Neonatal hyperbilirubinemia due to ABO incompatibility: does blood group matter?

Sinem Akgül[1], Ayşe Korkmaz[2], Şule Yiğit[2], Murat Yurdakök[2]

[1]Department of Pediatrics, [2]Division of Neonatology, Hacettepe University Faculty of Medicine, Ankara, Turkey. E-mail: sinemhusnu@yahoo.com

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Newborn infants with maternal-fetal ABO incompatibility are at a greater risk for developing subsequent significant hyperbilirubinemia, and therefore, prediction of probable risk factors, such as the degree of hemolysis, gains importance. In this study, we aimed to evaluate the effect of fetal-neonatal blood group on the severity of hemolysis and jaundice due to maternal-fetal ABO incompatibility. In a retrospective analysis of 166 cases with ABO hemolytic disease of the newborn, risk factors for the severity of jaundice were compared in infants with blood group A or B. Both groups had similar demographic parameters such as birth weight, gender and day of admission. Similarly, there were no statistically significant differences in hematological parameters, such as initial hemoglobin levels, initial and final indirect bilirubin levels, frequency of positive direct Coombs test and hemolytic findings on peripheral blood smear, duration of phototherapy, number of exchange transfusions, and intravenous immunoglobulin (IVIG) therapy ($p>0.05$). We conclude that blood type has no effect on the severity of the hemolytic jaundice in ABO incompatibility.

Key words: newborn, ABO incompatibility, hemolysis, blood group.

Maternal-fetal ABO blood group incompatibility, in which the mother has blood group O and the newborn has blood group A or B, occurs in 15-20% of all pregnancies[1]. Hemolytic disease develops in approximately 10% of such newborns and may be associated with clinically significant neonatal hyperbilirubinemia[2]. The hemolytic process results from maternal anti-A or anti-B immunoglobulin G (IgG) antibodies crossing the placenta and attaching to the appropriate antigens on the neonatal red cells. Resultant heme catabolism causes an increased indirect bilirubin (IB) production, leading to neonatal jaundice[3].

Considering that maternal-fetal ABO incompatibility can cause severe neonatal jaundice requiring an exchange transfusion and even kernicterus, the prediction of probable risk factors for hyperbilirubinemia, such as the degree of hemolysis, gains importance. In this study, we aimed to evaluate the effect of neonatal blood group on the severity of hemolysis and neonatal jaundice due to maternal-fetal ABO incompatibility.

Material and Methods

This retrospective study was conducted at Hacettepe University, İhsan Doğramacı Children's Hospital, Neonatology Unit, Ankara, Turkey, covering a 10-year period from 2000-2010. Term newborn infants (gestational age >36 weeks) with neonatal jaundice requiring phototherapy and/or exchange transfusion who had maternal-fetal ABO incompatibility were included in the study. The diagnosis of maternal-neonatal ABO blood incompatibility was made in the presence of indirect hyperbilirubinemia in a newborn infant with blood type A or B and maternal blood type O, in the absence of identified causes such as early and late neonatal sepsis or urinary tract infections, cephalic hematoma, neonatal polycythemia, dehydration, breast-feeding or breast-milk jaundice, inherited metabolic diseases, hypothyroidism, and other hemolytic diseases such as glucose-6-phosphate dehydrogenase deficiency and hereditary

spherocytosis. Direct Coombs test could be positive or negative. Infants with congenital anomalies were also excluded.

The hospital files of all patients were reviewed, and demographic and clinical parameters such as gestational age, birth weight, gender, day of hospitalization, plasma IB level on admission, hemoglobin level and peripheral blood smear on admission, blood group, the presence of positive direct antibody test (direct Coombs test), mode of therapy (phototherapy and/or exchange transfusion), duration of phototherapy, and need for intravenous immunoglobulin (IVIG) therapy were all recorded. IVIG treatment was administered to patients with a total bilirubin above 25 mg/dl. Hemolytic findings due to maternal-fetal ABO blood group incompatibility were defined as the presence of at least two of the followings: 1) anemia of varying degree, 2) circulating nucleated red blood cells, 3) spherocytosis, or 4) polychromasia on peripheral blood smear. Anemia was diagnosed by a venous hemoglobin of <13 g/dl. Pathologic hyperbilirubinemia requiring phototherapy or exchange transfusion was defined as any serum indirect (unconjugated) bilirubin level needing treatment with phototherapy during the first week of life, which was based on the 2004 American Academy of Pediatrics hyperbilirubinemia treatment guidelines[4].

Statistical Analysis

Data were analyzed statistically using the Statistical Package for the Social Sciences (SPSS) 16.0 software on a personal computer. Continuous variables were compared by using two-tailed t test for parametrically distributed data or Mann-Whitney for non-parametrically distributed data. Categorical variables were analyzed by χ^2 test or Fisher's exact test. A p value of <0.05 was accepted as statistically significant.

Results

The study group consisted of 166 term newborn infants with blood group A or B who were born to blood group O mothers and had no other predisposition to indirect hyperbilirubinemia. Ninety patients (54.2%) were male and 76 patients (45.8%) were female. The mean birth weight was 3142±542 (1650-4800) grams. One hundred and twenty-two infants (73.5%) had blood group A, while 44 infants (26.5%) had blood group B. 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 infants (9.0%) developed jaundice in the

Table I. Comparison of Demographic and Clinical Characteristics of Newborn Infants with Blood Group A or B with Indirect Hyperbilirubinemia

	Blood Group A (n=122)	Blood Group B (n=44)	p
Birth weight (g)*	3175±537 (1650-4800)	3049±551 (1930-4200)	0.186
Gender (M/F), n (%)	65/57 (53.3/46.7)	25/19 (56.8/43.2)	0.727
Day of hospitalization (day)*	4.4±2.4 (0-9)	4.1±2.4 (0-9)	0.405
Initial hemoglobin (g/dl)*	15.6±2.2 (9.8-20.8)	15.5±2.4 (8.2-20.7)	0.750
Initial hematocrit (%)*	45.3±6.4 (29.0-59.3)	44.6±7.3 (26.2-63.4)	0.592
Initial indirect bilirubin (mg/dl)*	20.2±5.7 (7.1-31.5)	18.9±5.4 (8.8-41.3)	0.200
Positive direct Coombs test, n (%)	13 (10.5)	4 (9.1)	0.769
Anemia (Hb <13.0 g/dl), n (%)	12 (9.8)	5 (11.4)	0.774
Presence of hemolysis, n (%)	17 (13.9)	7 (15.9)	0.749
Jaundice in the first 24 hours, n (%)	11 (9.0)	4 (9.0)	1.000
Duration of phototherapy (hr)*	46.6±21.2 (24-161)	45.6±15.9 (24-96)	0.772
Number of exchange transfusion, n (%)	16 (13.1)	2 (4.5)	0.160
Need for IVIG therapy, n (%)	13 (10.7)	5 (11.4)	0.897

*mean ±SD (min-max)
M: Male. F: Female. IVIG: Intravenous immunoglobulin.

first 24 hours of life and 17 infants (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 infants (14.5%) had hemolytic findings on peripheral blood smear, and 17 infants (10.2%) had positive Coombs test. Eighteen infants (10.8%) received exchange transfusion and 18 (10.8%) received IVIG.

In the comparison of newborn infants with blood group A or B, both groups had similar demographic parameters such as birth weight, gender and day of admission. Similarly, there were no statistically significant differences in hematological parameters such as initial hemoglobin levels, initial and final IB levels, frequency of positive direct Coombs test and hemolytic findings in peripheral blood smear, duration of phototherapy, number of exchange transfusions, and IVIG therapy ($p>0.05$) (Table I).

Indirect bilirubin (IB) level was 20-25 mg/dl in 47 patients, 26-30 mg/dl in 20 patients, and >30 mg/dl in 6 patients. In our study group, the highest IB level was found as 41.3 mg/dl in an infant with blood group B who developed kernicterus.

Two other patients, one with blood type A and one with blood type B with IB level >30 mg/dl, were hypotonic when evaluated on the day of discharge from the hospital, but re-evaluation was unremarkable for a neurologic sequela.

Discussion

Following routine immunoprophylaxis with Rh IG, ABO incompatibility has become the most common cause of isoimmune hemolytic disease of the newborn in developed countries[5]. In a previous study of a population of newborns in Turkey, there was a 14.8% incidence of ABO incompatibility, with 21.3% of these babies exhibiting significant hyperbilirubinemia and 4.4% exhibiting severe ABO hemolytic disease[6]. In our study, 10.8% of patients required exchange transfusion (for one of the patients, the exchange transfusion was repeated), and 10.8% of patients received IVIG, one of whom did not have direct antiglobulin test positivity.

The aim of this study was to determine whether the blood type of the neonate is a risk factor for increased hemolysis and thus hyperbilirubinemia. In our study, no significant relationship between the blood type of the newborn and severity of jaundice was noted, since there were no significant differences between the two groups in IB level on admission to hospital, duration of phototherapy, hemoglobin level on admission, the presence of direct antibody titer, or the need to perform an exchange transfusion. Similarly, a retrospective evaluation of 254 newborns with ABO incompatibility reported that gender, race, birth weight, and blood type of the infant showed no significant relationship with clinical outcome[7]. Another study from India evaluating 151 neonates also showed no difference in severity between O-A and O-B for hemolytic disease of the newborn[8].

In general, hemolysis due to ABO incompatibility is minimal, and the clinical course is relatively benign due to the relatively fewer group A or B antigenic sites on neonatal red blood cells[9]; however, severe cases demonstrating aggressive hemolysis and hydrops fetalis have also been reported[10]. Even though our findings suggest no significant relationship between the blood type of the newborn and the severity of hemolysis, evaluation of the literature shows that the most affected neonates in certain ethnic groups had blood group type B[9].

Two cases of hydrops fetalis in black infants caused by anti-B hemolysins were reported by McDonell et al.[10] Another study by Stiller et al.[11] reported a pregnancy complicated by anti-B isoimmunization that resulted in fetal ascites, anemia, hepatomegaly, and polyhydramnios. They concluded that ABO incompatibility may cause more severe fetal anemia in patients with type B blood. A study by Adewuyi et al.[12] compared the hemolytic activity of anti-A and anti-B antibodies in two racial groups, black and white Zimbabweans, living under similar conditions. Serum hemolytic activity was assessed, and within each racial group, anti-B antibodies showed greater hemolytic activity than anti-A antibodies.

Another study evaluating ABO hemolytic disease of the newborn compared the incidence of positive direct Coombs tests and the number of exchange transfusions performed to evaluate the severity of the condition. This study confirmed an increased incidence of hemolysis in black infants with blood type B, but showed

no increase in the severity of the disease[13].

The highest IB level in our study was 41.3 mg/dl, and this was the only child to develop signs of kernicterus. The child is still being followed in our outpatient clinic and has both developmental and motor delays. Subsequent damage and scarring of the basal ganglia and brainstem nuclei have been shown by magnetic resonance imagining studies. Another patient had a very high direct antibody titer (Direct Coombs +++). Interestingly, these two severe cases also had blood group type B. Two other patients, one with blood type A and one with blood type B with IB level >30 mg/dl, were hypotonic when evaluated on the day of discharge from the hospital, but re-evaluation was unremarkable for a neurologic sequela.

We conclude that blood type has no effect on the parameters that may influence the outcome of ABO incompatibility in Turkish newborns. However, the results of the present study may only be applicable to the Turkish population. Since it is well known that hemolysis can be more severe in certain racial groups, the need for further studies in different ethnic backgrounds may add to our knowledge regarding racial and blood antigen factors in ABO hemolytic disease of the newborn.

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