newborn and mother, direct and indirect Coombs test, and TSB on the 2nd and 3rd days were measured. TSB was measured by the colorimetric method. All enrolled neonates were kept in the neonatal care unit for observation for 3 days. Daily physical examination and estimation of bilirubin levels were done. Data were collected from the enrolled cases by a predesigned and pretested proforma.

Data were analyzed using the SPSS 15.0 software. The comparison between qualitative variables was performed by Chi-square or Fisher's exact test and $p<0.05$ was considered statistically significant. Receiver operating characteristic curve analysis was used to explore the discriminating ability of UCB in predicting NNH and optimum sensitivity and specificity were determined. NPV and positive predictive value (PPV) and likelihood ratios were calculated. Logistic regression analysis was used to analyze the pattern of bilirubin levels. The strength of association was evaluated using Pearson's correlation curve.

RESULTS

Out of the 301 mothers, oxytocin was used in 256 (85.3%), 130 (43.3%) had blood Group O, and 14 (4.6%) were Rh negative. There were 217 (72.3%) mothers who delivered by normal vaginal delivery while 84 (27.7%) required cesarean section or instrumentation for delivery. The parity ranged from 1 to 7. Out of the 301 neonates, 228 (76%) had clinical jaundice with 34 (14.9%) requiring phototherapy for treating jaundice (Table 1). Of these 34 neonates, 27 (79.4%) had exaggerated physiological hyperbilirubinemia, 6 (17.6%) had ABO incompatibility settings, 1 (2.94%) had Rh incompatibility, and 1 neonate (0.3%) required an exchange transfusion.

A cutoff of 2 mg/dL had 94% sensitivity and 93% specificity. Newborns with a UCB of 2 mg/dl or more had a significant risk of developing NNH by the 2nd or 3rd day of life, as shown in Tables 2 and 3 and Fig. 1.

Table 1: Baseline characteristics of enrolled neonates

Characteristic	n (%)
Males	153 (51)
Females	148 (49)
Birth weight 2–2.5 kg	34 (11.3)
Birth weight >2.5 kg	267 (88.7)
History of jaundice in the previous sibling	08 (3.3)
Blood group of the neonate	
A	38 (12.6)
B	117 (39.0)
AB	8 (2.6)
O	138 (46.0)
Rh positive	293 (97.3)
Rh negative	8 (2.6)
Phototherapy used	34 (11.3)
Exchange transfusion	01 (0.3)

Pearson's correlation was 0.347 on day 2 (fair) which was increased to 0.785 on day 3 (substantial). Hence, infants who were clinically jaundiced on the 2nd day were more likely to develop significant NNH later on. Considering a cutoff of 2 mg/dL, 61.5% of the newborns with UCB levels ≥2 mg/dL required phototherapy by the 3rd day of life. Hyperbilirubinemia requiring phototherapy developed in 34 (11.3%) neonates in the high intermediate or high-risk zones of whom 27 (79.4%) had physiological jaundice, 6 (17.6%) had ABO incompatibility (4 O-A and 2 O-B), and 1 (2.94%) had Rh incompatibility.

DISCUSSION

The incidence of NNH in the present study was 11.3% as compared to 11.5% in a study by Meshram *et al*. [2], 3.5% by Ahire *et al*. [3], and 26% by Shaikh *et al.* [4]. The incidence of normal delivery was 63.5%, cesarean section 31.7%, and vacuum extraction 4.8% in a study by Romagnoli *et al*. [5]. In the present study, normal deliveries were 72.3% and the cesarean section and instrumentation were 27.7%. Bilgin *et al*.[6] showed that the difference with reference to the mode of delivery (normal delivery vs. cesarean section) and type of anesthesia (general,

Table 2: Distribution of participant neonates according to cutoff 2 mg/dL of cord blood bilirubin with the need for phototherapy and predictive value with a relative risk

Cord bilirubin	Phototherapy (%)	No phototherapy (%)	Chi-square test	Relative risk
≥2 mg/dL	32 (61.5)	20 (38.5)	χ^2=158.38 p=0.001	RR=12.56 95% CI (8–19)
<2 mg/dL	2 (0.8)	247 (99.2)		

Table 3: Pearson's correlation coefficient

Parameter	2nd day serum bilirubin	3rd day serum bilirubin
Pearson's correlation	0.347*	0.785*
Significance (two tailed)	0.001#	0.001#

*** – correlation (0.0–0.2= Poor, 0.2–0.4=Fair, 0.4–0.6=Moderate, 0.6–0.8=Substantial, and 0.8 1.0=Strong), #correlation is significant at the 0.01 level (2-tailed)**

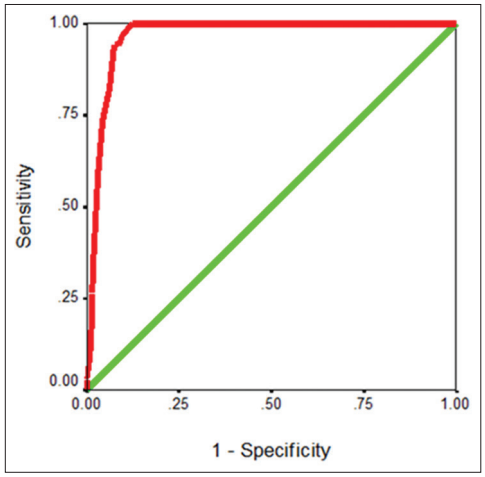

Figure 1: Receiver operating curve

spinal, and epidural) in UCB (p=0.70), 24 h bilirubin (p=0.52), and 48 h bilirubin (p=0.86) was not statistically significant.

In the present study, male-to-female ratio was 1.04:1. However, in a study by Rajpurohit *et al.* [7], the ratio was 1.22:1 and it was 1.1:1 in the study by Shaikh *et al*. [4]. In the present study, 43.3% of mothers had blood Group O while Jones *et al.* observed 39.7% of mothers with the O blood group [8]. In the present study, the incidence of ABO incompatibility was 17.6% and Rh incompatibility was 2.94%, whereas Bilgin *et al*. observed it in 23.9% and 6.44%, respectively [6]. In the present study, 85.3% of mothers received oxytocin for induction of labor; however, Rajpurohit *et al*. used it in 15% of mothers [7].

In the present study, UCB of 2 mg/dL cutoff had sensitivity of 94%, specificity was 93%, PPV 61%, and NPV was 99.2%. However, Rajpurohit *et al*. observed the values of 90%, 54%, 17.8%, and 98%, respectively, for the same UCB cutoff [7]. Jones *et al*. found that for UCB cutoff >2.04 mg/dL, sensitivity of 44.7%, specificity 94.2%, PPV 17.7%, and NPV 98.4% and UCB was significantly associated with the development of clinically significant jaundice (p<0.001) [8]. Other similar studies were conducted by Meshram *et al*. and Aktas *et al*., Castillo *et al.,* and Sehgal *et al*. [2,9-11].

There was a positive correlation between UCB and TSB at 24 and 72 h of life (p<0.001). The sensitivity, specificity, and PPV differ in various studies, but the NPV is found to be significant and more than 98% in all the studies. Castillo *et al*. observed that for every increment of 0.3 mg/dL in UCB, a neonate is 3.20 (95% CI 2.32–4.45), 2.10 (1.63–2.7), and 3.12 (2.44–3.99) times more likely to receive phototherapy or have a TSB concentration >95th and >75th percentile, respectively [10]. Hence, they concluded that most of the neonates with a UCB<1.85 mg/dL were unlikely to develop severe NNH requiring treatment.

Sehgal *et al*. concluded that the level of significant NNH was defined as >14 mg/dL at 72 h of life [11]. Levels of total UCB ≥2 mg/dL indicated 61.5% probability of the need for phototherapy and 99% of newborns who had UCB <2 mg/dL did not develop subsequent NNH and did not require phototherapy and hence could be discharged early. Hence, the cutoff of 2 mg/dL of total UCB with 94% sensitivity and 93% specificity can be used as a predictor for developing subsequent NNH.

This study had a few limitations. Neonates were admitted till day 3 of life with TSB measurements then followed up to day 5th of life. If there was no significant clinical jaundice on day 5, the neonates were not followed subsequently. Some of these neonates might have developed jaundice and were missed.

CONCLUSION

Early identification and treatment of jaundice with phototherapy is very effective, cheap, simple, and non-invasive as compared to exchange transfusion for severe jaundice. UCB can be used as an early biomarker for bilirubin estimation for the newborn.

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