Original Article www.pimr.org.in

DOI: 10.47799/pimr.1003.18

Early Predictors of Hyperbilirubinemia in Full Term Newborn

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Date of Submission: 06/06/2022 Date of Review: 25/08/2022 Date of Acceptance: 17/08/2022

ABSTRACT

Introduction: Predictive markers enabling Pediatricians to identify which neonates will develop jaundice have mandatory for prevention of severe hyperbilirubinemia. We aim to determine the critical cord bilirubin and albumin levels and bilirubin/albumin ratio.

Design: This prospective study included131full-termnewborns. Hyperbilirubinemia can be predicted by Measuring cord bilirubin , albumin and bilirubin/albumin ratio.

Results: Neonatal hyperbilirubinemia (67.8%) had cord albumin level less than or equal to 2.7gm/dl. CordBilirubin/albumin ratio cutoff value greater than 0.62 had a good predictive value with a sensitivity of 100% and specificity of 88.36%,

Conclusion: neonatal hyperbilirubinemia predictors are Cord BILIRUBIN/ALBUMIN ratio , serum bilirubin and albumin.

KEYWORDS: hyperbilirubinemia, albumin, bilirubin

INTRODUCTION

Hyperbilirubinemia may occur without obvious reason in infants, and few may develop kernicterus. [1]The prevention of poor outcomes necessitates early detection of neonates who are at risk of developing significant hyperbilirubinemia. Discharging early to term new born is common practice nowadays it has advantages such as prevention of nosocomial infections and maternal-infant bonding. The American Academic of Pediatrics (AAP) recommends that newborns discharged within 48 h of life should have a follow-up visit after 48 to 72 h for any significant jaundice or other problems. [2]In developing countries follow-up visits after early discharge is questionable as many mothers do not return owing to the distance and other reasons. Predictive markers enabling Pediatrician to identify neonates discharged within 48 hare at higher risk of hyperbilirubinemia. Several studies have shown the ability of cordbilirubin and albumin and first-day bilirubin levels to be tools for screening of subsequent neonatal hyperbilirubinemia. [3]The bilirubin/albumin(B/A) ratio is considered a measurable property for free bilirubin (Bf) and in the management of hyperbilirubinemia. It offers the pediatrician to measure the bilirubin binding to albumin until unbound bilirubin or albumin binding reserve can be measured clinically with accuracy. [4]There are no documented studies evaluating the significance of cord B/A ratio in early identifying neonatal hyperbilirubinemia. The present study helps determining the cord serum bilirubin and albumin level and bilirubin/albumin ratio that identify hyperbilirubinemia in term neonates.

MATERIAL AND METHODS

This is a prospective study that included 131 neonates born in Prathima institute of medical sciences Hospital Karimnagar, from July 2018 to June 2019. All neonates involved were full term (Gestational age ranging 38 to 41 weeks) of both gender without any illness or major congenital malformations. The neonates with conditions that could aggravate hyperbilirubinemia (sepsis, RDS, asphyxia , diabetic mothers,or IUGR) or cholestatic jaundice were excluded from the study. Detailed history taking including maternal medical diseases , consanguinity, siblings by hyperbilirubinemia, mode of delivery, Oxytocin use, Apgar score, and type of feeding. Complete physical examination of neonates was done with assessment of gestational age as per new Ballard score and birth weight by growth curves. The use of photo therapy or exchange transfusion were recorded as indicated by the American Academy of Pediatrics guidelines for management of neonatal hyperbilirubinemia. [2]Cord venous blood were collected after clamping the umbilical cord with clamps ,The collected blood sample was tested for serum albumin level using Bromocresol Green method (BCG), serum Bilirubin(Total and Direct) level by Colormetric method, hemoglobin concentration using cell counter T 660, and Reticulocytic count done manually after staining with Brilliant Cresyl Blue and examined under Oil Emersion lens. Blood groups (ABO, Rh) were determined for neonates and mothers. Follow up was done on 1,3 and 5 days by assessment of serum bilirubin level for all cases.Hyperbilirubinemia was defined as the need of pho-

totherapy or exchange transfusion based on the American Academy of Pediatrics guidelines for management of neonatal hyperbilirubinemia. [2]

Ethical approval: The study was approved by the Ethics Committee of Pediatric Department ,Prathima institute of medical sciences karimnagar.

SAMPLE SIZE

Sample size calculation was based on the sensitivity of cord blood Albumin and Bilirubin in predicting the occurrence of Indirect Neonatal Hyperbilirubinemia. We studied the independent cases and controls with 1 control(s) per case. We took cord blood samples from all newborns 18 cases with significant indirect neonatal hyperbilirubinemia. The other samples without indirect neonatal hyperbilirubinemia were considered. We used uncorrected chi-squared statistics to evaluate this null hypothesis with setting type I error probability to 0.05. Calculations were done using Flahault equation [5]

STATISTICAL ANALYSIS

Data were entered on the computer using Microsoft Office Excel Software program (2010) ,then transferred to the Statistical Package of Social Science Software (SPSS) program, version 23 to be statistically analyzed. facts were briefly prepared using range, mean, standard deviation, median and percentiles for quantitative variables or frequency and percentage for qualitative ones. Comparison between groups using Manne Whitney test for quantitative variables while comparison for qualitative variables through Chi square or Fisher's exact test. Receiver operating characteristics (ROC) curve analysis to explore the discriminant ability of different cord measures in predicting neonatal jaundice . P <0.05 assumed as statistically significant. Graphs were used.

RESULTS

The study population included 131 neonates with a mean gestational age of 37.5 (0.61) weeks and a mean birth weight of 2.5(0.3)kg. Of these , 21 neonates(16%) developed hyperbilirubinemia (group 1) and 110 neonates(84%) did not(group2). Among the 21 neonates who developed neonatal hyperbilirubinemia, 12 were males and 9 were females; 15 cases were delivered by caesarean section and 4 cases received oxytocin for induction of labor. As regards the 110 neonates who did not develop significant neonatal hyperbilirubinemia, 54 were males and 56 were females; 82 cases were delivered by caesarean section and 28 cases received Oxytocin for induction of labor. Group 1 infants had statistically significant higher cord reticulocyte count [(3.3 1.3%) versus (2.1 0.8%)] than those in group 2 (p < 0.001) with a diagnosis of Rh incompatibility in 9.7% of the cases (2patientsout of 21) and ABO incompatibility in 14.3% of the cases (3 out of 21 patients) in group 1 versus 1.4% and 4.1% respectively in group 2. Cases with significant neonatal hyperbilirubinemia (group 1)had statistically significantly higher cord total bilirubin [(2.40.2mg/dl)versus(1.40.4mg/dl)] (p<0.001) , significantly lower cord albumin [(2.80.3gm/dl) versus (3.30.5gm/dl)](p<0.001), And significantly higher cord B/A ratio [(0.860.14)versus(0.44 -0.19)]with p<0.001.Table 1

Total serum bilirubin levels measured on days 1, 3 and 5 were higher (P<0.001)in group1 [(8.8 1.5 mg/dl versus 4.1 1.2 mg/dl)], [(15.4 2.5 mg/dl versus 6.72.8 mg/dl)] and [(13.8 5.1mg/dl versus 4.4 2.4 mg/dl)] respectively. The cases with significant hyperbilirubinemia were all managed with phototherapy whether intensive (82.1%) or conventional (17.9%). intravenous immunoglobulin (IVIG) was indicated in 14.3% of the cases and none required ex-change transfusion. Among the neonates that developed significant hyperbilirubinemia,67.9% had low cord serum albumin <2.8 mg/dl, 25% had it ranging between 2.8 and 3.3 mg/dl and only 7% had a level over 3.3 mg/dl. For the prediction of neonatal hyperbilirubinemia, cutoff value of cord serum bilirubin of 1.84 mg/dl was chosen on the basis of the ROC curve analysis. The cord serum bilirubin of 1.86 had a sensitivity of 100%, specificity of 87.1%, positive predictive value of 59.4% and negative predictive value of 100% in the prediction of neonatal hyperbilirubinemiaFigure 1

The optimum cut off value for serum albumin as shown by the ROC curve for newborns with significant indirect hyperbilirubinemia was 3 gm/dl with a sensitivity of 85.6% and specificity of 67.4%, negative predictive value of 96.2% and positive predictive value of 33.34% (Fig. 2) (Table 2). Also, the cord B/A ratio cut off value of >0.61 had a good predictive value for neonates that developed significant neonatal hyperbilirubinemia with a sensitivity of 100%, specificity of 88.4%, positive predictive value of 62.2% and negative predictive value of 100.0%. The area under the curve is 0.936 indicating high significanceTable 2

	CORD TOTAL BILIRUBIN	CORD ALBUMIN	CORD B/A RATIO
SENSITIVITY	100%	86.7%	100%
SPECIFICITY	87.2%	67.2%	88.3%
PPV	>1.82	<2.9	>0.60
NPV	<0.001	<0.001	<0.001

Table 2: Comparison between ROC curves

DISCUSSION

The need for early prediction of hyperbilirubinemia has become very important for identifying those neonates at risk of neonatal jaundice considering the severe neurological morbidities caused by bilirubin toxicity. The Present AAP

	GROUP 1(n Z 21)	GROUP 2 (n Z 110)	P VALUE
CORD HAEMOGLOBIN(gm/dl)			
Range	15.3 - 18.5	14 - 18.2	0.07
Mean±SD	16.5±1	16±0.9	
Median	16.3	16.2	
CORD RETICULOCYTE			
Range	1 - 7	1 - 4	<0.001
Mean±SD	3.4±1.3	2.1±0.8	
Median	3	2	
CORD TOTAL BILIRUBIN(mg/dl)			
Range	1.9 - 3	0.6 - 2.6	<0.001
Mean±SD	2.4±0.2	1.4±0.4	
Median	2.4	1.3	
CORD DIRECT BILIRUBIN(mg/dl)			
Range	0.2 - 0.7	0.1 - 0.5	0.0029
Mean±SD	0.3±0.1	0.3±0.1	
Median	0.3	0.2	
CORD ALBUMIN(gm/dl)			
Range	2.4 - 3.6	1.8 - 4.8	<0.001
Mean±SD	2.8±0.3	3.3±0.5	
Median	2.7	3.3	
CORD BILIRUBIN/ALBUMIN RATIO			
Range	0.62 - 1.2	0.14 - 1	<0.001
Mean±SD	0.86±0.14	0.44±0.19	
Median	0.88	0.4	

Table 1: Comparison of laboratory data of cases with significant and insignificant neonatal Hyperbilirubinemia

guidelines for management of hyperbilirubinemia term and near-term newborns recommends total bilirubin concentration/albumin ratio in addition to the TBC ;In the present study the mean cord B/A ratio was higher in neonates who developed neonatal jaundice than in those who did not (0.860.14versus0.440.19). ROC curve of cord B/A ratio demonstrated that a cut off value 62mg/dl had a good predictive value with a sensitivity of 100 0%, specificity of 88 4%, Predictive value of 62.3%. They were lower in neonates who did not develop significant hyperbilirubinemia (1.40.4mg/dl) versus those who developed it (2.4-0.2mg/dl). This is consistent with Ipek et al. who found that the mean cord serum bilirubin was also lower in babies who developed neonatal hyperbilirubinemia versus those who did not (1.640.41mg/dl versus 2.050.9mg/dl [6]In the absence of an available assay for free Bilirubin ,the Bilirubin/Albumin ratio B/A might provide a better estimate of Bilirubin factor because It contains 2 of the 3 factors determining Bf (TSB ,albumin and the albumin binding affinity) [7]However, the value of B/A ratio may be reduced because of some factors that influence the intrinsic albumin-bilirubin binding constant [8]and the presence of other plasma constituents that bind unconjugated bilirubin [9]The current study demonstrated significant difference between the cord serum bilirubin levels in the studied groups . Few studies reported lower mean cord serum bilirubin levels in neonates who developed hyperbilirubinemia. [3] [10] [11]ROC curve analysis of cord total bilirubin demonstrated that a cutoff value1.84 mg/dl had a good predictive value with a sensitivity of 100.0%, specificity of 87.1%, and positive predictive value of 59.6%. Raj purohit

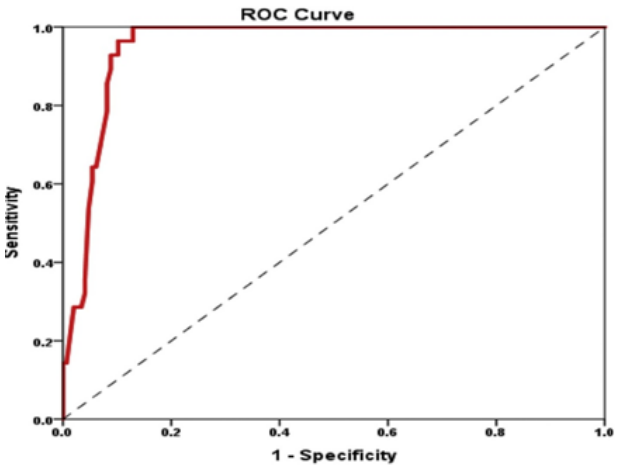

Figure 1: ROC curve analysis to explore the discriminant ability of cord total bilirubinin predicating significant hyperbilirubinemia

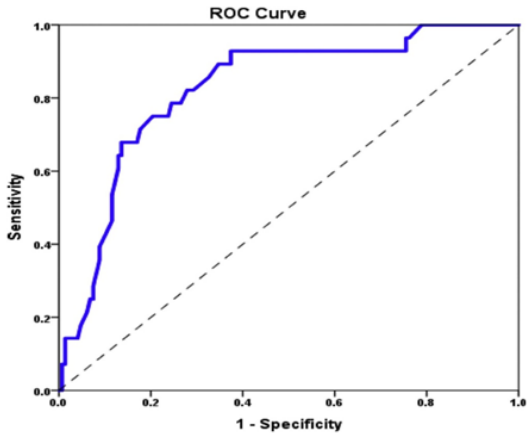

Figure 2: ROC curve analysis to explore the discriminant ability of cord albumin in predicating significant hyperbilirubinemia

et al. reported a cord bloo bilirubin cut off value > 2 mg/dl had a sensitivity of 90%, specificity of 53.89%, positive predictive value of 17.8%and negative predictive value of 98% in predicting the risk of neonatal hyperbilirubinemia [12] Knoopfer et al. reported that a cord bilirubin cut off level of 1.76 mg/dl for predicting hyperbilirubinemia had a sensitivity of 70.3% and a negative predictive value of 65.6%, and they concluded that cord blood bilirubin could be used as an early predictor of neonatal jaundice. Dwarampudi and Ramakrishna reported that neonates with cord bilirubin level less than 2 mg/dl were in a safe zone with respect to development of subsequent hyperbilirubinemia.

Albumin helps in hepatic transportation of bilirubin and its clearance. There was a significantly higher cord serum albumin level in neonates who did not develop neonatal hyperbilirubinemia in comparison tothose who did. 67.9% of cases that developed significant neonatal hyperbilirubinemia had cord albumin level 2.8gm/dl . Burtis et al. stated that the lower limit for serum albumin in term babies was 2.8gm/dl ;and Reshad et al.found that in the term group, 19(61.2%) newborns with serum albumin <2.8g/dl developed neonatal hyperbilirubinemia. Low albumin decreases bilirubin clearance and increases hyperbilirubinemia .The ability of albumin for predicting neonatal hyperbilirubinemia was assessed in the present study and similar results reported by several researchers [3] [11]that found cases with low albumin less than 2.8gm/dl developed hyperbilirubinemia requiring phototherapy and sometimes exchange transfusion Receiver operating characteristics analysis demonstrated that albumin cutoff value 3.0mg/dl had a good predictive value with a sensitivity of 85.6% and specificity of 67.4%. However, Rajpurohit et al. reported a lower cord blood albumin level (2.6 gm/dl) to have a sensitivity of 80% and specificity of 86.67% in predicting the risk of neonatal hyperbilirubinemia. [5]Aiyappa and colleagues found the sensitivity of cord albumin to detect hyperbilirubinemia to be 71.8%, while specificity was 65.1% [13]Similarly,Pahuja et al. stated a fair predictive value of cord albumin for development of neonatal hyperbilirubinemia of 75%. Also, Dwarampudi and Ramakrishna suggested that cord albumin levels(>2.8gm/dl) were probably safe to discharge a neonate in respect to the risk of development of neonatal hyperbilirubinemia. With lack of studies done on cord B/A ratio as an early predictor of significant hyperbilirubinemia, this work opens the window for further studies to be performed in this field, and we are aware that larger scale trial including preterm neonates are needed. In present study serum B/A ratio proved prediction of neonatal hyperbilirubinemia. Neonates with either total bilirubin 1.84 mg/dl, albumin 3.0 gm/dl or B/Aratio0.61,were at higher risk of developing indirect neonatal hyper-bilirubinemia. These can be considered possible early predictors for neonatal hyperbilirubinemia . We recommend measurement of cord serum albumin, albumin and bilirubin/albumin ratio in all healthy term babies at delivery to prevent dangerous consequences of hyperbilirubinemia as a cut bilirubin encephalopathy.

CONCLUSION:

Neonatal hyperbilirubinemia predictors are Cord BILIRUBIN/ALBUMIN ratio , serum bilirubin and albumin. To identify which neonates will develop jaundice have mandatory for prevention of severe hyperbilirubinemia and to determine the critical cord bilirubin and albumin levels and bilirubin/albumin ratio

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How to cite this article: Haq Hu, Raghunath SV, Amithkumar C. Early Predictors of Hyperbilirubinemia in Full Term Newborn. Perspectives in Medical Research. 2022;10(3):100-104
DOI: 10.47799/pimr.1003.18

Sources of Support: None: , Conflict of Interest: Nil: