ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2015; 1(8): 846-849
www.allresearchjournal.com
Received: 08-05-2015
Accepted: 11-06-2015

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To study Pathology prediction with lead blood analysis: ABO-incompatible babies commonly have hyperbilirubinemia

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Abstract
Background: Neonatal hyperbilirubinemia is associated with substantial morbidity and mortality, and ABO incompatibility is a leading cause of this condition. Thus, it is crucial to do newborn screenings for those at risk.
Materials and Methods: A descriptive study was done over the period spanning from May 2014 to April 2015. The participants in this study were selected randomly from the population of children born to O-positive women who underwent caesarian section at the Department of ENT, Mayo Institute of Medical Sciences, Barabanki, Uttar Pradesh, India.
Results: The study involved a total of 120 newborns who were identified as being at a high risk for ABO incompatibility. A cohort of 100 neonates exhibited clinical jaundice, with approximately 13% of these instances advancing to a more severe manifestation of jaundice. Our study exclusively included newborns with weights ranging from 2.5 to 4 kg.
Conclusion: There was no indication of notable reticulocytosis in cord blood from infants at risk of ABO incompatibility. Babies with a positive direct coomb's test developed pathological hyperbilirubinemia in 100% of cases, although only 15% of children with pathological hyperbilirubinemia had this result.

Keywords: ABO incompatibility, pathology, blood analysis, and hyperbilirubinemia

Introduction
During the neonatal era, jaundice is the prevailing abnormal observation. Clinical jaundice is observed in infants whose blood bilirubin levels above 5.0 to 7.0 mg/dL. Chemically hyperbilirubinemia is defined as serum total bilirubin levels of 2.0 mg/dL or higher, and it is observed in nearly all neonates within the initial week of life [1-3]. The prevalence of clinical jaundice in term neonates is 25-50%, with a higher incidence observed in preterm infants. In addition, 6.1% of newborns born at full-term have a blood bilirubin level over 12.9mg/dL. Merely 3 percent of neonates delivered at full-term exhibit a blood bilirubin concentration exceeding 15 mg/dL. As the degree of jaundice increases, there is a manifestation of skin yellowing that extends from the scalp to the feet [4-6].
Bilirubin encephalopathy and other serious consequences have been found to be related with hyperbilirubinemia [7]. Prompt diagnosis of pathological hyperbilirubinemia is crucial in order to initiate intensive treatment. Hospitalization for a minimum of 72 hours following delivery enables doctors to detect the highest point of the newborn's physiological jaundice and administer treatment, if deemed required. Infants exhibiting elevated levels of unconjugated bilirubin who are prematurely released from the medical facility may have supplementary phototherapy treatments. These readmissions not only subject a potentially healthy newborn to the hospital setting and result in additional expenses for both the family and the institution, but also lead to emotional distress and pose risks to breastfeeding. Consequently, this contributes to the decline of breastfeeding and the premature weaning of children [8-10].
With the exception of complications involving the mother or the child, the majority of infants are released from the Institute of Obstetrics and Gynecology within a timeframe of 48 to 72 hours following delivery.

Every month, a total of 1800 births occur at that location. Neonatal hyperbilirubinemia, primarily caused by ABO incompatibility, leads to the admission of 5-10% of neonates in the newborn ward. Therefore, it is crucial to conduct screenings on infants who are susceptible to ABO incompatibility. Taking this into consideration, we embarked on our investigation [11-13].

The process of heme catabolism results in the formation of bilirubin, a yellow waste product. The placenta eliminates the bilirubin generated by the fetus during pregnancy. Seventy-five percent of bilirubin comes from the breakdown of haemoglobin, whilst the remaining 25 percent comes from the degradation of other hemoglobin-related molecules, such as myoglobin and cytochrome. Albumin serves as a transporter for bilirubin on its route to the liver [14]. During the process of hepatocyte entry via membrane transport in the liver, bilirubin mostly forms a complex with ligandin, which is conjugated with two glucuronide molecules. Subsequently, bilirubin is ejected through the bile into the gastrointestinal tract. In the presence of beneficial bacteria in the gastrointestinal tract, the conjugated bilirubin will undergo degradation into innocuous stercobilins prior to elimination from the body. A mucosal enzyme can remove the glucuronide molecules from conjugated bilirubin in the absence of gut flora and decrease intestinal motility, allowing the unconjugated bilirubin to be reabsorbed [15].

Neonatal hyperbilirubinemia is associated with considerable morbidity and mortality, and ABO incompatibility is a leading cause of this condition. Therefore, it is imperative to perform screenings on neonates who are susceptible. Numerous research have been conducted to investigate the occurrence of newborn hyperbilirubinemia in infants who are at risk of ABO incompatibility, with the aim of identifying a dependable predictor. The next couple paragraphs will discuss about some of these studies.

Methods

A descriptive study was done over the period spanning from May 2014 to April 2015. The participants in this study were selected randomly from the population of children born to O-positive women who underwent caesarian section at the Department of ENT, Mayo Institute of Medical Sciences, Barabanki, Uttar Pradesh, India.

Results

Overall, 120 infants at high risk for ABO incompatibility participated in the study. Ninety-nine of the infants showed signs of clinical jaundice, while roughly thirteen cases showed signs of pathological jaundice. Only infants weighing between 2.5 and 4 kg were included in our study.

Table 1: Weight Distribution

Wt	No Jaundice	Jaundice	Pathological hyperbilirubinemia
2.5-3	25	50	05
3-3.5	11	20	02
3.5-4	04	02	1

Across the various weight groups, there was found to be no statistically significant difference in the incidence of clinical jaundice or pathological hyperbilirubinemia.

Blood group as a risk factor

There were 120 infants in all, with 60 in the A group and 60 in the B group. The B group had a higher rate of clinical jaundice than the A group. The change, however, did not reach statistical significance. The occurrence of pathological hyperbilirubinemia also did not vary significantly.

Table 2: Blood group as a risk factor

Blood group	No Jaundice	Jaundice	Pathological hyperbilirubinemia
A+	20	44	2
A-	4	2	1
B+	15	30	2
B-	1	1	0

The bilirubin levels on the fourth day of life correlate very well with those measured in the umbilical cord. Nomagram values on the fourth day were used in statistical analysis for those who began phototherapy before that time.

Table 3: Predictive value of cord hemoglobin levels

Sr. No.	Cord hemoglobin	Sensitivity	Specificity
1.	12.0	0.00	0.00
2.	12.12	0.00	0.02
3.	12.3	0.07	0.03
4.	12.12	0.07	0.04
5.	13.2	0.23	0.05
6.	13.10	0.23	0.06
7.	14.00	0.23	0.07
8.	14.14	0.38	0.08
9.	14.7	0.46	0.08
10.	14.13	0.53	0.29
11.	14.23	0.53	0.30
12.	15.32	0.53	0.30
13	15.78	0.61	0.49
14.	15.98	0.84	0.80
15.	16.78	0.92	0.97
16.	16.45	1.0	0.97
17.	17.47	1.0	0.98
18.	17.98	1.0	0.99
19.	19.45	1.0	1.0

With a sensitivity of 53.8%, specificity of 70.7%, positive predictive value of 15.9%, and negative predictive value of 93.4%, the area under the curve for haemoglobin values below 14.55g/ dL is a good predictor.

Discussion

The leading cause of pathological hyperbilirubinemia is ABO incompatibility 1. The goal of this study was to identify high-risk newborns who would benefit from routine cord blood sampling for the aim of predicting pathological hyperbilirubinemia. Results for bilirubin, hemoglobin, and reticulocyte count were compared to the peak bilirubin values in cord blood. These babies would be able to be released from the hospital earlier if these levels could predict when pathological hyperbilirubinemia would start [16].

Since the mothers of the 136 newborns in this study tested positive for O-globin, the babies were at risk of developing ABO incompatibility. That encompasses babies whose moms have blood types A or B as well. The infants were all born at a normal, healthy weight. Infants were not eligible to participate in the study if they exhibited any of the following non-protocol risk factors for jaundice: preexisting inflammatory haze, diabetes mellitus type 2, a mother with a history of diabetes, birth asphyxia, or sepsis. Due to differences in blood bilirubin levels and peak levels

associated with kernicterus risk, the trial was unable to include preterm infants. Finding out whether cord blood analysis can reliably predict when pathological hyperbilirubinemia will start was the goal of the study [16-18].

In our analysis of the cord blood, we looked at bilirubin levels, hemoglobin levels, reticulocyte counts, and direct coomb's tests, among other things. Babies with elevated reticulocyte counts, decreased cord hemoglobin levels, lower cord bilirubin levels, or a positive direct Coomb's test were more likely to develop pathological hyperbilirubinemia. Our goal was to find out whether characteristics such reticulocyte count, cord blood bilirubin, haemoglobin, and a positive direct Coomb's test were associated with pathological hyperbilirubinemia. Our main endpoint is pathological bilirubinaemia, which is defined as a bilirubin value above 15 mg/dL on day 4 or a serum bilirubin level above the 95th percentile for age in hours [19-21].

Out of 136 infants analyzed, 13 babies developed pathological hyperbilirubinemia. The peak bilirubin levels occurred on days 3 and 4. Phototherapy was necessary for twelve out of thirteen children with pathological hyperbilirubinemia, and an exchange transfusion was necessary for one infant. The baby who required an exchange transfusion had bilirubin levels of 4.2 mg/dL and haemoglobin levels of 13.2 mg/dL in his cord blood. Nevertheless, her reticulocyte count was 1% and the direct Cobb's test came out negative. In the study population, hemoglobin levels in the lead blood varied between 12.2 and 18.2 mg/dL, while in the neonates with hyperbilirubinemia, they ranged between 12.5 and 16.6 mg/dL. The average hemoglobin level in newborns with pathological hyperbilirubinemia was 14.73 mg/dL, higher than the healthy infant standard of 14.62 mg/dL. The beginning of pathology-induced hyperbilirubinemia could not be reliably predicted by hemoglobin levels [22, 23].

Reticulocytosis is a common complication of ABO hemolytic disorder, with documented prevalence rates ranging from 4-40%. The presence of reticulocytosis in cord blood is explained by the fact that hemolysis starts in utero when there is ABO incompatibility. The newborns we examined did not exhibit any symptoms of severe reticulocytosis, nevertheless. In infants born with an incompatible blood type, the direct coomb's test could be inaccurate or produce a weak positive result. Among the newborns in our study that had pathological hyperbilirubinemia, we only detected two cases of Direct coombs. No newborn with no signs of pathological hyperbilirubinemia had a negative result on the Direct Coombs test [24, 5].

Results showed a strong connection (r = 0.86) between bilirubin levels on day 4 and cord bilirubin in our study. Cord bilirubin is thus a very accurate predictor of pathological hyperbilirubinemia. Whyte *et al*. (2019) and Graham *et al*. (2019) came to similar conclusions in their investigations. Procianoy and colleagues, [25-27].

Babies with low levels of cord hemoglobin are at an increased risk of developing hyperbilirubinemia. A high reticulocyte count increases the likelihood of hyperbilirubinemia. There was very little association between the two. The Spearman correlation coefficient between the two datasets is 0.364. Although reticulocytosis was more common in infants with ABO incompatibility, the levels observed in these cases were not pathological. The direct coombs test was positive in just 1.5% of newborns [28, 29]. Fifteen percent of infants suspected of having pathogenic hyperbilirubinemia actually tested positive. All of the children who tested positive for direct coombs had pathological hyperbilirubinemia. Results showing a reticulocyte count >2% had a sensitivity of 46% and specificity of 67% in predicting the probability of pathological hyperbilirubinemia. A direct Coomb's test was positive in 15.4% of cases involving babies with pathological hyperbilirubinemia. Pathological hyperbilirubinemia was present in every single child who tested positive for direct coombs disease [30-33].

Conclusion

Babies at risk of ABO incompatibility can have their pathological hyperbilirubinemia predicted by cord blood tests. A high level of bilirubin in the cord blood is the most reliable indicator of future hyperbilirubinemia. Pathological hyperbilirubinemia is more likely to occur in neonates with cord bilirubin levels greater than 3 mg/dL. The level of bilirubin on the fourth day of life is correlated with the amount of haemoglobin in the lead blood. Babies were more likely to develop pathological hyperbilirubinemia if their cord haemoglobin level was less than 14.55 g/dL. Babies at risk of ABO incompatibility did not have a significant reticulocytosis in their cord blood. Nonetheless, all infants with a positive direct coomb's test went on to develop pathological hyperbilirubinemia, despite the fact that only 15% of infants with pathological hyperbilirubinemia had a positive direct coomb's test.

Funding support: Nil

Conflict of interest: Nil

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