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Original Research Article

Cord blood bilirubin level as a predictor of development of pathological hyperbilirubinemia in new-borns

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ABSTRACT

Background: There may be a delay in recognition of pathological hyperbilirubinemia which may lead to serious consequences in the new born. The purpose of this study was to verify whether the cord bilirubin levels predicted the development of pathological hyperbilirubinemia.
Methods: In this hospital based prospective cross-sectional study conducted at Central Referral Hospital, Gangtok from December 2014 to November 2015, 202 live new born meeting the inclusion criteria were enrolled. After birth, cord blood was collected for the estimation of cord blood bilirubin and the babies were followed up daily for the development of clinical jaundice. Peripheral venous blood was collected for the estimation of serum bilirubin levels in those who developed clinical jaundice.
Results: The incidence of pathological hyperbilirubinemia in our study is 12.87%. The mean gestational age is 38.3 weeks. There is a significant association between cord blood total bilirubin levels and the development of pathological hyperbilirubinemia in newborns with a P-value of 0.000. A critical cord bilirubin level ≥ 2.50mg/dl has sensitivity of 84.1%, specificity of 88.5%, positive predictive value of 98% and negative predictive value of 45.1% for predicting the risk of developing pathological jaundice.
Conclusions: This study concludes that cord blood total bilirubin levels reliably predict the occurrence of pathological hyperbilirubinemia as defined by current operational guidelines.

Keywords: Pathological hyperbilirubinemia, Cord blood bilirubin, New-borns, Prediction

INTRODUCTION

Neonatal hyperbilirubinemia is usually a benign condition observed during the first week of life in approximately 60% of term infants and 80% of preterm infants. Although most cases are physiological, it is imperative to identify those at risk of adverse outcomes of severe neonatal hyperbilirubinemia to initiate early therapy so as to prevent long term morbidity.[1] Although bilirubin may have a role as an anti-oxidant, elevations of unconjugated bilirubin are potentially neurotoxic.[2] The potential risk of developing bilirubin encephalopathy or even kernicterus is high in babies with elevated serum bilirubin level. The sequelae could be serious as patients may develop cerebral palsy, sensorineural deafness and mental retardation.

Early discharge of healthy term newborns especially after normal vaginal delivery i.e. after 24 hours has become a common practice, because of reasons like prevention of nosocomial infections, some social factors and also due to economical constraints. American Academy of Pediatrics (AAP) recommends that newborns discharged within 48 hours should have a follow up visit after 48 to

72 hours for any significant jaundice and other problems. This recommendation is not appropriate for our country like India due to limited follow up facilities in the country. There may be delay in recognition of pathological hyperbilirubinemia in these newborns hence close monitoring is essential for early detection and management. This has become a concern for paediatricians due to reports of bilirubin induced brain damage which have occurred in healthy term infants even without hemolysis.[3,4] Exact serum bilirubin levels that leads to development of kernicterus in icteric newborns is not known.

The concept of prediction of jaundice offers an attractive option to pick up babies at risk of neonatal hyperbilirubinemia. Physical examination is not a reliable measure of the serum bilirubin. Under these circumstances it would be desirable to predict the risk of neonatal hyperbilirubinemia in order to implement early treatment and thereby minimize the risk of bilirubin dependent brain damage.[5]

Hence, the purpose of the study is to verify whether the bilirubin levels in cord blood could predict the subsequent development of pathological hyperbilirubinemia requiring interventions like phototherapy or exchange transfusion.

METHODS

This hospital based prospective cross-sectional study was conducted at the department of Pediatrics and delivery room or operation theater of Obstetrics and Gynecology department of Central Referral Hospital (CRH), the teaching hospital of Sikkim Manipal Institute of Medical Sciences (SMIMS), Gangtok. Gangtok is the state capital of Sikkim, one of the northeastern states of India. The study was conducted from December 2014 to November 2015. After reviewing hospital records it has been found that the number of newborns with pathological jaundice admitted in our hospital in the past 3 years was around 320 per year. The sample is calculated as minimum of 175 with the confidence interval of 5% and 95% confidence level. After taking approval from Research protocol evaluation committee and, Institute Ethics committee, SMIMS, the study was commenced. Informed consent was taken from the parents/guardians of all the newborns. Data was collected as per the proforma. Detailed history, review of maternal files and examination of the newborns were used to obtain the required data.

After birth, cord was clamped then cut and baby kept under radiant warmer and stabilized. After the delivery of placenta, cord blood was collected with a sterile syringe by the investigator from the umbilical cord attached to placenta as per standard guidelines. The cord blood collected was immediately sent to the central laboratory of CRH for assaying of cord blood total bilirubin levels and blood grouping. The gestational age of the newborns was assessed using new Ballard score. Then all enrolled babies were followed up clinically for the development of jaundice by using Kramer dermal scale till discharge and further on follow up till 1 month of age. Detailed physical examination was carried out daily by the investigator. Those babies who on visual inspection had jaundice where the bilirubin level seemed to be above the 95th centile for age in hours of life as per Bhutani hour specific bilirubin nomogram were further investigated by estimation of serum total and direct bilirubin. The newborns detected to have pathological hyperbilirubinemia were further investigated by doing Direct Coomb test, complete blood count, reticulocyte count and peripheral smear and were managed according to standard protocols as per guidelines of American Academy of Pediatrics subcommittee on hyperbilirubinemia.[6] Pathological hyperbilirubinemia in our study was defined as:[1]

- Clinical jaundice in the first 24 hours of life.
- Any elevation in serum bilirubin levels requiring treatment.
- Rate of STB increase >0.2 mg/dl/hours or 5mg/dl/day.
- Direct serum bilirubin >2 mg/dl or >15% of total serum bilirubin.

The serum total and conjugated bilirubin were estimated by using 2-point assay calorimetric auto analyzer. Mother's and baby ABO and Rh grouping was done by using gel card method. Coombs test direct (DCT) or indirect (ICT) of babies and mother's blood was done by gel-card method.

Data was entered in Microsoft excel sheet version 2013. It was then imported into registered version of SPSS V 20. Data were analysed using simple statistics like mean, median and proportions for the general variables. Chi-square test was done for finding association between two or more categorical variables. The critical cord bilirubin level having the highest sensitivity and specificity was determined with the Receiver operating characteristics (ROC) curve analysis. Cord serum bilirubin and serum total bilirubin concentration were used for developing prediction test. The sensitivity and specificity were calculated for predicting hyperbilirubinemia.

RESULTS

A total of 254 new-borns cases were delivered over the period of one year from December 2014 to November 2015. Out of these 230 parents gave the consent. Among these only 202 cases met the inclusion criteria. Thus, the study was conducted on the total of 202 new-borns after obtaining a written consent from the parents. In our study, 51.5% were female babies and male babies were 48.5%. 23.8% of enrolled new-borns were less than completed 37 weeks of gestation but more than 35 weeks. The mean gestational age was 38.3 weeks and range

between 35 to 42 weeks with standard deviation (SD) ±1.350. The mean birth weight of babies enrolled in our study was 3.09 kg with range from 1.5 kg to 4.2 kg with SD±0.557. Newborns delivered by caesarean section were 48.5% and rest by spontaneous vaginal or assisted vaginal delivery (Table 1).

Table 1: Frequency distribution of the enrolled newborns according to gender, gestational age, birth weight and mode of delivery.

Characteristics		Frequency	(%)
Gender	Female	104	51.5
	Male	98	48.5
Gestational age	35-38 weeks	47	23.3
	>38 weeks	155	76.7
Birth weight	1.5-2.5 kg	31	15.9
	2.6-3.5 kg	131	64.9
	3.6-4.5 kg	40	19.8
Mode of delivery	Normal vaginal delivery	82	40.6
	Instrumental delivery	22	10.9
	Caesarean section	98	48.5

The most predominant blood group among the mothers was A positive and among the newborns was also A positive. Out of the 202 newborns enrolled 19 showed ABO incompatibility and 1 showed Rh incompatibility with their mother's blood group i.e. 9.9% of the newborns had blood group incompatibility with their mother's blood. Out of the 202 newborns 76 newborns were A positive. and 75 mothers of these newborns were A positive. 2 newborns and1 mother was Rh negative (Figure 1).

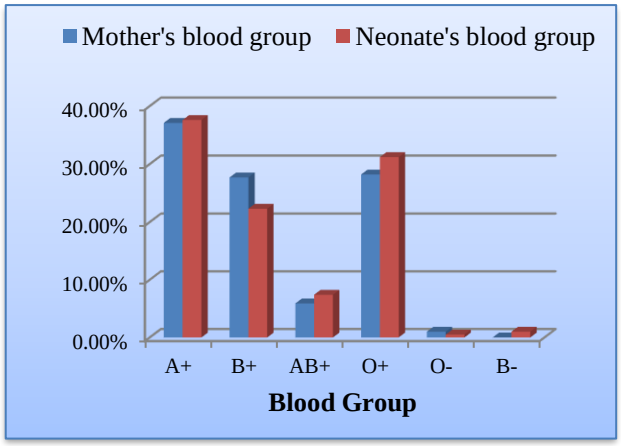

Figure 1: Frequency distribution of the mother's and neonate's blood group in percentages.

26 (12.87%) out of the 202 newborns developed pathological hyperbilirubinemia and required phototherapy. None of the babies required exchange transfusion. There was no significant association between baby's sex, new-born's birth weight and mode of delivery and the development of pathological hyperbilirubinemia. There was significant association between the gestational age of the baby and the development of pathological jaundice. Among 202 newborns in the study 47 newborns were of <37 weeks gestational age and 27.7% among them had significant hyperbilirubinemia (p=0.001). There was significant association between the ABO incompatibility and the development of pathological hyperbilirubinemia but no association with Rh incompatibility. Among 202 enrolled newborns 19 had ABO incompatibility of which 36.8% developed pathological jaundice (p=0.001).

Table 2: Difference in Cord blood total bilirubin with the development of pathological hyperbilirubinemia.

Cord blood total bilirubin	Hyperbilirubinemia		t- value	p-value
	Pathological	Physiological		
Mean (SD)	2.550 (0.324)	1.942 (0.33)	8.605	0.000
Median	2.7	2.0		
Range	1.5-2.8	1.0-2.7		

The mean cord blood total bilirubin was 2.474 with SD±0.358. Cord blood total bilirubin levels had no significant association with gestational age. Newborns with gestational age between 35-37 weeks had mean cord blood total bilirubin level 2.117 mg/dl with SD±0.441 and those with >37 weeks gestational period had mean cord blood total bilirubin level 1.991 mg/dl with SD±0.373. There was no significant association between the cord blood total bilirubin level and ABO and Rh incompatibility. Those newborns who had pathological hyperbilirubinemia had mean cord blood total bilirubin 2.55 mg/dl with SD±0.324. There was significant association between cord blood total bilirubin levels and the development of pathological jaundice (Table 2).

By ROC curve analysis it was found that total cord bilirubin level (≥2.50 mg/dl) had a high sensitivity (84.1%) and high specificity (88.5%). The positive predictive value of a cord bilirubin of ≥2.50 mg/dl was 98.0% and the negative predictive value was 45.1%. In

our study p-value was 0.000 which shows the significant correlation in between the total cord blood bilirubin levels at birth and development of pathological hyperbilirubinemia in new born (Figure 2).

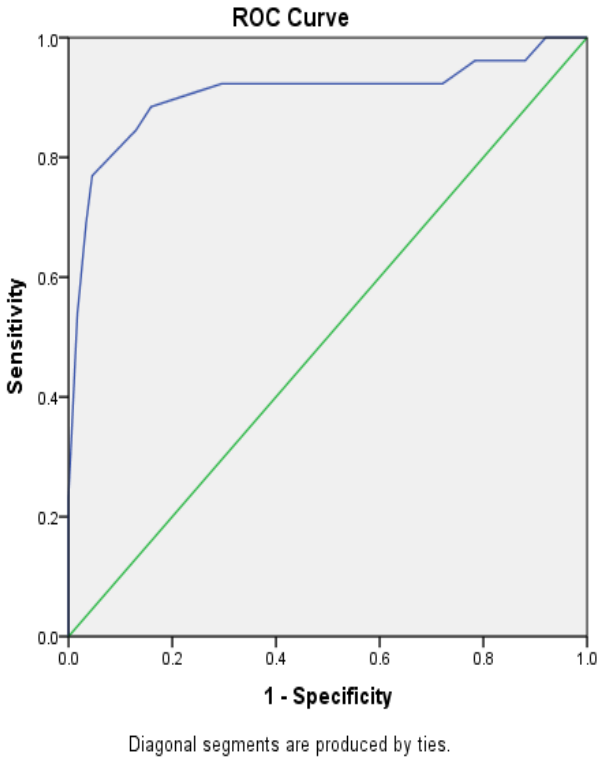

Figure 2: Receiver operating characteristics curve analysis (ROC).

DISCUSSION

Neonatal pathological hyperbilirubinemia is a frequent cause of readmission of newborns due to the recent trends of early discharge from hospital. This condition is susceptible to some kind of intervention that might prevent readmission. This study studied the reliability of cord blood bilirubin in predicting the occurrence of pathological hyperbilirubinemia in newborns as per current definition and guidelines.

Incidence of pathological hyperbilirubinemia in the present study is 12.87%. The incidence of neonatal hyperbilirubinemia varies from 5.8% to 12.8% in several previous Indian studies. The incidence of pathological neonatal hyperbilirubinemia was12.80% in a study by Awasthi S, et al, 12.00% as per a study by Randev S, et al,11.4% in a study by Dhanwadkar et al.[7-9] So the present study correlates with most of the Indian studies. The present study infers that the occurrence of pathological neonatal hyperbilirubinemia is independent of the sex of the newborns similar to the findings of the studies done by Amar Taksande et al and Rostami et al.[5,10] There is a significant association found between the gestational age of the new borns and the development of pathological jaundice in our study. This finding is similar to the findings of the study by Dhanwadkar et al.[9] In the present study there was no significant association between the mode of delivery and the development of pathological hyperbilirubinemia similar to observation made by Knudsen A, Amar taksande et al, Rudy Satrya et al.[5,11,12] There was no significant association between the birth weights of the babies and development of pathological hyperbilirubinemia in this study similar to the observation made by Rudy Satrya et al.[12] In the present study, the development of pathological hyperbilirubinemia as well as the total cord blood bilirubin level was significantly associated with the presence of ABO blood group incompatibility between the mother and the child. Risemberg et al, established a correlation between umbilical cord blood bilirubin level and the development of significant hyperbilirubinemia in newborns with ABO incompatibility.[13]

These researchers found that cord bilirubin level more than 4 m/100 ml predicted the development of severe hyperbilirubinemia. There was also a significant association found between the presence of ABO incompatibility between mother and child and the presence of significant hyperbilirubinemia as well as unconjugated bilirubin level in cord blood. The present study is in correlation with the study done by Bernaldo et al, in which among 380 newborns 38 (10%) were ABO-incompatible and 14 (36.8%) developed significant jaundice and significant association between ABO-incompatibility and development of significant jaundice with p-value <0.001 was observed.[14] Rh incompatibility did not seem to increase the risk of developing pathological hyperbilirubinemia as per our study. This observation may be attributed to the fact that in our study there was only one new born with Rh incompatibility.

There are various methods used to predict the occurrence of pathological hyperbilirubinemia in neonates. These include the percentile based hour specific bilirubin nomogram generated by Bhutani and colleagues, use of transcutaneous bilirubinometer, End-tidal carbon monoxide measurement, screening of cord blood albumin levels and screening of cord blood bilirubin levels.[15-17] Several studies have been published on the usefulness of cord blood bilirubin in predicting the occurrence of significant neonatal hyperbilirubinemia which are presented below.

In 1986, Rosenfeld analysed a group of 108 full-term newborns according to their risk of developing severe hyperbilirubinemia and concluded that babies with an umbilical cord blood bilirubin level of lower than 2 mg/100 ml had a 4% chance of developing significant jaundice, in comparison with a 25% chance presented by the ones with levels higher than 2 mg/100ml. In addition, the latter group also presented a higher chance of needing to undergo phototherapy.[18]

Knudsen A in 1989 established that if the cord bilirubin was below 20 µmol/l, 2.9% became jaundiced, as

opposed to 85% if the cord bilirubin was above 40 µmol/l. Furthermore, 57% of jaundiced infants with cord bilirubin above 40 µmol/l required phototherapy, but only 9% if the cord bilirubin was 40 µmol/l or lower (0.008), with p-value <0.001 which was significant.[11]

Amar Taksande et al, showed that the cord bilirubin level >2 mg/dl has a sensitivity 89.5%, specificity 85%, negative predictive value of 98.7% and positive predictive value of 38.8% and p-value 0.000, which was significant and is in correlation with the present study.[5] Zakia Nahar et al, showed that the cord bilirubin level ≥2.5 mg/dl has a sensitivity 77%, specificity 98.6%, with negative predictive value of 96%.[19]

In the present study, there was significant association between cord blood bilirubin and the development of pathological hyperbilirubinemia with the p-value of 0.000 similar to the observations made by above mentioned studies. By ROC curve analysis critical cord bilirubin level ≥2.50 mg/dl with high sensitivity and high specificity was selected. The probability that a neonate with cord bilirubin ≥2.50 mg/dl would later have pathological hyperbilirubinemia (positive predictive value) was 98.0%.

The negative predictive value, the probability of not having hyperbilirubinemia given a cord bilirubin lower than 2.50mg/dl was 45.1%. If a child develops hyperbilirubinemia, the probability that the cord bilirubin was ≥2.50 mg/dl was 84.1% (sensitivity). Given a non-hyperbilirubinemic child, the probability that the cord bilirubin was <2.50 mg/dl was 88.5% (specificity). In the other studies mentioned above the cord blood bilirubin level predicting the occurrence of clinically significant hyperbilirubinemia ranged from 2 to 2.5 mg/dl which is similar to our result.

Most of the previous studies analysed the correlation between cord blood total bilirubin levels and a defined level of serum total bilirubin levels considered as pathological hyperbilirubinemia. Whereas in the present study we assessed the ability of cord blood bilirubin level to be a tool for screening the risk of development of subsequent pathological hyperbilirubinemia as defined by the current guidelines for managing neonatal hyperbilirubinemia.

CONCLUSION

This study concludes that there is a significant correlation between the development of pathological hyperbilirubinemia in neonates and cord blood total bilirubin levels. Cord blood total bilirubin levels ≥2.5mg/dl has a good predictive ability to predict the occurrence of pathological hyperbilirubinemia as defined by the current operational guidelines. In an era focusing on quality improvement and wise utilization of medical care resources, one underutilized resource in early neonatal care is umbilical cord blood. This study reiterates cord blood bilirubin estimation as a personal profile for the new born. Hence cord blood bilirubin estimation helps in assuring safe early discharge of the new born.

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