Section: Paediatrics

Original Research Article

CORD BLOOD BILIRUBIN AS A PREDICTOR OF SIGNIFICANT NEONATAL HYPERBILIRUBINEMIA IN ABO INCOMPATIBILITY

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Received : 18/04/2024
Received in revised form : 31/05/2024
Accepted :15/06/2024

Keywords:
Cord blood bilirubin, jaundice, direct Coombs test.

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DOI: 10.47009/jamp.2024.6.3.187

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (3); 912-916

Abstract

Background: Hyperbilirubinemia is a common neonatal problem in clinical practice. One of the major risk factors for significant neonatal jaundice is ABO isoimmunisation. Early identification of significant hyperbilirubinemia and needed interventions has become more difficult owing to early hospital discharge of newborn and thus neonatal jaundice has developed as a frequent reason for readmission. Early prediction of subsequent jaundice helps in prompt recognition of high risk newborn babies. Umbilical cord blood bilirubin value is an important predictor of jaundice in ABO incompatible neonates. **Aim:** To assess the role of cord blood bilirubin in predicting significant hyperbilirubinemia in ABO incompatible newborns and to identify the critical cut-off value of cord bilirubin for early prediction of significant jaundice. **Materials and Methods:** This Prospective study was conducted in a tertiary hospital. Umbilical Cord blood bilirubin and serum bilirubin at 48 hours of all ABO incompatible study participants were checked. Direct Coombs test was done for all babies. Results were analyzed statistically. **Result:** Out of 108 babies with ABO incompatibility 32.4% developed significant jaundice. The critical umbilical cord bilirubin cut off value was 1.98 for the prediction of significant neonatal jaundice (p value < 0.001) with 88.6% sensitivity and 78.1%specificity .50% of direct Coombs test positive ABO incompatible newborns developed significant hyperbilirubinemia, even though statistically not significant. **Conclusion:** Umbilical cord bilirubin was observed as a good predictor of significant hyperbilirubinemia in ABO incompatible neonates with critical cord bilirubin cutoff value obtained as 1.98. This study also showed direct Coombs test has no statistically significant association with neonatal jaundice in ABO isoimmunisation.

INTRODUCTION

Neonatal jaundice is a common condition in newborn babies, requiring medical attention. 60% of term and 80 % of preterm newborns develop hyperbilirubinemia in the first week of life.[1] In most newborns it is benign and physiological, however in some newborns hyperbilirubinemia may leads to chronic bilirubin encephalopathy (kernicterus), which is a permanent disabling neurologic condition featured by athetosis, complete or partial sensorineural deafness, upward gaze palsy and sometimes intellectual deficits.[2] This can be easily prevented by early identification and prompt intervention.

One of the major risk factors causing neonatal unconjugated hyperbilirubinemia is blood group incompatibility. ABO incompatibility occurs in about 15% of pregnancies, only <1% develop significant jaundice, requiring treatment. Very high bilirubin levels can be seen in healthy term newborns with ABO incompatibility even with negative direct Coombs test.[3] Early postnatal discharge of healthy term newborns, usually within 48 hours of life has become common now a days, which allows the family to return to their daily routine at the earliest and reduces the economic burden on them. However, neonatal jaundice is the commonest cause for readmission, which goes unnoticed in those discharged early.[4,5] The American Academy of Paediatrics (AAP) recommends that neonates, who are discharged within 48 hours of delivery should have a follow up visit after 2 to 3 days to detect significant jaundice. Such follow up is not feasible in all cases in our country due to parental noncompliance due to fear of multiple pricks,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

difficulty in accessing health care facilities, financial constraints and ignorance.[6]

Even with better understanding of neonatal jaundice and its risk factors, there is no universally accepted predictive measure available to identify newborns who are at risk of developing significant hyperbilirubinemia, especially in ABO incompatibility. Predictive measure of risk of development of significant jaundice can decrease the hospital stay for those who are at low risk and can prevent complications like kernicterus for those who are at high risk. Early prediction of jaundice using umbilical cord bilirubin level help to detect neonates who are at the risk of developing hyperbilirubinemia. Our study was a prospective study in term healthy newborns to evaluate the predictive ability of umbilical cord bilirubin for significant hyperbilirubinemia in ABO incompatibility.

Aim

To assess the role of cord blood bilirubin for the prediction of significant hyperbilirubinemia in healthy term neonates with ABO incompatibility.

Objectives

To detect the proportion of ABO incompatible term new-borns developing significant hyperbilirubinemia.

To identify the critical cut-off value of umbilical cord blood bilirubin for the prediction of significant hyperbilirubinemia

To assess the relation of Direct Coombs Test (DCT) with significant hyperbilirubinemia in healthy term neonates with ABO blood group incompatibility.

MATERIALS AND METHODS

Study Setting: Neonatology department of a tertiary care hospital in south India

Design: Prospective study

Study Population: All term babies of A or B blood group born to O blood group mothers (ABO incompatibility) delivered in a hospital after obtaining informed consent from parents.

Inclusion Criteria

All Term (≥37 weeks) AGA (appropriate for gestational age) healthy neonates with ABO incompatibility, delivered during the study period, with informed consent of parents.

Exclusion Criteria

Preterm babies, Small for gestational age babies, Babies with conjugated hyperbilirubinemia, Rhesus incompatibility, Neonatal sepsis and major congenital anomalies

Methodology

This was a hospital based prospective study. Umbilical cord blood bilirubin and direct Coombs test were done for all study participants immediately after birth. These babies were clinically followed up and serum total bilirubin measured at 48 hours. Total serum bilirubin obtained was compared with reference values in the treatment threshold graph by NICE guidelines. Predictability and critical cut off value of cord blood bilirubin was estimated using statistical analysis. Correlation of direct Coombs test with significant hyperbilirubinemia was also assessed. The study was approved by the ethical committee of hospital institution. No external funding was utilised for this study.

RESULTS

Out of 108 newborn babies in present study 55% were males and 45% were female babies. 48 % neonates enrolled were born to primigravida mothers and 52 % neonates were born to multigravida mothers. 45% of babies born with a birth weight ranging between 2.5 kg to 3 kg and 47% % were having a birth weight of >3 kg. 8% of them were low birth weight babies (birth weight <2.5 kg), but weight appropriate for gestational age (AGA). Gestational age of study participants were 37 weeks 0 days to 37 weeks 6 days in 31 babies and > 38 weeks in 77 babies.

Table 1: Distribution of study participants by mother's blood group.

Mothers blood group	Frequency	Percentage
O Positive	102	94.4%
O Negative	6	5.6%
Total	108	100%

Table 2: Distribution of the study participants by baby blood group

Baby Blood Group	Frequency	Percentage
A Positive	39	36.1%
B Positive	52	48.1%
A Negative	11	10.2%
B Negative	6	5.6%
Total	108	100%

Table 3: Incidence of direct Coombs test positivity among study group

DCT	Frequency	Percentage
Negative	82/108	75.9%
Positive	26/108	24.1%

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 4: Incidence of significant hyperbilirubinemia among study group

Significant hyperbilirubinemia	Frequency	Percentage
Absent	73/108	67.6%
Present	35/108	32.4%

Incidence of significant hyperbilirubinemia was 32.4 % in our study and all babies with significant hyperbilirubinemia received phototherapy. No neonates developed severe jaundice above exchange transfusion line in treatment threshold graph proposed by NICE guidelines and no babies received any other treatment like IVIG.

Table 5: Mean and standard deviation of participants of cord blood bilirubin and total serum bilirubin at 48 hours

	Minimum	Maximum	Mean	Std.deviation
Birth weight	2.32kg	4.05kg	3.01	0.39857
Cord bilirubin mg/ dl	1.07	4.0	1.97	0.52379
Total SBR at 48 hours mg/dl	1.40	20.40	10.69	3.49680

Table 6: AUC of cord blood bilirubin in predicting significant neonatal hyperbilirubinemia

Area	Standard error [a]	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.833	0.043	0.0001	0.749	0 .917

Table 7: Logistic regression analysis showing association between cord blood bilirubin and significant hyperbilirubinemia

	B	S.E.	Wald	P value	Odds Ratio	95% C.I for Odds Ratio	
						Lower	Upper
Cord bilirubin	3.600	0.795	20.516	0.0001	3.603	1.708	17.3

Table 8: Comparison of various studies showing cord bilirubin cut off value for the prediction of significant hyperbilirubinemia

Study	Year	Umbilical cord blood bilirubin cut off value(mg/dl)
Chen J Y et al,[3]	1994	>4
S Arora et al,[7]	2015	>2.16
E Krishnan et al,[10]	2016	>1.8
R Singh et al,[13]	2019	>2.19
K Panneerselvan et al,[8]	2018	>2.25

ROC analysis shows that cord blood bilirubin was a good predictor of significant hyperbilirubinemia with area under curve of 0.833 and it was found to be statically significant (p value 0.001). The cord blood bilirubin value of 1.98 mg/dl was found as a critical cut off value for prediction of subsequent significant hyperbilirubinemia with sensitivity of 88.6% and specificity 78.1%. The positive predictive value and negative predictive value were 56.3 % and 92.45 % respectively. Logistic regression analysis shows positive correlation between cord blood bilirubin and significant neonatal hyperbilirubinemia that neonates with high cord bilirubin showing increased risk for developing significant hyperbilirubinemia with an odds ratio of 3.6

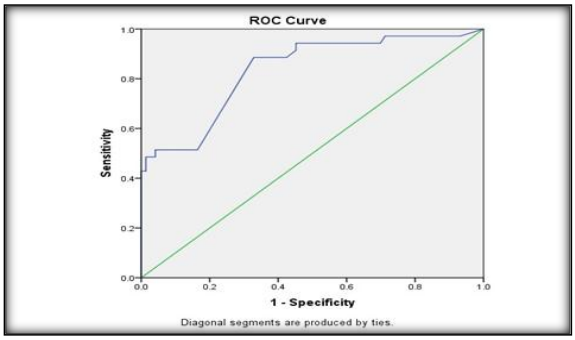

Figure 1: Receiver Operator Characteristic curve (ROC) – Predictive accuracy of cord bilirubin in significant neonatal hyperbilirubinemia

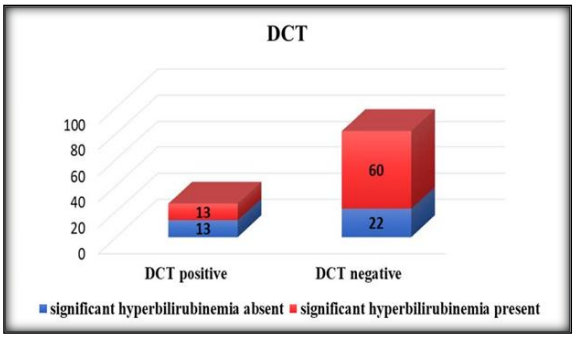

Figure 2: Association of Direct Coombs Test (DCT) with significant hyperbilirubinemia.

Occurrence of significant hyperbilirubinemia was almost double in DCT positive babies than DCT negative babies. But it was statistically insignificant (P value- 0.67) with a sensitivity of 37 % and specificity 82 %. The positive and negative predictive values are 50 % and 73 % respectively and the accuracy is 67.5 and found that DCT has no association with significant neonatal jaundice.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

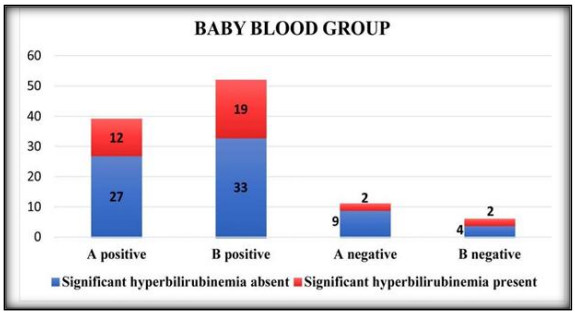

Figure 3: Association of baby blood group with significant hyperbilirubinemia

Significant hyperbilirubinemia in ABO incompatible babies was most among babies of B positive blood group with 36.5% incidence. The association was statistically insignificant with p value of 0.665

DISCUSSION

Our study showed that incidence of significant hyperbilirubinemia was 32.4 % in neonates of ABO incompatibility. Relatively similar results were reported by studies conducted by Sunita Arora et al[7], and K Panneerselvam et al [8],with 33% and 35 % of term neonates developed significant hyperbilirubinemia. H P Eldho et al [9] showed similar burden of significant hyperbilirubinemia (21 %). Much lower incidence of significant hyperbilirubinemia observed by E Krishnan et al [10] with incidence of 16.7 %. The difference in the percentage of significant jaundice could be due to different sample sizes. Moreover, serum total bilirubin measured at different postnatal hours and used different levels of serum bilirubin for diagnosing jaundice amongst the various studies could also be the possible reasons.

According to our study the cord blood bilirubin was a good predictor of significant neonatal hyperbilirubinemia with AUC of 0.833 and it was found to be statistically significant with p value <0.001. The cut off value of cord bilirubin for the prediction of significant hyperbilirubinemia was 1.98 mg/dl at which it had a sensitivity of 88.6 % and specificity of 78.1%. The positive predictive value was 56.3 % and negative predictive value was 92.45%. Higher negative predictive value in our study with a cord bilirubin cutoff of 1.98 mg/dl can eliminate unnecessary investigations in 92.45 % of babies who do not have the risk of developing significant hyperbilirubinemia. Prediction of significant hyperbilirubinemia in ABO incompatible neonates was a topic of research before 20th century itself and earlier studies by Graham H et al [11], Procianoy R S et al[12], and Chen J Y et al [3] recommended a high critical cord bilirubin level of 4 mg/dl. But many recent studies reported a lower cut off cord bilirubin value for the prediction of significant hyperbilirubinemia similar to our study. The study by Sunita Arora et al [7] found that cord bilirubin cutoff level as ≥2.16 mg/dl with 100% sensitivity and 100% positive predictive value and which has fairly high specificity (89.5 %) and negative predictive value (82.5 %) .E Krishnan et al [10] recommended cord bilirubin cut off of 1.8 mg/dl for the prediction of significant hyperbilirubinemia. Critical cord bilirubin value by R Singh et al [13] was 1.79 mg/dl with a high negative predictive value (94.06%), but with a low positive predictive value (27.04%). K Panneerselvam et al [8] found mean serum bilirubin on 4th day as 11.05 mg/dl and cord blood bilirubin cutoff value obtained was 2.25 mg/dl for prediction of significant hyperbilirubinemia with AUC 0.778 with sensitivity 84 % and specificity 71 %. Nevertheless, regardless of the critical cut off value all the studies had reported that umbilical cord bilirubin can be used for prediction of significant hyperbilirubinemia among the ABO incompatible newborns.

In the study, association of Direct Coombs test (Direct antiglobulin test) with significant hyperbilirubinemia was statistically insignificant with P value of 0.67 and with an accuracy of 67.5. Sensitivity and specificity were 37% and 82% respectively. Predictive values as 50% and 73% for PPV and NPV respectively. Levin D H et al [14] and R Singh et al [13] also concluded as direct antiglobulin test was neither specific nor diagnostic for neonatal hyperbilirubinemia in ABO incompatibility. Study conducted by P Han et al [15] in Asian people found that Coombs test, maternal antibody titre, cord blood bilirubin and haptoglobin were of low predictive value for severe haemolytic disease of newborn due to ABO incompatibility and also it is not cost effective for screening in ABO incompatibility. Many studies like R Mehta et al [16] found a positive correlation between Direct Coombs test with significant hyperbilirubinemia.

Limitations

This study was single centred with limited sample size and only term healthy newborns were included. Confounding factors were not considered in our study

CONCLUSION

Umbilical cord bilirubin was observed as a good predictor of significant jaundice in neonates of ABO incompatibility with critical umbilical cord bilirubin cutoff value obtained as 1.98 (p value <0.001). Direct Coombs test (DCT) positivity was not associated with significant hyperbilirubinemia in ABO incompatible neonates and statistical significance was not substantiated. Incidence of significant neonatal hyperbilirubinemia was 32.4 % in ABO incompatible neonates.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556