



A prospective study on correlation of cord blood bilirubin with occurrence of neonatal hyperbilirubinemia

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Abstract

Background: Neonatal hyperbilirubinemia is one of the most common problems that can occur in a healthy new-born. This physiological rise in indirect component of bilirubin resolves gradually without any intervention in majority of cases. But few babies require intervention in the form of phototherapy and exchange transfusion when the bilirubin levels exceed the normal physiological range for gestational age. The study was aimed to evaluate the predictive value of cord blood bilirubin level for identifying newborn for development of significant hyperbilirubinemia.

Methods: It was a prospective observational study carried out in Adichunchanagiri Institute of Medical Sciences, B.G. Nagara, Karnataka. The cord blood bilirubin at birth and 48 hrs serum bilirubin levels were measured. Also, blood group, Rh status and DCT (direct coomb's test) were tested to estimate the risk in development of hyperbilirubinemia.

Results: A total of 210 were included in the study, out of which 52 babies required phototherapy, with a sensitivity of 94.23% and specificity of 3.97%, with the mean cord blood bilirubin level of 2.6mg/dl, having sensitivity of 63.46% and specificity of 90.50%. The multivariate analysis showed ABO and Rh incompatibility, cord blood bilirubin level and lower gestational age had an increased the risk of hyperbilirubinemia requiring phototherapy.

Conclusions: Cord blood bilirubin may be used as a potential tool to determine hyperbilirubinemia in newborns. And initiation of phototherapy early in at-risk neonates may decrease the hyperbilirubinemia related morbidity and mortality.

Keywords: hyperbilirubinemia; cord blood bilirubin; phototherapy; newborn

Introduction

Neonatal hyperbilirubinemia is a benign, transient phenomenon that occurs in most neonates. It 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]. During the first week of life, an increase in bilirubin production and decrease in bilirubin elimination cause total serum bilirubin (TSB) concentrations to rise [3-4]. On the other hand neonatal hyperbilirubinemia could be a feature of underlying disorder like haemolytic anaemia, inborn errors of metabolism, infection or liver disorders [5]. In severe cases unconjugated bilirubin gets deposited in basal ganglia causing kernicterus [6].

There is an increased demand for early discharge of healthy term newborn because of social as well as

financial reasons [7]. Various strategies are being followed in predicting the occurrence of significant hyperbilirubinemia namely follow-up within 1 to 2 days of early discharge, umbilical cord bilirubin level at birth, routine pre-discharge serum bilirubin, and

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transcutaneous bilirubin measurements, as well as the universal clinical assessment of risk factors for developing jaundice [8]. During the early neonatal period hyperbilirubinemia is the most common cause of readmission in a significant number of babies [9]. These readmission leads to burden of extra expenses on the family and exposes the healthy new born to hospital environment and also poses risk for interruption of breast feeding [10].

It's a need of the hour to develop simple predictive guidelines which will help the paediatricians to identify or predict which of the newborns who are discharged early are at increased risk of developing significant hyperbilirubinemia and reduce the risk of developing kernicterus.

The study was aimed to evaluate the predictive value of cord blood bilirubin level for identifying newborn for development of significant hyperbilirubinemia.

Materials and methods

A prospective observational study was conducted in Adichunchanagiri Institute of Medical Sciences, B.G. Nagara, Karnataka from June 2021 to December 2021. The study was conducted with objectives to know the association of cord blood bilirubin value and development of hyperbilirubinemia requiring intervention and to derive the cut-off of cord blood bilirubin to predict clinically significant jaundice. It included healthy newborns after obtaining consent from parents. Excluded in this study were newborns who had significant illness requiring Neonatal Intensive Care Unit (NICU) admission, chronic maternal illness (Diabetes/ Hypertension in mother), major congenital malformations and history of drug intake by mother affecting the fetal liver. Ethical committee approval was obtained and well informed consent was taken from all the parents whose babies were involved in the study.

The study comprised of total of 210 healthy babies born during the study period who met the inclusion criteria. A proforma including the information of newborn about the gestational age, birth weight, blood group, direct coombs test, maternal blood group, cord blood bilirubin levels and 48 hours bilirubin levels were collected. The 48 hrs bilirubin levels were analysed using the AAP (American Academy of Paediatrics) bilirubin nomogram of 2004 and the intervention were done accordingly by giving phototherapy (PT).

The primary outcome was to correlate the predictive value of cord blood bilirubin for phototherapy requirement. At 48 hrs of life serum bilirubin levels were estimated and babies whose values fell in the

phototherapy range were shifted to NICU for the phototherapy. Data thus obtained was compiled and entered in MS Excel spread sheet. Chi-square test was applied to study the significant association of risk factors such as Rh incompatibility and ABO incompatibility with requirement of phototherapy. P values less than 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curve was drawn and area under curve (AUC) was calculated. AUC was used to know its correlation with cord bilirubin.

Results

The study included 210 normal healthy neonates born with the mean gestational age of 38.5 weeks +/- 1.5 weeks, with mean APGAR score at 1 and 5 minutes being 7 and 9 respectively, 67.62% were male and 32.38% were females. Out of 210 newborns 52 (24.76%) of them received phototherapy as an intervention to hyperbilirubinemia, 8(3.8%) of them had Rh incompatibility and 37 (17.6%) had ABO incompatibility. Mean cord blood bilirubin value was 1.5mg/dl and mean serum bilirubin level at 48hrs estimated was 13mg/dl. The mean cord blood bilirubin level requiring phototherapy after 48hrs was 2.6 mg/dl with a sensitivity of 63.46%, specificity of 90.5%, positive predictive value of 68% and negative predictive value of 88.27%. On applying chi-square test for the cord bilirubin level of >2.6gm/dl and <2.6gm/dl requiring phototherapy at 48 hrs of life p value was 0.000324 as shown in table 1.

Table 1: Cord bilirubin at birth with statistical significance in predicting requirement of phototherapy at 48 hours.

Total cord bilirubin (mg/dl)	Total	Phototherapy		P- value
		Yes	No	
>2.6	48	33	15	0.000324
<2.6	162	19	143	

On applying chi-square test for presence or absence of the Rh incompatibility and requiring phototherapy at 48hrs of life, we got a p value 0.000153 as shown in table 2.

Table 2: Rh incompatibility with statistical significance in predicting requirement of phototherapy at 48 hours.

Rh incompatibility	Total	Phototherapy		P- value
		Yes	No	
Yes	11	8	3	0.000153
No	199	44	155	

On applying the chi-square test for presence or absence of ABO incompatibility and requiring phototherapy at 48 hrs of life, we got p value 0.000136 as shown in table 3.

Table 3: ABO incompatibility with statistical significance in predicting requirement of phototherapy at 48 hours.

ABO incompatibility	Total	Phototherapy		p-value
		Yes	No	
Yes	109	37	72	0.000136
No	101	15	86	

On analysis of correlation of cord bilirubin value with requirement of phototherapy at 48 hours using ROC curve we found that raise in cord bilirubin will lead to progressive increase in serum bilirubin requiring intervention at 48 hours (table 4) (Figure 1).

Table 4: Area under curve (ROC) to evaluate the diagnostic efficacy of cord blood bilirubin levels to predict neonatal hyperbilirubinemia requiring phototherapy at 48hr of life.

Area under curve	SE	Significance	95% confidence limit	
			Upper limit	Lower limit
0.7674	0.072	<0.001	0.623	0.911

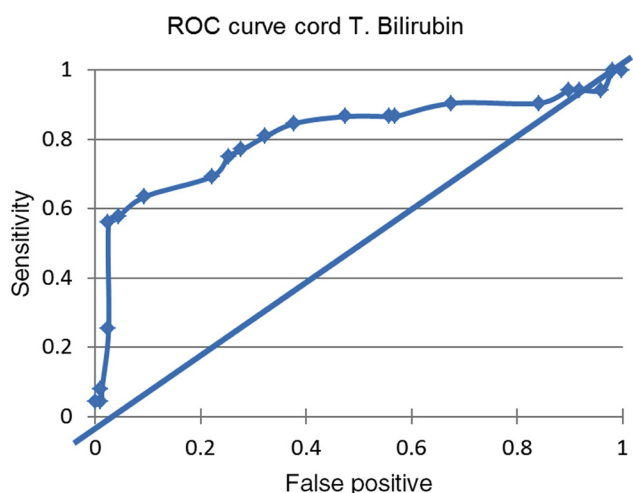


Figure 1: Receiver-operator curve analysis (ROC) showing predictability of cord total bilirubin.

The study showed that there was a significant relationship between Rh incompatibility, ABO incompatibility, gestational age of the baby and the cord blood bilirubin levels in developing hyperbilirubinemia at 48 hrs of life, but there was no relation between the mode of delivery, gender and birth weight, in development of hyperbilirubinemia.

The scattered diagram shows that most of the newborns having cord blood bilirubin of >2 had serum bilirubin of >12 by 48 hrs of life and those having cord blood bilirubin of >2.6 had serum bilirubin of >15 and required phototherapy as intervention for hyperbilirubinemia (Figure 2). Hence, ABO incompatibility, Rh incompatibility and gestational age were found to be the risk factors in development of hyperbilirubinemia at 48

hrs of life and cord blood bilirubin estimation being a very good tool in predicting the hyperbilirubinemia in healthy neonates.

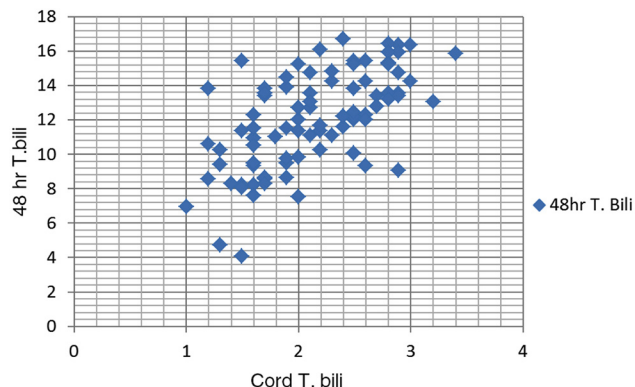


Figure 2: Scatter diagram showing correlation of cord bilirubin with 48 hours serum bilirubin.

Discussion

At birth serum bilirubin levels were 1-3mg/dl and gradually rises at a rate of less than 5mg/dl per day. Cord blood was chosen for initial bilirubin estimation as it is a simple, non-invasive method and doesn't cause any discomfort to the baby and the result of bilirubin levels is readily available. There is a re-emergence of kernicterus because of growing practice of early discharge of new-borns. Hence, it is of utmost importance to develop some markers for identifying new-borns who are at increased risk of developing significant hyperbilirubinemia. In our study we found out that there was significant association between cord blood bilirubin and development of hyperbilirubinemia. We have also found out the predictive cut off of cord blood bilirubin to be 2.6mg/dl to develop jaundice requiring phototherapy. Similar studies were done in different parts of the world which showed the association of cord blood bilirubin and development of significant jaundice.

This study found that newborns born to mother who had blood type O had higher cord blood bilirubin (CBB) levels and were prescribed PT more frequently. CBB predicted severe hyperbilirubinemia and the need for PT especially in babies with ABO maternal-fetal blood incompatibility. As a result, CBB screening may be used to identify neonates at a high risk of subsequent hyperbilirubinemia, reducing both unnecessary hospital stays and delays in recognising and treating serious hyperbilirubinemia.

Measurement of end-tidal carbon monoxide, serum bilirubin on the sixth hour and first day and transcutaneous bilirubin have all been investigated as screening assays to detect high-risk babies for hyperbilirubinemia (TCB) [11-13]. Evaluation of pre-

discharge serum bilirubin and application of Bhutani's et al [14] risk classification can be informative, although it is an intrusive procedure. Because TCB levels do not accurately reflect TSB levels, and because TSB levels are often higher than TCB measurements, it is recommended that instead of applying TCB levels to TSB nomograms, bias in the particular device can be corrected [15]. End-tidal carbon monoxide measurement is not cost-effective.

According to Risemberg et al, hyperbilirubinemia was more common in neonates with ABO incompatibility whose CBB was greater than 4 mg/dl. These infants should be re-evaluated on a regular basis. In this research, infants with ABO incompatibility's median CBB level 2.74 mg/dl in those who needed PT, which was lower than the results of Risemberg and colleagues [15].

Knudsen found that the incidence of PT was significantly higher in neonates with CBB levels over 2.34 mg/dl, and that the likelihood that an infant with CBB higher than 2.34 mg/dl would have PT was much higher [16]. The probability of becoming jaundiced after consuming less than 1.75 mg/dl was 67%. According to Knupfer et al, there is a direct relationship between the CBB value and the PT, and when the CBB level grew, so did the PT is a must. The CBB cut off level of 1.75 mg/dl corresponds to the sensitivity was 90% and the NPV was 99.1%, showing that newborns with CBB levels less than 1.75 mg/dl had a minimal risk of hyperbilirubinemia that is severe [17].

Considering a cut off level of 2.6 mg/dl, Ipek et al found the NPV to be 97.90% and specificity to be 97.02%. They also reported that PT administration rate was significantly higher in neonates with a CBB level of 2.6 mg/dl and above 3 [18]. Calkins et al reported that neonates who received PT had significantly higher CBB (2.5+/-0.5 mg/dl) as compared with controls (1.8 +/- 0.4 mg/dl). Additionally, CBB of newborns with ABO incompatibility who received PT was higher in comparison to newborns without ABO incompatibility who received PT (2.6 +/- 0.6 vs. 1.8 +/- 0.5 mg/dl). According to their study, a CBB cut off value of 2.05 mg/dl had 80% sensitivity and 78% specificity for predicting PT treatment [19]. Alpay et al found that babies with a mean TSB of 6 mg/dl in the first 24 hours developed substantial hyperbilirubinemia, the sensitivity and NPV for this value were 90 percent and 97.9%, respectively [11].

To summarise the study states that cord blood bilirubin estimation will be useful tool in predicting the

hyperbilirubinemia, considering the risk factors such as Rh incompatibility, ABO incompatibility, gestational age in healthy newborns by 48 hrs of life, and this helps in early intervention by phototherapy reducing the morbidity and mortality associated with the hyperbilirubinemia and also the length hospital stay.

The limitations in the study that cut off value of cord bilirubin in preterm and sick newborns could not be determined.

Conclusions

There is a correlation of cord blood bilirubin with occurrence of neonatal hyperbilirubinemia in healthy term newborns. Cord blood bilirubin level of 2.6mg/dl and greater can predict the development of hyperbilirubinemia in term newborns. It should prompt re-consideration of the applicability of this practical, cheap and non-invasive approach. Estimation of cord blood bilirubin is simple, inexpensive and effective tool in screening babies for the development of neonatal hyperbilirubinemia. Also, it helps paediatrician to decide on early discharge of babies and need for early follow-up.

Conflict of Interest

The authors declared no conflict of interest.

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