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Komal Mendapara
Ex-Post Graduate Student, Department of Paediatrics, P.D.U. Government Medical College and Hospital, Rajkot, Gujarat, India

Arti Makwana
Associate professor, Department of Paediatrics, P.D.U. Government Medical College and Hospital, Rajkot, Gujarat, India

Corresponding Author:
Arti Makwana
Associate professor, Department of Paediatrics, P.D.U. Government Medical College and Hospital, Rajkot, Gujarat, India

Factors affecting the severity of hemolytic disease of the new-born due to ABO incompatibility

Komal Mendapara and Arti Makwana

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Abstract
Background and Aim: ABO incompatibility is one of the most common cause of hemolytic disease of fetus and new born. Better understanding of the factors affecting its severity helps to optimise care. The objective of this study was to investigate the factors affecting the severity of HDN due ABO incompatibility in new-borns.
Methods: This study was a prospective observational study conducted in the NICU, department of Pediatrics, P.D.U Government Medical College and Hospital, Rajkot. The study was conducted from January 2019 to June 2019; 50 new-borns with ABO incompatibility i.e., having blood group A or B born to mothers with blood group O, presenting with jaundice and or anemia were enrolled in the study. Various maternal and neonatal factors and their possible association in affecting the severity of HDN were studied**.**
Results: In our study, 27 neonates (54%) were male and 23 neonates (46%) were female. Percentage of O-A and O-B incompatible neonates were 26 (52%) and 24 (48%) respectively. The various maternal and neonatal factors had no significant association in affecting the severity of the disease. The mean age of presentation was 3.74 ± 2.34 days. Jaundice was detected in the first 24 hours of life in 6% neonates. The mean initial indirect bilirubin was 19.77 ± 2.50, and initial hemoglobin was 14.41 ± 2.07. Ten neonates (20%) had anemia. Total of 15 neonates (30%) had evidence of hemolysis in the form of spherocytosis. Direct Coombs Test was positive in one case. The mean duration of phototherapy was 54.62 ± 5.79 hours. Three neonates (6%) required exchange transfusion and 4 neonates (8%) received IVIG. The mean duration of stay was 4.18 ± 1.04 days.
Conclusion: Although none of the factors had a significant association in affecting the severity of HDN due to ABO incompatibility, we should remember that ABO incompatibility is not always a benign condition and should be considered even in those with a negative DCT. Early identification of high-risk neonates with ABO incompatibility and prompt diagnosis and treatment can reduce morbidity and mortality.

Keywords: ABO incompatibility, Hemolytic disease of the new-born, Jaundice, Phototherapy

1. Introduction
Hemolytic disease of the newborn due to ABO Incompatibility occurs exclusively in newborns of blood group A or B having mothers of group O. Even though hemolytic disease of the newborn has been reported in a baby whose mother was group A with a high titres of anti B [1] Jaundice in hemolytic disease of the newborn is more frequent and severe in ABO incompatible black than white newborns and, furthermore, jaundice due to any other cause, is more likely to be more severe in ABO incompatible babies than compatible ones [2].
Hemolysis due to alloimmune antibodies is seen with acute and delayed RBC transfusion reactions, following stem cell transplantation where there is an antigenic blood type difference between the donor and stem cell recipient, and during the neonatal period as a result of differences in maternal and fetal RBC antigens [3], The spectrum of clinical problems in hemolysis occurring in the fetus ranges from minimal hyperbilirubinemia to severe anemia with hydrops fetalis and/or kernicterus. HDN is characterized by hemolysis as a consequence of maternal sensitization to fetal RBC antigens inherited from the father resulting in the presence of IgG antibodies in maternal circulation which causes hemolysis in the fetus by crossing the placenta [4].
Many Asian countries have identified alloantibodies other than anti D as a cause of moderate to severe haemolytic disease [5-6] ABO and Rh incompatibility can be differentiated by their presentation. Theoretically, selection in ABO incompatibility may operate at various stages from fertilization through pregnancy [7]. It may extend its impact on the neonate. It produces

A spectrum of haemolytic disease extending from cases in which there is little laboratory evidence of erythrocyte sensitization, haemolysis to cases of severe haemolytic disease.

The etiology of haemolytic disease of the newborn due to ABO incompatibility is complex because anti-A and anti-B antibodies are composed mainly of Immunoglobulin M. Since only Immunoglobulin G antibodies cross the placenta, those pregnant women with high levels of Immunoglobulin G anti-A or B with an ABO incompatible fetus will be the ones to give birth to a newborn with ABO hemolytic disease of the newborn. Although hemolytic disease of the newborn as a result of ABO incompatibility is clinically milder than Rhesus incompatibility, severe hemolysis occasionally occurs, such that some cases require exchange transfusion.

It has been noted that hemolytic disease of the newborn due to ABO incompatibility frequently occurs during the first pregnancy, and about 50% of infants are affected unlike Rhesus hemolytic disease of the newborn in which the first born- babies are usually spared or free of the disease and subsequent babies are the ones that are affected.

The diagnosis of Hemolytic disease of the newborn due to ABO incompatibility cannot be made serologically using one single test; however, several tests together make the diagnosis more probable. In contrast to Rhesus haemolytic disease, the immunological findings in hemolytic disease of the newborn due to ABO incompatibility do not correlate well with the severity of the clinical course [8].

Hemolytic disease of the newborn can be managed by using any of the following modalities; phototherapy, exchange transfusion or intravenous immunoglobulins. Early application of any of these methods in the treatment of hemolytic disease of the newborn prevents bilirubin encephalopathy and kernicterus with subsequent development of severe neurological sequelae or death. Nearly 50% of babies with hemolytic disease of the newborn due to ABO incompatibility do not require treatment. Of the remaining 50%, half of them become extremely jaundiced and without treatment, 90% of them will die and 10% become severely affected by kernicterus. The other half are severely affected in utero and become hydropic [9-10] The objective of this study was to investigate the factors affecting the severity of HDN due ABO incompatibility in new-borns.

Material and Methods

This study was a prospective observational study conducted in the NICU, department of Pediatrics, P.D.U Government Medical College and Hospital, Rajkot. The study was conducted from January 2019 to June 2019; 50 new-borns with ABO incompatibility i.e., having blood group A or B born to mothers with blood group O, presenting with jaundice and or anemia were enrolled in the study. Various maternal and neonatal factors and their possible association in affecting the severity of HDN was studied.

Exclusion criteria: The neonates with history of Birth asphyxia, Sepsis.

- The neonate with congenital anomalies.
- Neonate with other known causes of jaundice and hemolysis

Ethical approval was taken from the institutional ethical committee and written informed consent was taken from all the participants.

A pre drawn proforma was explained to the mother or the caregiver. Informed consent regarding participation in the study was obtained in the regional language Data was collected as per the proforma. Questionnaire method, maternal case file and examination of the newborn were used to obtain the required data. Maternal variables like history of jaundice, first trimester bleeding, gestational hypertension, mode of delivery and use of drugs during pregnancy were collected. Medication during labour, details of delivery, APGAR score and maternal blood group were collected from the maternal file. Babies were clinically assessed for age, sex, gestational age, birth weight, previous history of jaundice in the family, day of onset of jaundice, pattern of feeding, fever and other neurological symptoms. Thorough clinical examination of the baby was done to identify: Pallor, temperature, icterus, hepatosplenomegaly, extravasation of blood, excessive bruising, neurological signs like opisthotonus.

Thus, all term neonates admitted to NICU with neonatal jaundice and or Anemia were subjected to thorough clinical examination. The following investigations were done.

- Blood Grouping and Rh typing of mother and baby: The blood grouping was done by using known antisera with slide and tube methods. Complete blood count of baby including hemoglobin, total count, differential count, band cells, peripheral smear examination and reticulocyte count.
- Estimation of hemoglobin was done by cyanmethemoglobin method.
- Peripheral smear was stained by Leishman stain.
- Estimation of serum Bilirubin on Auto analyser by Diazo method of Pearlman and Lee.
- Reticulocyte count was done by supravital stain using Brilliant cresyl blue.
- Direct Coombs Test (DCT) Other relevant investigations required for the management of the case were carried out as per the clinical indication. Standard treatment by using any of the following modalities; phototherapy, exchange transfusion or intravenous immunoglobulins was given for each case and the outcome of treatment modalities were studied and compared with other studies

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.

Results

Table 1: Demographic information of study participants

Variable	Number	Percentage (%)
Gender		
Male	27	54
Female	23	46
Blood Group		
O-A	26	52
O-B	24	48

In our study, 27 neonates (54%) were male and 23 neonates (46%) were female. Percentage of O-A and O-B incompatible neonates were 26 (52%) and 24 (48%)

respectively. (Table 1) The various maternal and neonatal factors had no significant association in affecting the severity of the disease. The mean age of presentation was 3.74 ± 2.34 days. Jaundice was detected in the first 24 hours of life in 6% neonates. The mean initial indirect bilirubin was 19.77 ± 2.50, and initial hemoglobin was 14.41 ± 2.07. Ten neonates (20%) had anemia. Total of 15 neonates (30%) had evidence of hemolysis in the form of spherocytosis. Direct Coombs Test was positive in one case. The mean duration of phototherapy was 54.62 ± 5.79 hours. Three neonates (6%) required exchange transfusion and 4 neonates (8%) received IVIG. The mean duration of stay was 4.18 ± 1.04 days.

Discussion

Hemolytic disease of fetus and newborn occurs when there is trans-placental passage of maternal antibodies resulting in hemolysis of fetal/neonatal red cells. Implicated Ab could be naturally occurring (Anti A, Anti B) or immune antibodies developed following sensitization. This occurs in 15-20% of all pregnancies. This hemolytic process results in fetal anemia/hyperbilirubinemia in 10% of the cases.

In this present study, various parameters and their association with the clinical manifestation of ABO Incompatibility were analyse. Neonatal jaundice was the main clinical feature in majority of the cases and mild anemia in few cases. Maternal factors like parity, gestational hypertension, mode of delivery, medication with oxytocin and initiation of breast feeding within 30 minutes and neonatal factors like sex, weight, blood group were considered. The association between these parameters and development of jaundice and or anemia in ABO Incompatibility was studied and the results were compared with other studies.

The various maternal and neonatal factors had no significant association in affecting the severity of the disease. Observations were comparable with that of studies by Kumar A *et al*, Akgul S, Shah A and Preethi *et al* [11-14]. Male newborns had more risk of jaundice, in studies by Mantani *et al*, Sharma *et al* and Maisal *et al* [15-17]. The serum bilirubin levels and weight of the newborn had no correlation but in the studies by Nepal D *et al* (19.2%) and Chaudhary et al (42%) observed significance with weight of the newborn (SGA) [18-19]. The mean age of presentation was 3.74 ± 2.34 days. Jaundice was detected in the first 24 hours of life in 6% neonates. The mean initial indirect bilirubin was 19.77 ± 2.50, and initial hemoglobin was 14.41 ± 2.07. Ten neonates (20%) had anemia. The serum bilirubin was independent of the parity of the mother (p value 0.97) as similar to that of in studies by Shah A *et al* and Kalakheti *et al* [20-21].

Total of 15 neonates (30%) had evidence of hemolysis in the form of spherocytosis. Direct Coombs Test was positive in one case. The mean duration of phototherapy was 54.62 ± 5.79 hours. Three neonates (6%) required exchange transfusion and 4 neonates (8%) received IVIG. The mean duration of stay was 4.18 ± 1.04 days. In a study by Akgul, Mean age on the day of admission to hospital was 4.4±2.4 (0-9) days. Mean initial IB was 19.9±5.7 (7.1-41.3) mg/dl. Fifteen neonates (9.0%) developed jaundice in the first 24 hours of life and 17 neonates (10.2%) had anemia in the first complete blood count examination. Mean initial hemoglobin was 15.6±2.3 (8.2-20.8) g/dl. Twenty-four neonates (14.5%) had hemolytic findings on peripheral blood smear. In study by Bhat YR, hemolysis was present in 25 (54.3%), with the range of indirect bilirubin from 11.9 to 25.6 mg/dl, 47.8% babies presented with jaundice in 24 hours. In study by Shah A, mean age of presentation was 2.97±1.2 days, mean bilirubin level, 15-19-9 mg/dl (52,4%). In a study by Thakkar B *et al*, lowest hemoglobin (9.0mg/dl), highest reticulocyte count (10%) and maximum rise in serum bilirubin (30.0mg/dL) were seen in cases of ABO compatibility [22]. The hallmark of HDN due to ABO incompatibility is the presence of microspherocytes on the peripheral blood smear.

The present study infers that early identification of high risk neonates with ABO incompatibility might reduce the morbidity and mortality due to jaundice and or anemia. Small sized study population was limitation of this study.

Conclusion

Although none of the factors had a significant association in affecting the severity of HDN due to ABO incompatibility, we should remember that ABO incompatibility is not always a benign condition and should be considered even in those with a negative DCT. Early identification of high-risk neonates with ABO incompatibility and prompt diagnosis and treatment can reduce morbidity and mortality.

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