Section: Paediatrics

Original Research Article

CORD BLOOD BILIRUBIN AS A PREDICTOR FOR NEONATAL HYPERBILIRUBINEMIA IN NEWBORNS WITH A SETTING OF ABO INCOMPATIBILITY

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Abstract

Background: The objective is to study the relation between cord bilirubin and neonatal hyperbilirubinemia in ABO incompatibility and to find a cut off of cord bilirubin which can be used as a predictor for neonatal hyperbilirubinemia in ABO incompatible neonates. **Materials and Methods:** 140 Healthy full-term newborns with A and B positive blood groups born to O positive mothers born in the Department of Paediatrics and Neonatology of Travancore Medical College, Kollam was enrolled in the study after attaining an informed consent from the parents of new-born. Demographic profile and relevant information including name, age, maternal complications if any, was collected by using a structured proforma, by interviewing the mother of the newborn. Gestational age was calculated using the New Ballards Score. Cord blood bilirubin and 72 hours serum bilirubin was estimated from serum samples. Proportion of significant hyperbilirubinemia was calculated and was compared with the cord blood bilirubin to obtain a cut off value for the prediction of neonatal hyperbilirubinemia. Significant jaundice was defined as total serum bilirubin ≥15mg/dl at 72 hours of life. **Result:** 45.7% of neonates with ABO incompatibility developed neonatal hyperbilirubinemia. There was no statistical significance noted in development of neonatal hyperbilirubinemia in regards of baby sex, blood group, gestation age, birth weight or parity of mother. Cord bilirubin of ≥1.6mg/dl was found as a reliable cut off for the prediction of neonatal hyperbilirubinemia with a sensitivity of 89%, specificity of 80%, positive predictive value of 79% and negative predictive value of 90%. **Conclusion:** There was increased incidence of neonatal hyperbilirubinemia in ABO incompatibility. Cord bilirubin, being a non-invasive, simple test can be used as a reliable predictor for neonatal hyperbilirubinemia. Cord bilirubin levels ≥1.6mg/dl can be used as a predictor for the development of neonatal hyperbilirubinemia in ABO incompatible babies in our hospital.

INTRODUCTION

Jaundice is one of the commonest problems that can occur in a newborn. Many at times it is physiological in the newborn because liver is not mature enough to handle the bilirubin. The neonates have about 1% of uridine diphospho glucuronosyl transferase (UDPGT) activity as that of an adult.[1] Apart from this there is an increased load of bilirubin in neonates as they have a higher circulating erythrocyte volume, a shorter mean erythrocyte life span and a larger early labelled bilirubin peak.[2] This hyperbilirubinemia is due to unconjugated bilirubin which is toxic to central nervous system. More than two thirds of all newborns appear jaundiced clinically because at some point during the first week of life almost every newborn has a total serum bilirubin (TSB) level of > 1 mg/dl, the upper limit of normal for an adult. Approximately 85% of all term newborns and most premature infants develop clinical jaundice. Also, 6.1% of well term newborns have a maximal serum bilirubin level 12.9 mg/dL. A serum bilirubin level 15 mg/dL is found in 3% of normal term babies.[3] Hyperbilirubinemia is one of the commonest causes of admission to hospital in the neonatal period amongst term babies in all settings.[4-6] Prevention of serious complications depends on effective early treatment, but clinically significant jaundice may not develop until one or more days after delivery. Hospital readmission for neonatal hyperbilirubinemia is a cause of concern among clinicians in neonatal departments. Current practice, which usually promotes early discharge after delivery, may introduce delays in recognition and initiation of medical therapy.[7,8] Identification of

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biomarkers that could be measured within a few hours following birth, which robustly predict impending jaundice, would represent a significant advance.

ABO incompatibility is the major reason for immune haemolytic disease of newborn. Various studies have shown ABO incompatibility occurs in 15-20% of deliveries and have double the risk to develop jaundice requiring treatment.

Though, the relationship between cord blood bilirubin and neonatal hyperbilirubinemia has been already established, no extensive studies for the same with ABO setting was done in our area. Early identification of neonatal hyperbilirubinemia in ABO Setting will help in early prediction leading to decrease in hospital stay and better prevention of complications which prompted the need for the study.

MATERIALS AND METHODS

It was a prospective study conducted in the Department of Paediatrics and Neonatology, Travancore Medical College, Kollam. All healthy term newborn babies with blood group A or B positive born to mothers with O positive blood group born in our department was taken for study by simple random sampling. Inclusion criteria was healthy full term newborn of blood group A or B positive born to consented mothers with O positive blood group for a period of 18 months. Exclusion criteria was Rhesus blood factor incompatibility, Babies with O positive blood group, preterm babies, significant illness requiring NICU admission, major congenital malformations, chronic maternal illness (like DM) and those who didn't give consent for follow up.

520 babies of mothers with O blood group was screened for ABO incompatibility of which 140 Healthy full term newborns with A and B positive blood groups born to O positive mothers was enrolled in the study after attaining an informed consent from the parents of new-born. Demographic profile and relevant information including name, age, maternal complications if any, was collected by using a structured proforma by interviewing the mother of the newborn. Gestational age was calculated using the New Ballads Score. Cord Blood bilirubin and 72 Hour serum bilirubin was estimated from serum samples. Proportion of significant hyperbilirubinemia was calculated and compared with the cord blood bilirubin to obtain a cut off value for the prediction of neonatal hyperbilirubinemia. Total serum bilirubin of ≥15mg/dl was taken as significant hyperbilirubinemia at 72 hours of life. Collected data was statistically analyzed.

RESULTS

520 babies of mothers with O blood group were assessed for ABO incompatibility and identified 140 babies with ABO incompatibility. Prospective clinical study consisted of 140 healthy term newborns. Incidence of neonatal hyperbilirubinemia in our study population is 45.7%. 40.7 % of mothers in my study was <25 years of age, 34.3% was between 25-30 years, 6.6% of mothers was between 35-40 years of age. Healthy mothers with O group were included. Primigravida were 45.7 (n=64) and Multigravida constituted 54.3 % (n=76).45.7% of babies in the study was delivered by normal vaginal delivery (n-64) and 54.3% was delivered by LSCS delivery. Male babies 43.6% (n- 61) and female babies 56.4%(n-79). 24.3% of neonates in the study was between 37-38 weeks of gestation, 48.6% between 38-39 weeks of gestation and 27.1% between 39-40 weeks. Babies with birth weight between 2.5-3.0 kg were 54(38.6%); between 3.01-3.5 kg had 74 babies (52.9%) and above 3.5 constituted only 12 (8.6%). In our study there is a increase in the number of female babies with neonatal hyperbilirubinemia. However, there is no statistical significance found for the same.

Mean cord bilirubin of the study was 1.65(range-0.81-3.64, SD-0.4). Mean total bilirubin at 72 hours was 11.08(range- 1.44-20.76, SD- 0.99). Mean of Cord bilirubin of babies who developed neonatal hyperbilirubinemia- 1.95(SD- 0.41). Mean of cord bilirubin of babies who had no neonatal hyperbilirubinemia – 1.43(SD- 0.24). Cord bilirubin levels are high in babies who developed neonatal hyperbilirubinemia.

Cut off value of cord bilirubin for prediction of neonatal hyperbilirubinemia in our study is 1.62mg/dl. The value can predict neonatal hyperbilirubinemia with a sensitivity of 89.06% and specificity of 80.26%. Positive predictive value of the test is 79.17% and the negative predictive value is 89.71%.

Table 1: CORD BILIRUBIN AND 72 HOUR BILIRUBIN PROFILE OF THE STUDY

Variable	N	Minimum	Maximum	Mean	SD
Cord total bilirubin	140	0.81	3.64	1.6535	0.43446
Cord direct bilirubin	140	0.02	0.82	0.3606	0.14528
Cord indirect bilirubin	140	0.29	3.28	1.2921	0.46395
Total bilirubin at 72 hours	140	1.44	20.76	11.0838	2.97499
Total direct bilirubin at 72 hours	140	0.01	7.00	0.5170	0.99354
Total indirect bilirubin at 72 hours	140	0.41	20.14	10.5448	3.16043

Table 2: CORD BILIRUBIN PROFILE IN BABIES WITH NEONATAL HYPERBILIRUBINEMIA

	Group	N	Mean	SD	Independent sample t test	p value
	Yes	64	1.9519	.41542	9.258	0.001

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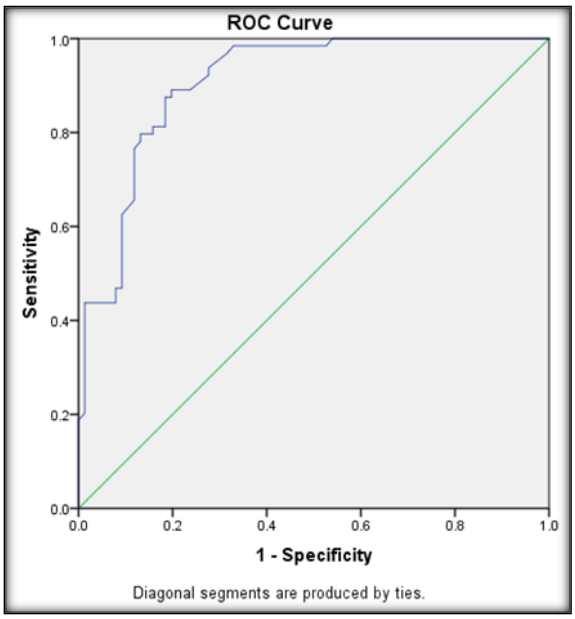
Cord total bilirubin	No	76	1.4286	.24351		

Area under the curve (AUC)	0.908
95% CI	0.860 to 0.955
p value	0.001

Diagnostic measures	**Value**
Sensitivity	89.06
Specificity	80.26
True Positive	57
True Negative	61
Positive Predictive Value	79.17
Negative Predictive Value	89.71



DISCUSSION

The most common cause of blood group incompatibility in neonates causing neonatal hyperbilirubinemia is ABO incompatibility. The appearance of jaundice is the main clinical presentation. Approximately 50% of cases seen in first born. In our study we tried to find out a reliable cut off of cord bilirubin levels which can be used for practical purpose as a screen for babies who might develop neonatal hyperbilirubinemia. Cord bilirubin is a non-invasive way and results are available within few hours. Hence, the testing can be done in low resource areas also instead of invasive test.

The diagnosis of ABO haemolytic disease depends on the clinical, serological and biochemical findings in the newborn. Hydrops fetalis in association with ABO incompatibility is extremely rare and has been reported in two cases (12). Microspherocytosis is the most prominent feature of ABO haemolytic disease. Coombs test in ABO incompatible infants does not necessarily indicate disease. It has been observed that 1/3rd of babies born to O group mothers had a positive DAT. Development of safe marker will help in preventing fatal outcome due to Jaundice.

To address this issue AAP recommends that follow up should be provided to all neonates discharged less than 48 hours after birth by a health care professional in an office, clinic, or at home within 2 to 3 days of discharge. Compliance with this is questionable, especially in rural areas.

A reliable method of anticipating neonatal hyperbilirubinemia is absent in our setting in less invasive methods. A reliable predictor if present can reduce the hospital stay and decrease the risk of missing cases of neonatal hyperbilirubinemia and kernicterus.

Many factors are used as predictor in ABO incompatibility. Coombs test, serum bilirubin, cord bilirubin, reticulocyte count, IgG anti A or anti B titre can be used.

Our study was conducted on term neonates with A and B blood group delivered to O positive healthy mothers. Development of neonatal hyperbilirubinemia was studied and a cut off value for prediction of the same in cord bilirubin was tried to establish.

There are many studies which showed relation of cord bilirubin and neonatal hyperbilirubinemia. The cut off values used by different authors is different. Technical errors in estimating bilirubin, sample size and the cut off value for neonatal hyperbilirubinemia are the main causes of this variation. Hence the need to define a cut off for our locality was all the more important.

In our study jaundice was seen equally in both OA and O-B incompatibilities. In our study O-B blood group had more frequency of neonatal hyperbilirubinemia, but was not statistically significant. The degree of hemolysis and incidence and severity of neonatal hyperbilirubinemia among O-A and O-B in studies is inconsistent.[11] Kaplan et al study using end-tidal carbon monoxide corrected for room air (ETCOc) as predictor for neonatal hyperbilirubinemia showed more significant jaundice in O-B blood groups.[12]

Neonatal hyperbilirubinemia showed increase frequency in females, but this was also again not statistically significant in our study. Again, the review of literature of the same is inconsistent with some studies showing increased significant jaundice in male babies and some studies showing increased

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frequency of neonatal hyperbilirubinemia in female babies. In a retrospective analysis of 254 cases Dufour D R found that sex, race, gravidity, birth weight and blood type of the infant did not have any significant relationships to outcome.[13,14] In our study also none of these variables were statistically significant. There was no statistical significance noted in development of neonatal hyperbilirubinemia in association with maternal parity or gestational age or weight of the neonates.

The mean cord bilirubin in babies with neonatal hyperbilirubinemia is 1.95mg/dl and in babies with no neonatal hyperbilirubinemia 1.4 mg/dl. Thus, the cord bilirubin levels are higher in babies who developed neonatal hyperbilirubinemia.

In our study cord bilirubin levels >1.62 predicted neonatal hyperbilirubinemia with a sensitivity of 89% and specificity of 80%. Positive predictive value is 79% and negative predictive value is 89.7%. There was statistically significant relation between cord bilirubin and neonatal hyperbilirubinemia with a p value of 0.001.

Summary

The study group consisted of 140 full term neonates delivered in our hospital. Cord blood bilirubin and Total Serum Bilirubin at 72 hours of age was estimated for all neonates. Incidence of significant jaundice in our study population is 45.7%. Female were slightly more affected than the male newborns in the significant jaundice group. But this was not statistically significant. The incidence of significant jaundice was more in B-blood group, but with no statistical significance. There were no statistical significant differences with the risk of hyperbilirubinemia in association with gender, gestational age, birth weight and blood group. Mean cord bilirubin level was 1.65±0.4 mg/dl. Mean total bilirubin at 72 hours of post-natal age was 11±3mg/dl. There was a positive correlation between cord bilirubin and third postnatal day serum bilirubin. Using cord bilirubin level of ≥ 1.6mg/dl, Hyperbilirubinemia can be predicted with sensitivity of 89%, specificity of 80 %, and positive predictive value of 79% and negative predictive value of 90% Healthy term babies with ABO incompatibility with Cord Blood Bilirubin <1.6 mg/dl are unlikely to require further evaluation and intervention hence these newborns can be discharged with assurance to parents. The babies who are discharged with a Cord Blood Bilirubin level ≥ 1.6 mg/dl should have unfailing frequent follow-ups in the postnatal 1st week. A clearly written description of neonatal hyperbilirubinemia including risks, what to look for, and when to call or bring the infant back should be given to parents whose babies are discharged early. CBB<1.6mg/dl seems a "cost effective" screening method for early discharge of newborns.

CONCLUSION

ABO incompatibility has become the forerunner cause of immune hemolytic disease of newborn. This is mainly due to increased RHD alloimmunization with anti- D prophylaxis. 15- 25% of pregnancies have ABO incompatibility according to various studies and in this every 10th newborn with ABO incompatibility develops disease requiring treatment. Early identification of these neonates who are at risk of developing neonatal hyperbilirubinemia by simple test is very important and can help in preventing bilirubin induced neurological outcomes.

As the negative predictive value of using the cord bilirubin is nearly 90%, it shows that this test can be used to identify the neonates who are unlikely to develop neonatal hyperbilirubinemia and thus not requiring close monitoring. Babies with cord bilirubin levels more than 1.6 should be monitored more frequently to identify neonatal hyperbilirubinemia and thus intervening earlier.

Thus, cord bilirubin being a simple noninvasive test can be used as an initial screen for babies at risk of developing neonatal hyperbilirubinemia and can be used to reduce unwanted hospital stays. It also helps to not to miss out on babies as the raised cord bilirubin will raise a red flag sign to paediatricians, making us more vigilant.

Abbrevations:

CBB- Cord Blood Bilirubin

DAT- Direct Antiglobulin Test

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