Original Article

Cord blood bilirubin levels in prediction of significant neonatal hyperbilirubinemia

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Abstract

Background : Neonatal hyperbilirubinemia (NH) is a universal problem affecting nearly 60% of term and 80% of preterm neonates during first week of life. Early discharge of healthy term newborns is a common practice because of various constraints. **Objectives:** Present study was conducted to determine predictive ability of cord blood for subsequent significant hyperbilirubinemia in healthy term newborns. **Methods:** Study was conducted on a prospective cohort of 250 term neonates delivered in tertiary care hospital. The main outcome measured was significant hyperbilirubinemia. Serum bilirubin level was estimated soon after delivery from cord blood. Newborns were followed up till 5th day of life. In case of clinical jaundice presenting before 5 days, serum bilirubin level was rechecked on the same day. Values of bilirubin on fifth day were taken. **Result:** Total 250 healthy newborns were enrolled and followed up. Significant neonatal hyperbilirubinemia in our study was 16%. By ROC analysis cord blood bilirubin level of > 1.85mg/dl was found to have high sensitivity of 90%, specificity of 84.3%, positive predict value of 52.2% and negative predict value of 97.8%. Newborn babies with cord blood bilirubin level of > 1.85mg/dl, as observed by the serum bilirubin levels on day five. **Conclusion:** There is a significant association between cord blood bilirubin level to predict neonatal hyperbilirubinemia. Cord blood bilirubin level of >1.85mg/dl can predict the development of significant hyperbilirubinemia during early neonatal period.

Keywords: Cord blood bilirubin, neonatal hyperbilirubinemia.

Introduction

Neonatal hyperbilirubinemia (NH) is a common problem in neonates and a cause of concern not just for parents but also for treating pediatricians[1]. Sixty percent of the term healthy neonates and eighty percent of preterm neonates develop jaundice in the first week of life [2]. In majority it is benign and no intervention is required. Approximately 5-10% of them have clinically significant hyperbilirubinemia requiring intervention[2]. NH remains a public health concern because of kernicterus. Kernicterus in newborns is preventable, provided hyperbilirubinemia is promptly identified and treated[3]. With the intent to facilitate such identification, universal screening for severity of bilirubinemia may predict that extraordinary segment of the neonatal population which is at risk for excessive hyperbilirubinemia during the first week after birth[4]. Early discharge of healthy term newborns after delivery has become a common practice because of medical, social reasons and economic constraints[5, 6]. In 6.5% of babies, hyperbilirubinemia is common cause for readmission during early neonatal period[7]. Up to 4% of term newborns who are readmitted to the hospital during their first week of life, approximately 85% are readmitted for jaundice[8]. Severe jaundice and even kernicterus can occur in some full term healthy newborns discharged early[9]. It is difficult to predict which newborns are at increased risk for developing significant hyperbilirubinemia (Total Serum Bilirubin >15mg/dl) [10]. American Academy of Pediatrics (AAP) recommends that newborns discharged within 48 hours should have a follow-up visit to detect significant jaundice and other problems[11] which is not possible in developing countries due to limited follow up facilities. Treatment of severe neonatal jaundice by exchange transfusion is costly, associated with complications and requires skilled manpower[12]. Early treatment of jaundice with phototherapy is effective, simple and cheap[13, 14]. The concept of prediction of jaundice offers an attractive option to pick up babies at risk of NH. A total Serum Bilirubin level of >15 mg/dl is found in 3% of normal term babies[15]. The incidence of NH depends on regional variations, ethnic makeup of the population[16, 17], laboratory variability in the measurement of bilirubin, and breastfeeding[18]. Several investigators have tried to find a simple marker to predict NH. Some of them used

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transcutaneous bilirubin measurement[19-25], and ETCO measurement[26, 27] CBB estimation, predischarge hour specific bilirubin estimation[28], to predict the subsequent course of jaundice. There is an obvious need to develop simple predictive guidelines that will enable the physicians to identify which of the early discharged newborns will develop significant hyperbilirubinemia, and minimize risk of bilirubin dependent brain damage. An association between cord bilirubin levels and subsequent risk of hyperbilirubinemia has been previously reported. However, the utility of cord bilirubin as a screening test to predict subsequent hyperbilirubinemia has been debated[29-31]. Hence present study was conducted to evaluate predictive value of cord blood bilirubin level for significant hyperbilirubinemia.

Aims & Objectives

1. To determine the predictive ability of cord blood bilirubin for subsequent significant hyperbilirubinemia in healthy term newborns. Hyperbilirubinemia requiring intervention (either phototherapy +/- Exchange transfusion) was labeled "significant"

2. To establish cut-off values which have best sensitivity, specificity and predictive values for significant hyperbilirubinemia.

Materials and Methods

Study Design

The present study is a hospital based prospective study. This study was conducted on 250 full term healthy newborns delivered at tertiary care hospital.

Inclusion Criteria

1. All consecutive inborn neonates, from any type of delivery.
2. Gestational age of >37week as measured by New Ballard's score
3. Birth weight >2.5 kgs

Exclusion Criteria

Neonatal sepsis, IUGR, Intrauterine infections, Maternal infections, Maternal drugs, Sick babies admitted to NICU, Prematurity,Gross congenital anomalies, Maternal gestational diabetes, Birth asphyxia (APGAR < 7/5min), Rh incompatibility.

Data Collection

Inborn baby who fulfilled inclusion criteria were recruited after taking consent form parents/mother. Clinical history was recorded in a specially designed proforma. Cord blood was collected from all newborns. The newborns were followed up for 5day period with daily physical examination according Kramer dermal zones. In case of clinical jaundice presenting before 5 days, serum bilirubin level was rechecked on the same day. Values of bilirubin on fifth day were taken. Blood grouping tests of both the mother and their newborns were done. Other investigations for identifying the etiology were done according to the clinical indication.

Methodology

The study group was evaluated by a designed protocol. In all newborns a detailed history, gestational assessment by New Ballard's score, systemic general examination with particular attention to factors known to be associated with hyperbilirubinemia was carried out.

Laboratory evaluation (Bilirubin estimation)

Serum bilirubin estimation was done by Diazo method. This method for bilirubin estimation is based on principle that bilirubin reacts with diazotized sulphanilic acid in acidic medium to form pink coloured azobilirubin with absorbance directly proportional to bilirubin concentration. Direct bilirubin, being water soluble directly reacts in acidic medium. However indirect or unconjugated bilirubin is solubilised using a surfactant and then it reacts similar to direct bilirubin. Cord bilirubin levels were estimated soon after delivery by above method. The neonates were followed up clinically every 12 hrs for 5days, in case of early discharge they were followed every 24 hrs for 5 days. 2nd bilirubin estimation (TSB S) was done whenever clinical suspicion of jaundice was present. Primary outcome was significant hyperbilirubinemia defined as requiring phototherapy or serum bilirubin levels >15 mg/dl.

Analysis of Data

The analysis was carried out using the statistical package for social sciences (SPSS 15) program for windows. Statistical test using chi-square test of significance was applied and predictive values (sensitivity, specificity, negative and positive predictive values) were calculated using the conventional formula. '*p*' values with significance of <5% were considered statistically significant. Receiver Operating Characteristics (ROC) curve analysis was carried out to establish the cut off value for best prediction of significant hyperbilirubinemia. All infants were classified into four groups depending on the Umbilical cord serum bilirubin <0.9mg/dl (group-1), 1.0-1.9mg/dl (group-2), 2.0-2.9mg/dl (group-3) , and >3mg/dl (group-4).

Observation and results

Total 250 healthy term newborns were enrolled. The baseline characteristics of newborns were noted and shown in Table 1.

Table 1 Baseline characteristics of Neonates

Male Female	140 (56%) 110(44%)
Birth weight kg (mean)	3.07 ± 0.43
Icterus in previous sibling	10 (4%)

Among total 250 cases, 40 neonates developed significant hyperbilrubinemia. The prevalence of significant hyperbilirubunemia in this study population was 16%.

Association between the neonatal significant hyperbilirubinemia and the birth weight of baby.

In this studied group birth weight of baby divided into three groups 2.5-3 kg were 138 (51.2%) cases and 3-3.5kg were 92 (36.8%) cases and >3.5 kg were 4 (1.6%) cases. Among 40 neonatal significant hyperbilirubinemia cases 2.5-3 kg were 22 (17.1%) cases and 3-3.5 kg were 14 (15.2%) cases and >3.5 kg were 4 (13.3%) cases. In the present study, there is no statically significant association between ('*p* '*value* 0.335, chi-square value 0.846) significant hyperbilirubinemia and birth weight of baby. Hence the present study infers that the neonatal significant hyperbilirubinemia is independent of the birth weight of baby.

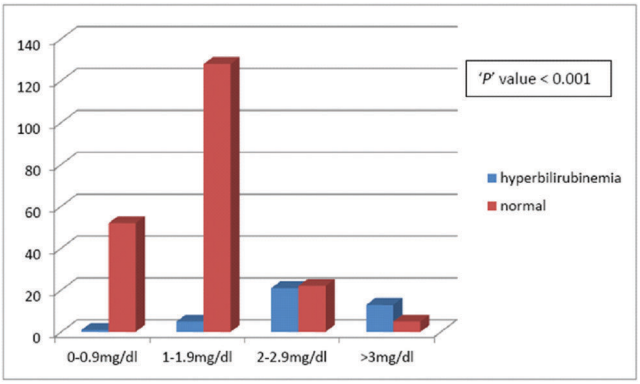
Association between the neonatal significant hyperbilirubinemia and cord blood bilirubin level.

In the present study all infants were classified into four groups depending on the UCSB levels <0.9mg/dl (group-1), 1.0-1.9mg/dl (group-2), 2.0-2.9mg/dl (group-3), and >3mg/dl (group-4). Majority 133 (53.2%) of newborns had cord blood bilirubin level between 1-1.9mg/dl. 53 (21.2%) newborns had cord blood bilirubin level between 0-0.9 mg/dl. 43 (17.2%) newborns had cord blood bilirubin level between 2-2.9 mg/d. 21 (8.4%) newborns had cord blood bilirubin level >3 mg/dl . The range of cord blood bilirubin was 0.5 – 3.4 mg/dl with mean cord blood bilirubin of 1.622 mg/dl. Among 40 newborns who developed significant neonatal hyperbilirubinemia, majority were in group-3(49%) and only one in group-1 (1.9%). There was statistically highly significant ('*p*' value <0.001, chi-square value 90.1) association between new born babies developed significant hyperbilirubinemia and increasing Umbilical cord serum bilirubin levels. This study shows that number of newborns developed hyperbilirubinemia proportionately increase as the UCSB increases i.e.: from 1.9% in group-1 to 62% group-4. The association between hyperbilirubinemia and cord blood bilirubin is shown in Table 2.

Table 2: Association between neonatal significant hyperbilirubinemia and cord blood bilirubin level.

cord blood bilirubin Levels	Total	Hyperbilirubinemia		'*p*' value
		yes	no	
0-0.9 mg/dl	53	1 (1.9%)	52	<0.001
1-1.9mg/dl	133	5 (3.7%)	128	
2-2.9mg/dl	43	21 (48.8%)	22	
>3 mg/dl	21	13 (61.9%)	8	

Fig 1 :Association between neonatal hyperbilirubinemia and cord blood bilirubin level

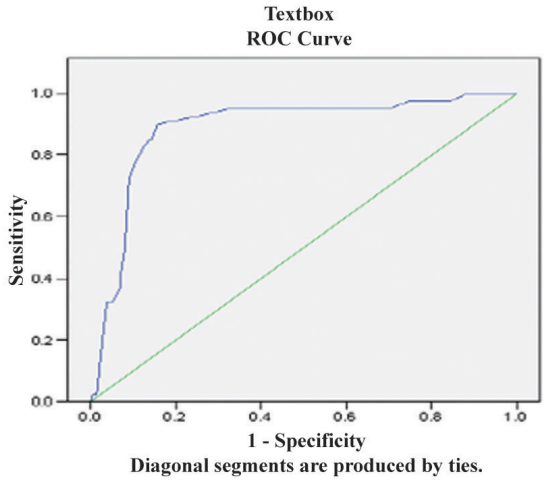


Correlation between cord blood bilirubin and fifth day bilirubin level

In the present study there is a significant association (r=0.481, 'p' value <0.01) between cord blood and fifth day serum bilirubin levels.

Diagnostic predictability of cord blood bilirubin for significant neonatal hyperbilirubinemia

Figure 2:ROC curve for cord blood bilirubin level



UCSB level of >1.85 mg/dl was determined to have the highest predicting ability according to ROC curve (Chisquare value 92.8, '*p*' value =<0.001) to predict the newborns who develop neonatal significant hyperbilirubinemia. In this study, using UCSB level of >1.85mg/dl hyperbilirubinermia could be predicted with sensitivity of 90%, specificity of 84.3 %, positive predict value (PPV) of 52.2% and negative predict value (NPV) of 97.77%. The area under the ROC curve is 0.89, which makes the test fall under the category of a good test.

Table 3: Cord blood bilirubin level of >1.85 mg/dl cut off value is chosen on the ROC analysis to predict significant hyperbilirubinemia.

USCB level	total cases	Hyperbilirubinemia		'*p*' value
		yes	no	
<1.85mg/dl	181	4(2.2%)	177	<0.001
>1.85mg/dl	69	36 (52.1%)	33	

Discussion

Jaundice is a clinical condition that constitutes a major issue in neonatal practice. Debate and dilemma continue to pass on regarding length of stay in the hospital, safety and risk of early discharge from hospital, framing a follow-up schedule benefiting each country considering her health resources and economic constrain, attitude in the community etc.

There is concern about an increasing incidence of hyperbilirubinemia and possibility of kernicterus in healthy term newborns. Hyperbilirubinemia is one of the most common causes of readmission of newborn infants especially in Middle East and Asia[2]. The need for prediction of healthy neonates at risk for hyperbilirubinemia, limits stay in hospital and allows simple bilirubin reducing methods to be implemented before bilirubin level reaches critical levels .We have assayed the validity of cord bilirubin level in predicting infant at low or high risk for post natal hyperbilirubinemia. Serum bilirubin levels are usually 1-3 mg/dl at birth and rise at rate of less than 5 mg/dl per day peaking at 3-5 days in term.

Our study hypothesis is that a high serum bilirubin level soon after birth would also predict a high peak that occurs in first week of life.

250 normal healthy term newborns were enrolled in tertiary care hospital for neonatal hyperbilirubinemia using cord bilirubin as predictor. We considered peak serum bilirubin level > 15 mg/dl as "Significant" since specific treatment is usually considered at or above this level[11].

In the present study, study group is distributed with 140 (56%) male and 110 (44%) female babies. Among 40 newborns with neonatal significant hyperbilirubinemia 21 (15%) are male and 19 (17%) are females. There is no significant association ('*p*' value 0.63) between the neonatal significant hyperbilirubinemia and the sex of baby. Hence the present study infers that the neonatal hyperbilirubinemia (>15mg/dl) is independent of the sex of the newborn. Maisal et al (1998), showed in a study consisting of 29934 infants, factors associated with readmission for jaundice. Male sex in the study group is 74.8% compared to control with 49.6%, with '*p*' value 0.007, showing that male sex has more risk of readmission for neonatal hyperbilirubinemia[32]. Amar Taksande et al (2005), in a study on 200 neonates with 82 males and 118 females, 8 males and 11 females have serum bilirubin level of >15mg/dl with '*p*' value of 0.323. So they found no association between the sex of the newborn and the neonatal hyperbilirubinemia (>15mg/dl) [33]. Rudy Satrya et al (2009), showed significant association between the sex of the newborn and neonatal hyperbilirubinemia with '*p*' value <0.05. Of 88 newborns 21 develop hyperbilirubinemia, 16 were males and 5 females[34]. Singhal v et al (2012) showing male infants constituted 290 (58%) and females constituted 210 (42%). Rostami et al (2005), in Iran in a study showed that there is no association between the neonatal significant hyperbilirubinemia and the sex of the newborn[35]. The present study is in correlation with the study done by Amar Taksande et al[33], Rostami et al[35].

Association between the cord blood bilirubin levels of >1.85mg/dl with neonatal hyperbilirubinemia

In the present study, on ROC curve analysis critical cord bilirubin level (>1.85 mg/dl) with high sensitivity and high specificity is selected. The probability that a neonate with cord bilirubin >1.85 mg/dl would later become hyperbilirubinemia (positive predictive value) was 52.2%. The negative predictive value of the probability of nonhyperbilirubinemia at a cord bilirubin lower than 1.85 mg/dl was 97.7%. If a newborn baby becomes hyperbilirubinemic, the probability that the cord bilirubin was >1.85mg/dl was 90% (sensitivity). Given a non-hyperbilirubinemic child, the probability that the cord bilirubin was <1.85mg/dl was 84.3% (specificity).

Amar Taksande et al (2005), showed that the cord bilirubin level >2mg/dl has a sensitivity 89.5%, specificity 85%, negative predictive value of 98.7% and positive predictive value of 38.8% in correlation with the present study[33]. Zakia Nahar et al (2009) showed that the cord bilirubin level >2.5mg/dl has a sensitivity 77%, specificity 98.6%, with negative predictive value of 96% in correlation with the present study[36].

Singhal v et al (2012) In this study showed that the cord bilirubin level > 1.9mg/dl has a sensitivity 90% ,specificity 82.55 % ,negative predict value of 98.07 % ,and positive predict value of 45.65% in correlation with present study. Knupfer et al (2005) in this study showed that the cord blood level >1.74mg/dl has a sensitivity 97%,specificity 41.4%, negative predict value of 99.8 % ,and positive predict value of 4.8 %[37] .

Knudsen et al In this study showed that the cord bilirubin level > 2.33mg/dl has a sensitivity 13% specificity 99 % ,negative predict value of 72% ,and positive predict value of 85%[38].

All studies show significant association between rising UCSB and development of jaundice in subsequent postnatal days. Present study shows that UCSB is a useful indicator of subsequent neonatal hyperbilirubinemia and aids in identifying the low risk group children with UCSB level of <1.85 mg/dL. NPV in this low risk group can prove useful in using this parameter for making decisions regarding early discharge or request for review of the newborns for evaluating neonatal hyperbilirubinemia.

Recommendations from the study

The present study was done to assess the usefulness of the cord blood bilirubin as a predictor of subsequent neonatal hyperbilirubinemia in a healthy term infants who require phototherapy.

Since the cord blood bilirubin level of more than >1.85mg/dl has a sensitivity of 90% and specificity of 84.3%, babies having serum cord bilirubin level of >1.85mg/dl can be followed up in the hospital for 5 days, the time of peak neonatal hyperbilirubinemia to prevent the babies discharged early and later readmission for neonatal hyperbilirubinemia.

It is recommended to have cord blood bilirubin estimation of all healthy term babies delivered in an institution to prevent the dangerous consequences of neonatal hyperbilirubinemia like Kernicterus. This can reduce the morbidity and mortality due to hyperbilirubinemia.

Conclusions

In the present study infants with neonatal hyperbilirubinemia (>150mg/dl) had significantly higher levels of cord bilirubin than neonates with serum bilirubin of <15mg/dl. So it is possible to define a group of neonates risk of developing jaundice needing phototherapy at birth itself. And thereby influence a decision of early discharge vs. prolonged observation of high risk neonates.

From the present study, cord bilirubin level of >1.850mg/dl has a correlation with incidence of significant early neonatal hyperbilirubinemia in term newborns. So this level of >1.850mg/dl of cord bilirubin could predict the development of significant hyperbilirubinemia.

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