

To Study the Predictive Value of Umbilical Cord Blood Bilirubin Levels Term Neonates as Marker of Neonatal Hyperbilirubinemia

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ABSTRACT

Background: Infants who are clinically jaundiced in the first few days are more likely to develop hyperbilirubinemia. Hyperbilirubinemia is the most common medical problem in newborn infants. It is the most important cause for hospital readmissions during the early neonatal period and also the cause for neonatal morbidity.

Objective: In this prospective study we are going to evaluate the predictive value of cord bilirubin level for identifying term neonates for subsequent hyperbilirubinemia.

Materials and Methods: Cord bilirubin levels at birth and subsequently serum bilirubin levels at 72 h were assessed in 291 neonates. The cutoff value was estimated beyond which there was significant hyperbilirubinemia. Statistics employed include quantitative data which is expressed in terms of mean and SD and qualitative in terms of proportions and receiver operator characteristic curve used to find cut-off value and to find sensitivity and specificity.

Results: The cutoff value of cord bilirubin >2 mg/dl had sensitivity and specificity of 77.97 and 56.90%, respectively, with positive predictive value of 31.51 and negative predictive value of 91.03% for subsequent hyperbilirubinemia.

Conclusion: To decrease the significant burden of untreated severe neonatal jaundice, cord serum bilirubin can be used as a screening tool to identify the neonatal jaundice in term and this prediction of neonatal hyperbilirubinemia has widespread implication especially in our country where there are limited resources.

Keywords: Hyperbilirubinemia, Neonatal morbidity, cord serum bilirubin

INTRODUCTION

Hyperbilirubinemia also known as “jaundice” is yellowish green pigmentation of the sclera and skin caused by an increase in bilirubin production or a defect in bilirubin elimination. It is one of the most common problems in neonatal period estimated to occur in nearly 60 % of the term infants in the first week of life. Under normal circumstances, the level of indirect reacting bilirubin in umbilical cord serum is 1-3mg/dl and rises at a rate of less than 5mg/dl/24hrs. Thus jaundice becomes visible on the 2nd – 3rd day (36 to 72hrs) usually peaking by the 3rd day of life. Among preterm babies, age of onset of physiological jaundice is similar to term babies, it may manifest earlier but never before 24 hours of age. The maximum intensity of jaundice is reached on the 5th or 6th day and may persist upto 14 days ^[1]. Worldwide neonatal hyperbilirubinemia is one of the major issues in clinical practice. Most of the newborns have mild jaundice but all the newborns should be carefully monitored because of the potential toxicity of bilirubin. Severe untreated neonatal hyperbilirubinemia can lead to acute bilirubin encephalopathy (ABE) ^[2]. Every newborn develops an unconjugated serum bilirubin level >1.8 mg/dl initial week of life after birth. The concentration of total serum

bilirubin (TSB) is the standard method to evaluate hyperbilirubinemia in neonates. When the TSB concentration will be more than 5 mg/dl, yellow coloration of skin could be visible which indicates jaundice. 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 [3]. When serum bilirubin in term newborn is ≥ 12 mg/dl at 24 hrs of life, 15 mg/dl at 48 hrs, and 17 mg/dl at 72 hrs then it is said to be neonatal hyperbilirubinemia [4].

The American Academy of Pediatrics (AAP) recommends that newborns discharged within 48 hours should have a follow-up visit after 2-3 days to detect significant jaundice and other problems. In developing countries like India, this recommendation is not practical due to limited follow up facilities. Early treatment of jaundice with phototherapy is effective, simple and cheap as compared to the treatment of severe neonatal jaundice with exchange transfusion which is time consuming, costly, associated with complications and requires skilled personnel. Thus the early prediction of jaundice offers an attractive option for picking up babies at risk of Neonatal Hyperbilirubinemia. Many investigators have tried to find a simple marker to predict hyperbilirubinemia and its subsequent course in newborns like cord bilirubin estimation, bilirubin estimation during 6 to 24 hours of age, pre-discharge hour specific bilirubin estimation and transcutaneous bilirubin measurement. Cord Bilirubin levels are easy to perform and may offer an attractive predictive marker for hyperbilirubinemia occurring later on [5]. Prompt treatment of hyperbilirubinemia is crucial, as well as assessment of the risk of development of hyperbilirubinemia. Thus, the investigation of parameters that might help in predicting the development of

significant hyperbilirubinemia is justifiable and necessary.

Over the years many efforts have been made to identify the newborns likely to develop severe hyperbilirubinemia. Various strategies have been studied in order to reduce the duration of hospital stay for normal babies and identify those who may need prior treatment before developing significant hyperbilirubinemia. Follow up within 1-2 days of early discharge; umbilical cord bilirubin levels; routine pre-discharge serum bilirubin levels; transcutaneous bilirubin measurement and clinical assessment of risk factors of jaundice are various strategies to predict significant hyperbilirubinemia [5]. Others have studied the relevance of cord blood albumin levels, hydrogen peroxide levels, alfa fetoprotein levels & alkaline phosphatase levels as predictors of significant neonatal hyperbilirubinemia.

In current scenario, it's desirable to identify term newborns, who are at risk of developing significant hyperbilirubinemia much before clinical diagnosis, in order to implement early treatment and minimize the risk of bilirubin dependent brain damage. There are very few studies done in India to find out predictive values of bilirubin in cord blood in term newborns as marker for hyperbilirubinemia.

However, the aim of the present study is to see the predictive cord blood bilirubin levels in term neonates as marker of neonatal hyperbilirubinemia.

MATERIAL AND METHODS

Present prospective study was conducted in the Department of Pediatrics, Chalmeda Anand Rao Institute of Medical Sciences, over a period of 12 months from January 2019 to December 2019. The study was approved by Institutional Ethics Committee. Written consent was obtained from the parents or legal guardians before recruitment. Only full-term (gestational age >37 weeks) neonates were recruited to the study. Neonates of both genders delivered consecutively by any type of delivery in the

Department of Obstetrics and Gynecology were prospectively enrolled in the study. Neonates with aggravate hyperbilirubinemia, birth weight <2000 g. The samples of 219 patients were enrolled in the study.

INCLUSION CRITERIA

- All healthy newborns with gestational age ≥ 37 weeks
- Both genders
- From any mode of delivery
- Apgar score of more than 7 at fifth minutes of life

EXCLUSION CRITERIA

- Newborns who later develop significant illness requiring NICU admission like Septicemia, meningitis ARDS etc
- Newborns with major congenital malformations.
- Conjugated hyperbilirubinemia
- Newborns with Gestational age < 37 weeks

Statistical Analysis

Result was analyzed using statistical software statistical package for the social sciences 25. Qualitative data were expressed in frequency and percentage, while quantitative data were expressed in mean \pm standard deviation. Receiver operating characteristic (ROC) curve were used to analyze the pattern of bilirubin levels.

RESULTS

Maximum newborns (91.10%) had birth weight between 2.5-3.99kgs. 8.20% of newborns had birth weight below 2.5kgs Only 0.70% newborns had birth weight >4kgs. Among 219 newborns enrolled in the study, 47.1% were female babies and 52.9% were male babies. B group was the most common blood group (86 newborns). Caesarean Delivery was observed in most of the patients shown in bellowed table no. 1

With ROC analysis, (Figure 1), the mean cord bilirubin level was 1.64 ± 0.62 mg/dl. The area under curve was 0.745. The mean total bilirubin at 72 h was 10.57 ± 3.38

mg/dl. There were 48 newborns who had serum bilirubin >14 mg/dl at 72 h (Table 2).

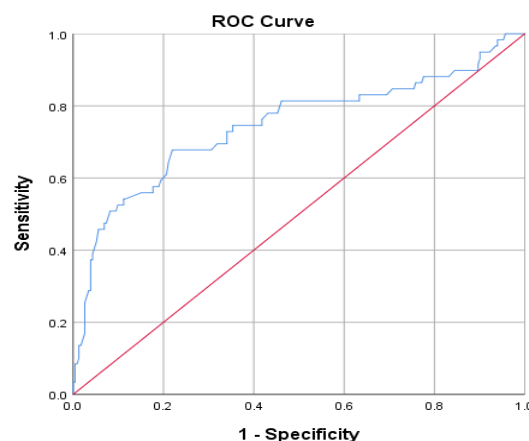


Figure 1: Receiver operating characteristic curve showing association of cord bilirubin levels and requirement of phototherapy at 72 h of life

Table 1: The baseline characteristics of enrolled mothers and newborns.

Variable	Frequency (%) / Mean \pm SD
Sex	
Male	154(52.9)
Female	137(47.1)
GA (Mother)	38.15 \pm 0.948
Birth Weight(Baby)	2.95 \pm 0.39
≤ 2.499 Kg	24(8.20%)
2.5 - 3.99 Kg	265(91.10%)
≥ 4 Kg	2(0.70%)
Cord Bilurubin	1.64 \pm 0.62
Total Sr. Bilirubin	10.57 \pm 3.38
Mode of Delivery	
Vaginal Delivery	72(24.80%)
Ceaserean Delivery	218(75.20%)
Cord Bilurubin	
<2	145(49.8)
≥ 2	146(50.2)
Blood Group (Mother)	
A	77(26.5)
B	84(28.9)
AB	49(16.8)
O	81(27.8)
Blood Group (Baby)	
A	84(28.9)
B	86(29.6)
AB	44(15.1)
O	77(26.5)

Table 2 : Relationship between cord bilirubin and serum bilirubin at 72 h

Serum Bilirubin	Cord Bilirubin Level		Total
	<2	≥ 2	
<14	137(47.1)	106(36.4)	243(83.5)
>14	8(2.7)	40(13.7)	48(16.5)
Total	145(49.8)	146(50.2)	291(100)

The cord bilirubin of >2 had sensitivity and specificity of 77.97% and 56.90%, respectively, with positive predictive value of 31.91% and negative predictive value of 91.03. The strength of

association of cord bilirubin >2.02 mg/dl and requirement of phototherapy at 72 h was found to be significant ($p<0.001$).

DISCUSSION

The present prospective observational study undergone among 291 term babies born in a tertiary care hospital. The objective was to identify whether umbilical cord serum bilirubin values soon after birth could predict the risk of significant neonatal hyperbilirubinemia in early neonatal period.

High cord bilirubin levels among neonates who later become severely icteric is compared to cord bilirubin levels in non-jaundiced neonates. The above was based in the fact that the mechanisms of development of jaundice in early post-natal period had already occurred in late fetal life. Mostly all fetal bilirubin is unconjugated, due to a decreased ability of the fetal liver to conjugate bilirubin.

Cord blood estimation was chosen because it is a non-invasive method and the results are available within few hours after birth. Thus, the babies at risk for developing hyperbilirubinemia can be detected at birth in a non-invasive way if the neonate leaves the hospital within the first few postnatal days. In addition, the use of cord blood bilirubin values may help predict infants with low risk for hyperbilirubinemia and minimize an unnecessary prolongation of hospitalization^[6-8]. In a study by Taksande et al., prevalence was 9.5% only because the cutoff for significant hyperbilirubinemia on 3rd day of life was taken as 17 mg%^[9].

In present study, newborns who developed significant hyperbilirubinemia male:female ratio was 1.18:1 54.23% (32/59) newborns who developed significant hyperbilirubinemia were male babies and 45.76% were female babies.

Male gender is a known risk factor for hyperbilirubinemia. In a study done by Naranget al, incidence of hyperbilirubinemia in males was 64.2%. In similar study done by Alpay et al, 37(61.6%) newborns who developed

significant hyperbilirubinemia were male babies.^[10-12]

In the present study, ROC curve analysis with cord bilirubin levels >2 mg/dl had area under the curve of 74.5%. Sensitivity was found to be 77.97% while specificity was found to be 56.90%. The above indicated that at the bilirubin value of >2 mg/dl, the test would predict more true positives than true negatives. Several studies also reported the importance of cord bilirubin levels at birth in prediction of hyperbilirubinemia. Taksande et al found that the cord serum bilirubin values >2 mg/dl has a sensitivity 89.5%, specificity 85%, negative predictive value of 98.7% and positive predictive value of 38.8% which is similar to that of the present study.^[9]

Ahire et al. predicted the serum bilirubin >3 mg/dl on the first day of life had 100% sensitivity of predicting subsequent jaundice at 48 h of life with bilirubin levels >10.58 mg/dl^[13]. Knupfer et al. observed that serum bilirubin >1.74 mg/dl on the first day of life had 97% sensitivity of predicting a subsequent serum bilirubin levels >16 mg/dl at 72 h of life.^[14]

In our study, the cord bilirubin level >2 mg/dl had the highest sensitivity (77.97%), and this critical bilirubin levels had a very high negative findings, a critical cutoff level of cord bilirubin was 2 mg/dl predicted 78% of newborn who developed jaundice. However, the cord bilirubin <2 mg/dl did not completely exclude the development of significant hyperbilirubinemia. Only 2.7% of newborn with cord bilirubin levels of <2 mg/dl developed jaundice. A 91.03% of negative predictive value suggests that the measurement of cord serum bilirubin can help in identifying those newborn who are unlikely to require further evaluation and intervention.

The strength of present study, bilirubin cut off value was determined using receiver operating characteristic analysis and the test is highly significant (P value <0.0001). The data was not evaluated on

nomograms. This would better reflect the geographic, cultural and various demographic characters distinctive to present population. Study also has some limitations like other studies. Some of the neonates did not turn up in outpatient department for follow-up and the access to sample collection at 72 h of life was denied by some of the parents which made it difficult to consider them as cases. The sample size was small which causes difficulty in creating significant relationships between the two values of bilirubin levels.

CONCLUSION

Cord blood bilirubin values can be used as a predictor of neonatal jaundice. The present study shows Cord bilirubin level >2 mg/dl had more sensitivity and specificity can be taken as a cutoff value above which, a neonate would develop hyperbilirubinemia.

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