Original Article

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Paediatrics Section

Umbilical Cord Bilirubin as a Predictor of Neonatal Jaundice in Babies with ABO Blood Group Incompatibility versus without Incompatibility

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ABSTRACT

Introduction: Severe hyperbilirubinaemia cause long-term morbidity that can be prevented by early prediction of the development of significant jaundice by measuring Umbilical Cord Bilirubin (UCB).

Aim: To measure the predictability of UCB as an early marker of development of significant hyperbilirubinaemia, needing phototherapy.

Materials and Methods: The study was a prospective observational study conducted at Vinayaka Mission Medical College, Karaikal, Puducherry, India. A total of 50 babies born between February and August 2022 were included in the study. Bilirubin levels were obtained at birth by umbilical cord sampling and rechecked again at third or fourth day. Blood group incompatibility was defined as A or B blood group babies, born to O group mothers. Phototherapy was started when the bilirubin levels were above or upto 2 mg/dL below the cut-off for that patient as indicated by the curve for the risk group of the patient as per the American Academy of Paediatrics (AAP) guidelines. Phototherapy also was started if clinically indicated by visual assessment by Kramers rule.

Results: Results were analysed by Receiver Operating Characteristics (ROC) curve analysis, for measurement of sensitivity and specificity for predicting significant neonatal hyperbilirubinaemia. ROC curve anlaysis revealed that a cut-off of UCB of 1.95 mg/dL resulted in an accepatable sensitivity and specificity for predicting significant jaundice requiring phototherapy at 75% and 68% respectively. ROC curve analysis revealed that Area Under Curve (AUC) for UCB levels of all babies for predicting jaundice requiring treatment was 0.765, 95% CI 0.592 to 0.937. Separate ROC analysis showed that, AUC for UCB for predicting phototherapy in babies with blood group incompatibility (AUC 0.80, 95% CI 0.418 to 1.00) was more significant than the AUC for babies without blood group incompatibility (AUC 0.490, 95% CI 0.29 to 0.69).

Conclusion: UCB has high predictability for significant jaundice requiring phototherapy. The prediction is more when babies with blood group incompatibility is considered compared to babies without blood group incompatibility.

Keywords: Hyperbilirubinaemia, Morbidity, Phototherapy

INTRODUCTION

Clinical jaundice occurs in 85% of term and preterm newborns [1]. Physiologic jaundice and other causes like breast feeding jaundice and breast milk jaundice accounts for the majority of cases. Other causes include immune and non immune haemolytic anaemias, genetic disorders of bilirubin clearance, metabolic and endocrine disorders. ABO incompatibility usually occurs in A or B blood group infants born to O group mothers. It doesn't usually occur in A or B group infants born to B or A group mothers respectively because the antibodies are of the IgM type [2]. Bilirubin is the end product of haeme catabolism which circulates in the blood after being reversibly bound to albumin [3]. Upon uptake in the liver, bilirubin is conjugated by the enzyme Uridine Diphosphate (UDP) glucuronyl transferase and excreted in the bile. Increased production of bilirubin accounts for the physiologic jaundice. In addition, in babies with ABO incompatibility in utero haemolysis occurs due to transplacental transfer of IgG antibodies. Hence, it is predicted that measurement of UCB at birth can detect a significant proportion of infants, which later develop pathologic jaundice requiring phototherapy.

Neonatal hyperbilirubinaemia is a common condition in newborn and severe hyperbilirubinaemia can lead to long-term morbidity, if not recognised and treated early [1]. Several methods are proposed to predict the likelihood of developing significant hyperbilirubinaemia. Of these UCB, Umbilical Cord Albumin (UCA) and bilirubin-albumin ratio are proposed as useful indices [4]. Though measurement of free bilirubin (which is an ideal indicator for development of hyperbilirubinaemia and neurotoxicity) is not available, other indices like Umbilical Blood Bilirubin (UBB), UCA and bilirubin-albumin ratio can serve as a useful surrogate markers for developing significant hyperbilirubinaemia. It was found long before that, there is an association between UCB and peak postnatal bilirubin levels [5-7]. Categorisation of infants into high and low-risk groups based on the UCB levels helps to focus attention on high-risk groups thereby preventing early discharge and preventing complications of hyperbilirubinaemia [8]. Infants categorised into low risk groups can be discharged early, thereby preventing unnecessary care [9]. The use of a non invasive test like UBB and other risk factors like maternal Asian race and gestational age can be used to predict severe hyperbilirubinaemia risk [10]. Though UCB samples are routinely done in babies born to Rh negative mothers, its application in babies at risk of ABO incompatibility especially in Indian population needs to be studied. The study was aimed at examining the usefulness of UCB in predicting the need for phototherapy, in babies with ABO blood group incompatibility vs without incompatibility.

MATERIALS AND METHODS

The study was conducted as a prospective observational study at a tertiary care hospital at Vinayaka Mission Medical College, Karaikal, Puducherry, India, from February to August 2022. The study was approved by the Institutional Ethical Committee (IEC) of Vinayaka Mission Medical College and Hospital, Karaikal (VMMC/PEAD/2022/July /06). Sample size was calculated as per convenience sample.

Inclusion criteria: Term babies (>37 weeks), born by either natural delivery or Caesarean section were included in the study.

Exclusion criteria: Preterm babies and babies with other risk factors like Rh incompatibility sepsis, cholestasis, respiratory distress syndrome, meconium aspiration syndrome and babies with haemodynamic instability were excluded from the study.

Study Procedure

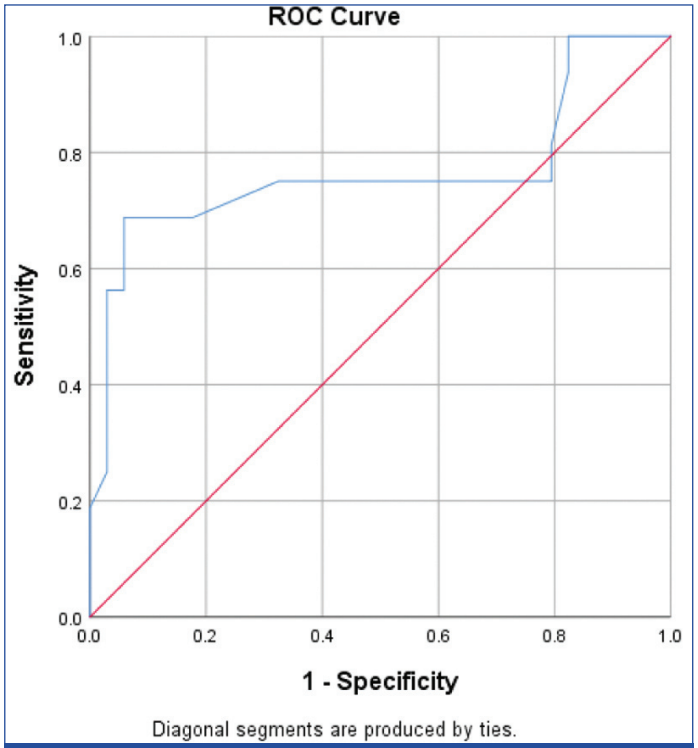
Term babies without these risk factors born during the time period were enrolled and umbilical blood samples were collected after obtaining informed consent from the parents. Samples were processed for bilirubin and blood grouping and typing. Mothers blood grouping and Rh typing was also done. In addition, data like gestational age and parity were also obtained. Bilirubin levels were obtained for babies on 3rd or 4th day as per clinical judgement of jaundice by Kramers rule [11]. Peak postnatal bilirubin levels were noted on the third or fourth day, which was better correlated with UCB levels. Significant hyperbilirubinaemia is defined as bilirubin levels requiring phototherapy as per AAP guidelines for phototherapy [6]. Bilirubin levels above 15 mg/dL or 17 mg/dL for babies without blood group incompatibility on the 3rd or 4th day respectively and levels above 13 mg/dL or 14 mg/dL, for babies with ABO incompatibility on the 3rd or 4th day respectively were started on phototherapy. Phototherapy was initiated, if Total Serum Bilirubin (TSB) was greater than the cut-off for that patient, as indicated by the curve for the risk group of the patient. Phototherapy was also started, if TSB was upto 2-3 mg/dL below the cut-off. Also, phototherapy was also started, if clinically indicated by visual assessment as per Kramers rule.

STATISTICAL ANALYSIS

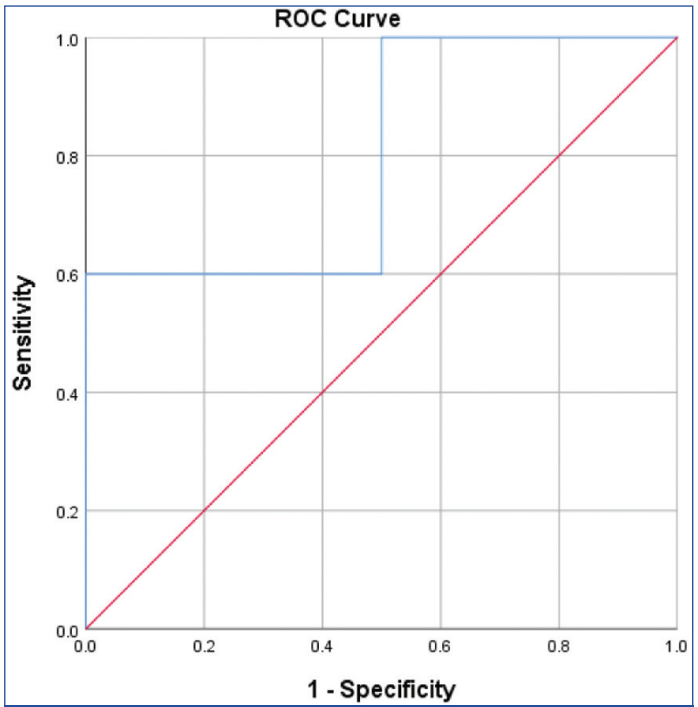
Statistical analysis was done using ROC curve analysis for sensitivity and specificity of UBB for predicting significant hyperbilirubinaemia requiring phototherapy. Separate ROC curves for babies with and without blood group incompatibility were obtained. Continuous variables were analysed by Independent t-test for comparing means. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 26.0.

RESULTS

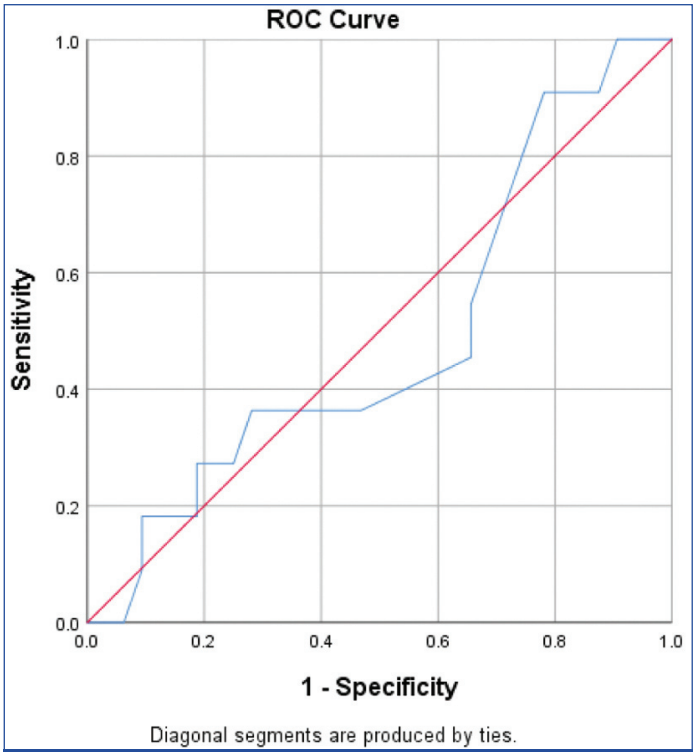
A total of 95 babies were delivered, between February 2022 to August 2022. Of these, 50 babies were included in the study after exluding preterm babies and babies with other risk factors. Among the included cases, 17 mothers had O group. Of these, seven babies had blood group incompatibility. Blood group incompatibility was said to be present when A or B blood babies born to O group mothers. The mean UBB levels of all babies was 1.91±0.51 mg/dL). The mean UBB levels of 43 babies without blood group incompatibility was 1.84±0.51 mg/dL, whereas the mean UBB levels of seven babies with incompatibility was 2.35±0.20 mg/dL. Babies with blood group incompatibility had significantly higher cord bilirubin than babies without blood group incompatibility (p-value <0.05). About 16 babies were treated with phototherapy. Of these, 11 babies had no blood group incompatibility whereas five babies had ABO incompatibility. The mean UBB for babies requiring phototherapy was 2.26±0.47 mg/dL, whereas the mean UBB for babies not requiring phototherapy was 1.75±0.45 mg/dL. Babies requiring phototherapy had significantly higher UBB levels, than babies not requiring phototherapy (p-value <0.001). ROC curve analysis revealed that there was significant predictability of UBB for phototherapy (AUC 0.765, 95% CI 0.592 to 0.937). The analysis showed that a cut-off of 1.95 mg/dL has a sensitivity of 75% and specificity of 68% in predicting the need for phototherapy. Separate analysis of ROC curves for babies with and without blood group incompatibility revealed that, the predictability for phototherapy is lost in babies without blood group incompatibility (AUC 0.490, 95% CI 0.29 to 0.69), when compared to babies with blood group incompatibility (AUC 0.80, 95% CI 0.418 to 1.00). UCB levels are not predictive for phototherapy when babies without blood incompatibility were considered separately, as shown by the ROC analysis [Table/Fig-1-3]. This could be due to smaller sample size, of the present study.



[Table/Fig-1]: ROC analysis for predictability of phototherapy in all babies including babies with and without blood group incompatibility (AUC 0.765, 95% CI 0.592 to 0.937).



[Table/Fig-2]: ROC curve analysis for predictability of phototherapy in babies with blood group incompatibility (AUC 0.80, 95% CI 0.418 to 1.00).



[Table/Fig-3]: ROC curve analysis for predictability of phototherapy in babies without blood group incompatibility (AUC 0.490, 95% CI 0.29 to 0.69).

DISCUSSION

The present study demonstrated that, UCB could be a useful predictor for later development of significant jaundice requiring phototherapy, especially in babies with blood group incompatibility. Increased foetal bilirubin production due to haemolysis and decreased clearance of foetal bilirubin by maternal circulation results in elevated bilirubin levels in umbilical cord blood at delivery [11]. A combination of transcutaneous bilirubin and UCB can increase the prediction of hyperbilirubinaemia considerably [12]. Another study found that, post-test probability of UCB increased exponentially in different subgroups characterised by Direct Antiglobin Test (DAT) and ABO incompatibility results [13]. The prediction for phototherapy increased significantly with elevated UCB levels in babies at risk of blood group incompatibility and haemolytic disease [6]. Early prediction of significant hyperbilirubinaemia by UCB, could minimise duration of hospitalisation post delivery [9].

When cord blood bilirubin was combined with gestational age and maternal race, the predictability for babies developing severe hyperbilirubinaemia improved significantly, than when UCB was used alone [10]. Substantial differences in reported sensitivity and specificity of UCB may be due to different cut-offs used in these studies. UCB could be predictive for development of severe jaundice and need for phototherapy in at risk babies like ABO incompatibility [6]. This could minimise prolonged hospital stay and delay in diagnosing and managing significant neonatal jaundice [8]. A significant difference in UCB could not be found in babies with Rh incompatibility treated with phototherapy vs babies without Rh incompatibility treated with phototherapy. In another study, which compared babies with and without blood group incompatibility, it was found that, it is a better predictor of jaundice due to haemolytic disease, than jaundice due to other causes [14].

Cord blood albumin ≤3 mg/dL had a sensitivity of 85.7% and specificity of 67.3% in predicting significant hyperbilirubinaemia [4]. They also concluded that, cord bilirubin/albumin ratio cut-off value >0.61 had sensitivity of 100% and specificity of 88.4% in predicting significant hyperbilirubinaemia. Similar study inferred that, cord blood albumin cut-off of 3.17 g/dL and 0.719 had sensitivity and specificity of 40.8%, 34.8% for development of hyperbilirubinaemia requiring phototherapy. Also, they showed that cord blood bilirubin/cord blood albumin ratio cut-off of 0.719 had sensitivity and specificity of 97.4% and 62.6%, respectively. Hence, it is shown that, cord blood albumin and cord blood bilirubin/albumin ratio together with cord blood bilirubin, could be better predictors than cord blood bilirubin alone for significant jaundice requiring treatment [15].

The UCB cut-off of >2 mg/dL had a sensitivity of 76.85% and specificity of 69.58%, in detecting hyperbilirubinaemia that develops in the first 48 hours [16]. However, the study had not done separate analysis for babies with and without blood group incompatibility [16]. Jones KDJ et al., found that predictive value of UCB for all cause jaundice was strong in babies with blood group incompatibility (AUC- 0.88), whereas it was weak (AUC- 0.46) in babies without blood group incompatibility [14].

Other parameters like cord blood Erythropoietin (EPO) and cord blood Reticulocyte Count (RC), when combined with CBB were also sensitive and specific, for neonatal hyperbilirubinaemia [17]. There was also a significant correlation between cord bilirubin and cord haemoglobin [18]. They also found that cHb (cord Haemoglobin) and vaginal delivery were correlated significantly with bilirubin levels >9 mg/dL. Hence, they suggested that a UCB should be added as one of the risk factors for neonatal hyperbilirubinaemia. In another study, it was concluded that, low umbilical cord bilirubin <2.6 mg/dL could predict low risk of hyperbilirubinaemia and early discharge [19]. Sun G et al., found that UCB could be a significant predictor of neonatal jaundice [20]. Various studies have shown various cut-offs for UCB for prediction of significant jaundice with different sensitivities, specificities, positive predictive value and negative predictive value and is shown in [Table/Fig-4] [4,8,9,15-17,19,20].

Study	Sample size	UCB cut-off (mg/dL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Sharma IK et al., 2020 [15]	388	1.9	97.4	40.6	71.09	
Elfaragy MS et al., 2021 [17]	90	1.8	89	78		
Kardum D et al., 2021 [16]	1360	2	76.85	69.58		
Aktas S et al., 2019 [8]	418	1.67	82	99		
Ipek IO et al., 2021 [19]	350	1.7	78.57	54.76	6.75	98.4
Sun G et al., 2007 [20]	523	2	68.27		45.68	
Knüpfer M et al., 2005 [9]	1341	1.76	90			99.1
Khairy MA et al., 2019 [4]	175	1.84	100	87		
Present study 2023	50	1.95	75	68	48	81

[Table/Fig-4]: Umbilical cord bilirubin cut-off and their sensitivities and specificities for prediction of phototherapy/significant hyperbilirubinaemia across various studies [4,8,9,15-17,19,20].

Limitation(s)

The present study had limited sample size which was a major limitation. Also other parameters like umbilical cord albumin and bilirubin albumin ratio were not done. Rh incompatibility was excluded, since some mothers would not have been sensitised. Minor blood group incompatibility could not be ruled out, as testing for minor blood group antigens were not done.

CONCLUSION(S)

The study highlights the usefulness of UCB in predicting the need for phototherapy, especially in babies with blood group incompatibility. The present study in contrast to western studies has high prescription rates for phototherapy probably due to Asian ethnicity and high prevalence of breast feeding jaundice and other causes in the Indian population. To extrapolate the findings of the

study to the larger Indian population, more research involving larger samples are needed.

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