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Original Research Article

Correlation of cord blood bilirubin and neonatal hyperbilirubinemia in the setting of ABO incompatibility

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ABSTRACT

Background: Neonatal hyperbilirubinemia (NHB) is the most common clinical condition requiring evaluation and treatment in neonates. Umbilical cord bilirubin measurement is a cheap, readily available, non-invasive procedure which helps in predicting the developing of hyperbilirubinemia in newborns. The aim of the study was to determine the correlation between cord blood bilirubin and subsequent development of clinically significant NHB in ABO incompatibility at 24 hours of life.
Methods: 120 healthy term inborn neonates with A, B or AB blood group born to healthy mothers with O blood group were enrolled in this prospective clinical study, during the study period of 12 months, from June 2020 till May 2021. Cord blood (2 ml) was collected from placental side of cord and blood group and total and direct serum bilirubin were estimated. Venous blood (2 ml) sample was collected from peripheral vein of the baby and total and direct serum bilirubin estimation was done at 24, 48 and 72 hours of life.
Results: During the study period, incidence of significant hyperbilirubinemia at 24 hours of age was 21.6%. Using cord bilirubin level of ≥3.5 mg/dl, hyperbilirubinemia can be predicted with sensitivity of 38.4%, specificity of 90.4% and positive predictive value of 52.6% and negative predictive value of 84.1%. Cord bilirubin and 24 hours postnatal serum bilirubin showed a positive correlation in this study.
Conclusions: From the results and observations of the present study, one can consider the umbilical cord blood to be an important predictor for the occurrence of significant hyperbilirubinemia in newborns subsequently.

Keywords: NHB, Cord blood bilirubin, ABO incompatibility, American academy of pediatrics, Jaundice, Kernicterus, Neonates

INTRODUCTION

NHB is the most common clinical condition requiring evaluation and treatment in neonates. It is a frequent cause of readmission during the first postnatal week of life.[1] Visible jaundice is seen in approximately 60% of term babies and 85% of preterm babies.[2]

NHB, if not detected early, may lead to bilirubin induced neurological dysfunction sequelae in healthy newborns. Newborns can be screened for bilirubinemia before getting discharged from hospital and thus lead to early detection of the newborns with excessive hyperbilirubinemia during the first week of life.[3]

ABO incompatibility is the most common cause of immune Hemolytic disease of newborn (HDN).[4,5] Various studies has shown ABO incompatibility occurs in 15-20% of all pregnancies, and have double the risk to develop jaundice requiring treatment, 5-10 times risk of exchange

transfusion, and it was in 1/10th of newborn that this incompatibility become manifested as HDN requiring treatment.[6] ABO incompatibility is one of the major cause of significant jaundice which occurs within the first 48 hours of neonatal period. So early detection of the jaundice and management is very important. Cord blood bilirubin can be one of the markers of early detection of hyperbilirubinemia at 24 hours of age.[7]

Since jaundice is the most common cause of hospital readmission, it is important to identify newborns at risk of hyperbilirubinemia. Some of the newborns with severe jaundice are at risk of developing potentially dangerous neurological damage like kernicterus.[8] Kernicterus in such newborns is preventable, provided excessive hyperbilirubinemia for age is promptly identified and appropriately treated.[9,10] Universal screening for severity of bilirubinemia before hospital discharge can predict, that special segment of the neonatal population which is at risk for excessive hyperbilirubinemia during the first week after birth.[11]

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.[12] This recommendation is not possible in our country due to limited follow up facilities in the community.

The incidence of hyperbilirubinemia depends on regional variations, ethnic makeup of the population, laboratory variability in the measurement of bilirubin, and the incidence of breastfeeding.[13-15] There are some simple markers to predict hyperbilirubinemia in newborns. Some of them which are used are transcutaneous bilirubin measurement and end tidal carbon monoxide measurement cord blood bilirubin estimation, predischarge hour specific bilirubin estimation.[11,16-20] Umbilical cord bilirubin measurement is a cheap, readily available, noninvasive procedure which helps in predicting the developing of hyperbilirubinemia in otherwise healthy newborns and thus aid in the decision of early discharge of newborn babies.[8] Cord blood bilirubin (CBB) concentration measures in utero hemolysis and represent a possible biomarker for severe hyperbilirubinemia secondary to hemolytic disease of newborn (HDN).[7]

The aim of the study was a prospective observational study to find out the correlation between cord blood bilirubin and significant NHB in the setting of ABO incompatibility at 24 hours of life.

METHODS

All healthy term inborn neonates with A, B or AB blood group born to healthy mothers with O blood group born in Jorhat Medical College, Jorhat, Assam during the time period from June 2020 till May 2021 were enrolled in the study. The study was conducted in department of pediatrics in association with department of obstetrics and gynecology, Jorhat Medical College, Jorhat, Assam.

Study type

The study type was prospective observational study.

Sample size

Considering the prevalence of ABO incompatibility cases in last 3 years in Jorhat Medical College and Hospital, the sample size for the present study was calculated as 120 by purposive sampling technique.

Inclusion criteria

We included only healthy term inborn neonates with ABO incompatibility: (a) babies with blood group A, B or AB positive born to mothers with blood group O positive; and (b) babies with blood group A, B or AB negative born to mothers with blood group O negative.

Exclusion criteria

Neonates with major congenital malformations or significant illness requiring NICU admission at birth were excluded from the study.

Ethical clearance

Ethical clearance was taken from the Institutional Ethics Committee (H) of Jorhat Medical College and Hospital, Jorhat.

Informed consent

All the parents of the study participants were given an explanation of the study and informed written consent was taken from parents before enrolment into the study.

Method of collection of data

Clinical data

Demographic profile and relevant information of all the babies included in the study were collected using a structured proforma by interviewing the parents. Gestational age was assessed by the Modified new Ballard score.

Babies were clinically assessed for age (hours/days), sex, gestational age, birth weight, previous jaundice in the family, day of onset of jaundice, pattern of feeding, fever and neurological symptoms like poor sucking, hypotonia and seizures.

All babies were clinically assessed twice daily for presence and extent of jaundice based on Kramer criteria and for the appearance of any other illness. Visual inspection of

jaundice was by examining a naked baby in bright natural light and in absence of yellow background. Thorough clinical examination of the baby was done with special emphasis on icterus, hepatosplenomegaly, extravasation of blood (cephalhematoma/sub-galeal bleed), excessive bruising, neurological signs of bilirubin induced neurological damage (BIND).

Laboratory data

Cord blood bilirubin was estimated, followed by serum bilirubin estimation in the neonate at 24, 48 and 72 hours of age.

Cord blood (2 ml) was collected from placental side by free flow of blood from cord in an EDTA vial and clot vial within 1-2 min of birth and subjected to following investigations-(a) blood group by test tube method; and (b) total and direct serum bilirubin by calorimetric method.

Venous blood (2 ml) sample was collected from peripheral vein of the baby at 24, 48 and 72 hours of life and subjected to following investigations.

Statistical analysis

Prospective statistical analysis has been carried out in the present study. Quantitative data were expressed as mean±standard deviation (SD). Qualitative data were expressed as number and percentage. Qualitative data were analyzed using Chi square (χ^2) test. Pearson's correlation coefficient (r) was used to measure correlation between quantitative variables. Significance was assessed at 5% level of significance (p value <0.05). The statistical analysis of all the data was performed using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 20.0 Chicago, SPSS Inc.) and Microsoft excel 2010.

RESULTS

In this study conducted in Jorhat Medical College and Hospital, during the study period from June 2020 till May 2021, 120 healthy term newborns with ABO incompatibility were enrolled. Cord blood bilirubin and total serum bilirubin at 24 hours of life were estimated for all neonates. Incidence of significant hyperbilirubinemia (TSB >10 mg/ dl at 24 hours of age) is 21.6% in this study population (Table 4).

In the study, 62 (51.6%) neonates were male and 58 (48.3%) neonates were female (Table 1). Babies weighing between 2.5-3.0 kg were 89 (74.1%), babies weighing between 3.01-3.5 kg were 26 (21.6%) and babies weighing above 3.5 constituted only 5 (4.1%) (Table 2).

Mothers with only O positive group were included in the study. Primigravida mothers were 64 in number (53.3%) and multigravida mothers were 56 in number (46.6%) (Table 3).

Out of 26 babies who developed significant jaundice in 24 hours of life, 18 babies received phototherapy and 8 babies have undergone exchange transfusion. In this study group, females were slightly more affected than the male newborns in the significant jaundice group which was found to be statistically not significant. A-blood group babies have higher incidence of significant jaundice than B or AB-blood group newborns (Table 5).

Significant statistical differences were not there between the cases who had cord bilirubin level <3.5 mg/dl and ≥3.5 mg/dl with respect to various factors that may be associated with the risk of hyperbilirubinemia, such as gender, gestational age, birth weight and blood group. Mean cord bilirubin level was 2.75 mg/dl while mean total bilirubin at 24 hours of postnatal age was 8.53 mg/dl.

Cord bilirubin and 24 hours postnatal serum bilirubin showed a positive correlation in this study (Figure 1).

Using cord bilirubin level of ≥3.5 mg/dl, hyperbilirubinemia can be predicted with sensitivity of 38.4%, specificity of 90.4%, and positive predictive value of 52.6% and negative predictive value of 84.1% (Table 6).

Table 1: Distribution of neonates according to sex.

Gender of neonates	N	%
Male	62	51.6
Female	58	48.3
Total	120	100.0

Table 2: Distribution of neonates according to birth weight.

Birth weight (kg)	N	%
2.50-3.00	89	74.1
3.01-3.50	26	21.6
3.51-4.00	5	4.1
Total	120	100.0

Table 3: Parity of mothers.

Parity	N	%
Primigravida	64	53.3
Multigravida	56	46.6
Total	120	100.0

Table 4: Significant jaundice in 24 hours of life among neonates.

Total	Neonates with significant jaundice in 24 hrs of life (N)	%
120	26	21.6

Table 5: Significant jaundice in 24 hours of life in relation to blood groups.

Blood group	N	P value
A (n=40)	11	27.5
B (n=51)	11	21.5
AB (n=29)	4	13.7

Table 6: Diagnostic predictability of cord blood bilirubin (CBB≥3.5 mg/dl) for significant hyperbilirubinemia in 24 hours of life.

Cord bilirubin	Significant jaundice in 24 hrs of life N (%)	Insignificant jaundice in 24 hrs of life N (%)	P value
≥3.5 (n=19)	10 (52.6)	9 (47.3)	
<3.5 (n=101)	16 (15.8)	85 (84.1)	0.00035
≥3.5 (n=19)	10 (52.6)	9 (47.3)	
Prediction parameters			%
Sensitivity			38.4
Specificity			90.4
Positive predictive value			52.6
Negative predictive value			84.1

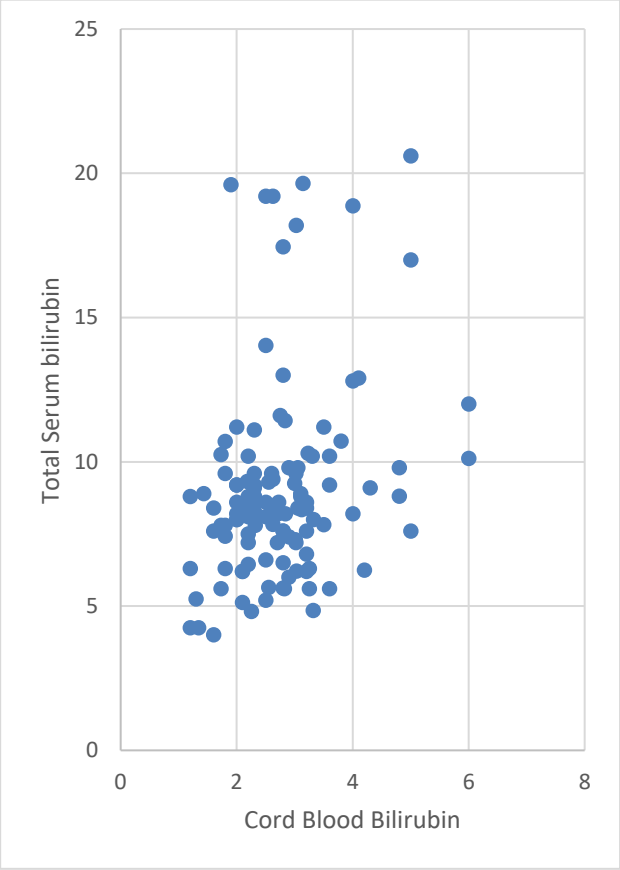

Figure 1: correlation of cord blood bilirubin with significant hyperbilirubinemia at 24 hrs of life.

DISCUSSION

The most common materno-fetal blood group incompatibility is ABO incompatibility which is usually a problem of the neonate rather than the fetus. Jaundice is the main clinical problem in the first 24 hours of life (icterus praecox). Approximately 50% of cases occur in the firstborn infant. Recurrence in subsequent infants doesn't have any predictable pattern. The study hypothesis was that a high serum bilirubin level at birth would also predict a high peak later in life. Here we chose cord bilirubin because it is a non-invasive method and the results are available within few hours after birth and estimation of bilirubin can be done even in resource limited rural areas.

This prospective observational study was done to determine the correlation of cord blood bilirubin with significant NHB in ABO incompatibility at 24 hours of life. In this study, peak serum bilirubin levels ≥10 mg/dl at 24 hours of age is considered as significant jaundice since specific treatment is considered at or above this level.

In the present study, 120 healthy term inborn neonates with A, B or AB blood group born to healthy mothers with O blood group in Jorhat Medical College and Hospital, were taken up for the study after fulfillment of the inclusion and exclusion criteria.

In the present study, 62 newborns were male and 58 were female. In a study conducted by Janaki et al, 21 newborns were male babies and 16 were female babies. In the present study, babies weighing between 2.5-3.0 kg were 89 (74%), between 3.01-3.5 kg were 26 (22 %) and babies weighing above 3.5 constituted only 5 (4 %).[22]

Significant jaundice was seen more in O-A blood group than O-B blood group or O-AB blood group in this study.[11] The previous literatures shows that there is an inconsistency with regard to the degree of hemolysis and the incidence and severity of hyperbilirubinemia among O-A and O-B pairs. Kaplan et al in their study using ETCOc as predictor for hyperbilirubinemia showed O-B blood group had more significant and severity of jaundice.[4] This study showed a positive correlation only and observations were not statistically significant.

Female babies (22.4%) showed higher significant jaundice as compared to male babies (21%) in the study, though it was not significant statistically. In 1989, Hodr et al, observed that among neonates treated successfully by phototherapy, boys prevailed significantly whereas there was significantly higher prevalence of girls among the most severe forms of ABO haemolytic disease.[23] In a retrospective analysis of 254 cases, by Dufour DR found that sex, race, gravidity, birth weight and blood type of the infant did not have any significant relationships to outcome.[24] In this study also none of these variables were statistically significant.

In the present study, ≥3.5 mg/dl was used as cut off value for predicting significant hyperbilirubinemia in ABO incompatibility. A positive correlation was found between cord blood bilirubin and significant hyperbilirubinemia (r=0.301). The relation between high levels of cord bilirubin and increased incidence of significant hyperbilirubinemia are researched and reported in many studies. Azma et al in 2011, have found that CBB cannot be used as a prediction of subsequent hyperbilirubinemia.[25] The reasons for variability seen in these above tables were probably due to sample size and different cutoff values decided for significant hyperbilirubinemia.

In the present study using serum bilirubin levels ≥3.5 mg/dl in the cord blood, hyperbilirubinemia could be predicted with sensitivity of 38.4%, specificity of 90.4%, positive predictive value of 52.6% and negative predictive value is 84.1%. Development of significant hyperbilirubinemia was found to be more with cord blood bilirubin ≥3.5 mg/dl. (p=0.00035) which is statistically significant. The study done by Pradhan et al in 2017, established that a neonate with cord bilirubin ≥2.5 mg/dl had sensitivity of 84.1%, specificity of 88.5%, NPV of 45% and PPV of 98% for developing significant NHB.[26]

The study done by Kara et al in 2015, established that cord blood bilirubin cut off value was 2.05 mg/dl had 80% of sensitivity and 78% of specificity for predicting administration of phototherapy.[27] The study done by Farhat et al in 2013, showed that umbilical cord bilirubin of 2 mg/dl, had a positive predictive value of 66%, a negative predictive value of 64.2%, sensitivity of 68.86% and specificity of 61.8% for developing significant NHB.[28]

The study done by Janaki et al in 2018, showed the cut-off value of umbilical cord bilirubin for development of significant hyperbilirubinemia for the study population was 1.85 mg/dl. This value predicts the development of significant hyperbilirubinemia with a sensitivity of 70.6% and specificity of 82.7%.[22]

The study however, had certain limitations. Only full-term healthy neonates were taken for the study. In view of early discharge, vaginally delivered babies were excluded. This study was conducted in a comparatively small sample size.

CONCLUSION

From the results and observations of the present study, one can consider the umbilical cord blood to be an important predictor for the occurrence of significant hyperbilirubinemia in newborns subsequently. It will be a substantial addition in the existing diagnostic array of tools in assessing NHB. Cord blood bilirubin constitutes an additional predictive method for evaluating the occurrence of severe hyperbilirubinemia at the earliest by 24 hours of age.

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