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Evaluation of Subgroup Incompatibility in Newborn Jaundice

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Abstract

Background: Hyperbilirubinemia is one of the most serious problems encountered in the newborn period. There are many reasons for newborn jaundice etiology. In this study, we aimed to investigate the frequency of subgroup incompatibilities in the etiology of hyperbilirubinemia, its association with blood group incompatibilities and the treatments given.

Methods: In this retrospective study, we evaluated 240 newborn patients who were diagnosed as hyperbilirubinemia in Dicle University Faculty of Medicine Neonatal Unit between January 2016 and June 2017.

Results: Subgroup incompatibility was detected in 32% of cases. Only 35.4% of cases with subgroup incompatibility were found just subgroup incompatible. Subgroup C incompatibility was found in 43%, Rh incompatibility in 35% and subgroup E incompatibility in 33% of cases. Direct Coombs Test positivity was detected in 38% of cases. Blood exchange procedure was performed in 16.5% of cases with subgroup incompatibility. Blood exchange was applied to 40.9% of those with Rh and C incompatibility. Only 50% of those with Rh and C subgroup incompatibility were applied blood exchange (this group was not accompanied by Rh or ABO incompatibility). Intravenous immunoglobulin treatment was given in 24.1% of cases with subgroup incompatibility in total. Intravenous immunoglobulin treatment was given also to 17.85% of cases with only subgroup incompatibility that did not accompany Rh and ABO incompatibility.

Conclusion: Detection of subgroup blood incompatibilities in cases with neonatal jaundice is important in diagnosis, treatment and follow-up.

Key Words: Subgroup incompatibility newborn jaundice hyperbilirubinemia.

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1- INTRODUCTION

Jaundice is a condition in which the skin, whites of the eyes and mucous membranes turn yellow because of a high level of bilirubin, a yellow-orange bile pigment(1). Jaundice is still one of the most common serious health problems in newborn babies (1). In newborns, jaundice occurs as a result of temporary disruption of the balance between the production and elimination of bilirubin from body (1). After 72 hours in term newborns, the total serum bilirubin level higher than 17 mg/dL is defined as pronounced, higher than 20 mg/dL is defined as serious, higher than 25 mg/dL is defined as excessive, and higher than 30 mg/dL is defined as dangerous hyperbilirubinemia(2). Hyperbilirubinemia can cause serious sequelae and deaths that can be prevented by early diagnosis and treatment. For this reason, jaundice remains important today, as it has been for many years (3, 4).

Most of kernicterus cases in the world are seen in US (27%), then in Singapore (19%) and Turkey (16%) respectively (5). Because of more publication published about kernicterus cases in the world lead to American Academy of Pediatrics to create a new guide in 2004 with recommendations on newborn jaundice. There are studies that report serious complications related to hyperbilirubinemia later on in term babies who appear healthy at discharge. It is noted that these complications can be prevented by follow-up after discharge (3). Stating that risk factors may not be obvious when jaundice occurs, it emphasizes the importance of detecting high-risk babies (6). Although there are more than 100 antigens on erythrocytes, very few of them can cause hemolytic anemia and jaundice (7). The pathophysiology of hemolysis is similar to Rh and ABO incompatibilities (8). The clinic of the disease ranges from subclinical hemolysis findings to hyperbilirubinemia, which requires active hemolysis and blood exchange (3). Cases of hydrops fetalis due to hemolytic disease caused by anti-Kell antibodies have been reported (9). Subgroup incompatibilities gradually become more prominent in the hemolytic disease of the newborn as a result of the decrease of isoimmunization due to Rh incompatibility with the use of Rhogam (10). In studies conducted on newborn jaundices, the frequency of subgroup (C,E,Kell) incompatibilities was found to be above classical information(11). Pathophysiology, diagnosis and treatment of subgroup incompatibilities are the same as in Rh hemolytic disease (12).

In this study, the effects of antigens and antibodies causing subgroup blood incompatibility on newborn jaundice were evaluated.

2- MATERIALS AND METHODS

In this retrospective study, we evaluated 240 newborn patients who were diagnosed as hyperbilirubinemia between January 2016 and June 2017. The other diseases that could cause hyperbilirubinemia and patients with hyperbilirubinemia that did not require treatment were excluded from the study. Study ethics committee approval was received. Maternal age, maternal blood group, maternal subgroup antigens (D^4+, C, E, c, e C^w, Kell), parent kinship, number of pregnancies, type of delivery, gender, hospitalization age, duration of hospitalization, infant blood group and subgroup antigens, Direct Coombs Test (DCT), and the treatments were recorded.

Subgroup incompatibility is accepted, if C, E, c, e C^w, Kell antigens are negative in the mother and any of the C, E, c, e C^w, Kell antigen is positive for newborn. Rh incompatibility is accepted when the Rh positive baby born from the Rh negative mother. Direct Coombs Test; the blood taken into the tube with EDTA was studied

for the examination examined by the agglutination method. 1 ml of diluent (solution containing Rabbit anti-Ig G and monoclonal anti-C3d) was added to the dry tube, and blood was collected from the blood taken into a 10 microliter EDTA tube. Thus, 8% erythrocyte suspension was prepared. 50 microliters were pipetted onto the Liss-coombs card. After centrifugation for 10 minutes, the positive or negative status was evaluated.

Determination of blood group; the blood taken into the tube with EDTA was studied. 0.5 ml of ID-diluent 2 solution was added to the dry tube and 25 microliters of EDTA was added to the blood taken from the tube. Thus, a 5% erythrocyte suspension was prepared. Pipette 25 microliters of 5% red blood cell suspension into monoclonal cards (Ortho). It was evaluated after centrifugation for 10 minutes. Complete blood count was done with the CELL-DYN Ruby model.

The diagnosis of hemolytic indirect hyperbilirubinemia was made by the presence of at least two of the following: hematocrit below 45%, reticulocyte over 5%, positive DCT, indirect hyperbilirubinemia, and hemolysis in the peripheral blood smear.

Phototherapy treatment was given to all cases with Dräger's tunnel-style phototherapy devices, which provide phototherapy with or without the top. According to the neonatal jaundice treatment guide published in the American Academy of Pediatrics in 2004, intensive phototherapy treatment was given to the patients who needed blood exchange until exchange blood was ready (13). Blood exchange was applied to patients whose bilirubin level was on the exchange border. Intra venous immunoglobulin (IVIG) treatment was given to patients with DCT positivity and hydrops fetalis and/or anemia and/or resistant hyperbilirubinemia.

While evaluating the data obtained from newborns included in the study, "SPSS for Windows v17.0.0" program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation and percentile) were used while evaluating the obtained data.

3- RESULTS

Subgroup incompatibility was detected in 79(32%) of 240 newborn with jaundice. 44.3% of the cases with subgroup incompatibility were female, 55.7% were male, 63.6% were normal spontaneous vaginal route and 36.4% were delivered by cesarean section (C/S). 16.45% of the mothers were primipara and 83.55% were multiparous. There was kinship between mother and father in 30.8% of the cases with subgroup incompatibility.

The mean age of newborns with subgroup incompatibility was 4.52±3.28 days, mean birth weights was 2921.2±602.4 grams, the mean hospital stay time was 7.7±5.1 days, the mean gestation age was 37.63±2, at 29 weeks. The mean total bilirubin level was 21.17±5.98 mg/dL, while the mean indirect bilirubin level was 20.34±5.79 mg/dL. In addition, the mean Hb level of the cases was 15.06±3.7 g/dL and the mean age of the mothers of the cases was 29.65±6.94 years.

While 13.8% Rh and C were the most common subgroup incompatibilities, (E) incompatibility was 8.8% and c incompatibility was seen as 8.2%. When compared it alone and with other subgroup incompatibilities, the most common was C incompatibility with 43%, then Rh with 35% and E incompatibility with 33%.

While DCT was negative in 62% of cases with subgroup incompatibility, it was positive in 38%. DCT positivity was found in 59.1% of 22 cases with Rh and C together. In our study, DCT was negative in all 3 cases with Kell incompatibility. The relationship between DCT positivity

and subgroup incompatibilities is shown in Table 1.

While phototherapy was applied to all the cases, 16.5% (Table 2) of the patients with subgroup incompatibility underwent blood exchange procedure. Blood exchange procedure was performed in 40.9% of the subgroup incompatibility with Rh and C, and this group constituted as 69% of all cases which blood exchange procedure is done. No blood exchange procedure was required for the Rh, C + e, C + Kell, Rh + C + C^w, e and c subgroups (Table 1).

Table-1: DCT, IVIG treatment and blood exchange frequency in subgroup blood incompatibilities

Subgroup blood incompatibilities	n	DCT Positive n(%)	IVIG therapy (treated) n(%)	Blood Exchange (applied) n(%)
C	9	3(33.3)	2(22.2)	1(11.1)
E	14	3(21.4)	2(14.3)	1(7.1)
c	13	4(31.8)	1(7.7)	0(0)
e	2	1(50)	0(0)	0(0)
C^w	0	0(0)	0(0)	0(0)
Kell	3	0(0)	0(0)	0(0)
Rh and C	22	13(59.1)	11(50)	9(40.9)
E and c	8	3(37.5)	2(25)	1(12.5)
Rh and E	4	1(25)	1(25)	1(25)
C and e	1	0(0)	0(0)	0(0)
C and Kell	1	0(0)	0(0)	0(0)
Rh, C and C^w	1	1(100)	0(0)	0(0)
Rh	1	1(100)	0(0)	0(0)
Total	79	30(38)	19(24.1)	13(16.5)

DCT: Direct coombs test, IVIG: Intravenous immunoglobulin

Table-2: Frequencies of subgroup blood incompatibilities (alone and together)

Subgroup blood incompatibilities	n (%)
C	9 (11.4)
E	14 (17.7)
c	13 (16.5)
e	2 (2.5)
C^w	0 (0.0)
Kell	3 (3.8)
Rh and C	22 (27.8)
E and c	8 (10.1)
Rh and E	4 (5.1)
C and e	1 (1.3)
C and Kell	1 (1.3)
Rh, C and C^w	1(1.3)
Rh	1(1.3)
Total	79(100)

IVIG treatment was given to 24.1% of cases with subgroup incompatibility. IVIG treatment was given to 24.1% of cases with subgroup incompatibility. 50% of the subgroup incompatibility with Rh and C was given IVIG treatment and this constituted 57.8% of all cases given IVIG.

While only subgroup incompatibility was detected in 35.4% of 79 cases with subgroup incompatibility. Subgroup incompatibility was together with 34.2% OA-OB incompatibility, 35.4% Rh incompatibility and 5% both ABO and Rh incompatibility. In all cases with Rh incompatibility, C incompatibility was found in 24(87.5%) cases and Rh incompatibility was found in 24(87.5%) cases. Out of 28 cases that did not accompany Rh and ABO incompatibility, only 28 (32.1%) c of the subgroup incompatibility were seen as the most common subgroup incompatibility. In addition, E incompatibility was found alone in 6(21.4%) cases. DCT was positive in 57.14% of 28 cases with Rh incompatibility with subgroup incompatibility. The most common subgroup incompatibility associated with Rh incompatibility group was Rh and C cases (53%). DCT positivity of this group was 66.7%. DCT was positive in 17% of 28 cases that did not accompany Rh incompatibility and ABO incompatibility only. Blood exchange was performed in 46.9% of the cases with Rh and Rh and C incompatibilities. IVIG was used in the treatment of 19 patients with previous subgroup incompatibility. 60% of Rh and C coexistence was given IVIG treatment, which constituted 47% of all IVIG cases. A total of 3 (11.1%) cases accompanied by ABO incompatibility were given IVIG. IVIG treatment was given to 5 (17.85%) of only subgroup incompatible cases not accompanying Rh and ABO incompatibility. In cases with Rh, AO, and BO incompatibilities with subgroup incompatibility, IVIG treatment, blood exchange and DCT positivity frequency are given in Table 1.

4- DISCUSSION

Jaundice is one of the most common problems in healthy newborns with many risk factors (14). Gender is one of the important risk factors for newborn jaundice. In many previous studies, it has been reported that male gender is a risk factor in hyperbilirubinemia (8). In this study, similar to previous studies, higher rates of jaundice were observed in male (55.7%) patients with subgroup incompatibility.

In the neonatal hemolytic disease, minor blood group incompatibilities started to become more prominent as a result of the reduction of Rh incompatibility isoimmunization due to the use of RhoGAM(8). Most of the subgroup antibodies are anti-c, anti-Kell, anti-C, anti-E, anti-e(15). Subgroup incompatibilities are responsible for 5% of newborn hemolytic diseases and most of them are related to anti-c, anti-E anti-e and anti-Kell(3). In studies conducted on newborn jaundices, the frequency of subgroup (C, E, Kell) conflicts is reported to be above classical information (11, 16, 17). Subgroup incompatibility rate was reported to be 7.2-10.4% in newborn jaundice and in the newborn with indirect hyperbilirubinemia, subgroup incompatibilities were determined as 37.7-66% C, 20.8% c, 1.6-28.3% E, 8.5% e and 4.7% Kell group incompatibility(11,17,18). In a study conducted in Canada between 2002 and 2004, where newborn with Rh incompatibility were not included in the study group because they were closely monitored (258 newborn), they reported that 4.65% of the causes of high bilirubin values constituted subgroup blood conflicts(19). In our study, while 32% of 240 newborns with jaundice were found to have subgroup incompatibility, the most common form of subgroup incompatibility

was Rh and C with 13.8%, whereas E incompatibility was 8.8% and c incompatibility was observed with a frequency of 8.2%. The most common incompatibility seen alone and with other subgroup incompatibilities were 43% C incompatibility, 35% Rh and 33% E incompatibility (Table 2). According to these results, it is seen that subgroup incompatibilities, which are often not considered due to cost or not considered at first, are important reasons for neonatal jaundice with both subgroup incompatibility and other blood group incompatibilities. In this respect, especially common subgroup incompatibilities need to be evaluated. As it is seen in our study, it is included in subgroup incompatibility c, C, Rh and E in a significant amount. We believe that more extensive and comprehensive studies should be carried out on this subject.

Direct Coombs Test is used to detect whether antibodies or complementary system factors bind to RBC surface antigens in vivo. Generally, DCT is used clinically when immune-mediated hemolytic anemia is suspected. Positive DCT indicates that the patient's immune mechanism attacks the patient's RBCs. This mechanism may be due to autoimmunity, alloimmunity, or a drug-dependent immune-mediated mechanism. In cases where DCT positivity cannot be explained by ABO and Rh incompatibilities, it is reported that other minor incompatibilities may be reason. Therefore, antibody screening will be helpful to figure out exact reason (20). In Deveci study (21), 19.4% of DCT was positive in all cases. In DCT positive cases, it was reported that 26.6% ABO incompatibility, 10% Rh incompatibility, 13.3% only subgroup incompatibility, 43.6% subgroup and other blood group incompatibility, and 6.6% cases did not have it. DCT positivity was found only in 14.2% of those with subgroup incompatibility, and 37.1% of those with subgroup and other blood group incompatibilities. In this study, DCT positivity was detected in 38% of cases with subgroup incompatibility. DCT positivity was detected in 59.1% of 22 cases with Rh and C association. DCT was negative in all 3 cases with Kell incompatibility. The relationship between DCT positivity and subgroup incompatibilities is shown in Table 1. DCT was positive in 57.14% of 28 cases with Rh incompatibility with subgroup incompatibility. The most common subgroup incompatibility Rh and C associated with 53% of the cases with Rh incompatibility, and DCT positivity in this association was 66.7%. DCT was positive in 17% of 28 cases that did not accompany Rh incompatibility and ABO incompatibility only. Therefore, we believe that cases with Rh and C subgroup incompatibility should be carefully monitored. Subgroup incompatibility also causes problems as much as Rh incompatibility. Since prophylaxis is also out of the question, we think that subgroup antigens should be investigated in coombs positive newborns that do not depend on known antigens. We believe that new and comprehensive studies on this subject will be of great benefit.

Reducing bilirubin production by preventing hemolysis, the use of IVIG has been shown to significantly reduce the need for blood exchange in patients with Rh incompatibility in hemolytic diseases. Administration of IVIG (0.5 g/kg) to newborns with Rh isoimmunization immediately after birth also decreases the rate of bilirubin increase. IVIG is being used more and more because it significantly reduces blood exchange, which is an invasive and complicated application in Rh isoimmunization cases. It can also alleviate the course of the ABO incompatibility. IVIG may also be useful in anti-E and anti-C type Rh

incompatibilities (13, 22). In our study, IVIG treatment was given in 24.1% of all cases with subgroup incompatibility. IVIG was given to 50% of the incompatibilities group with Rh and C and this subgroup constituted 57.8% of the cases with IVIG with incompatibilities (Table 1). 60% of Rh and C incompatibility coexistence was given IVIG treatment and this constituted 47% of all IVIG cases. It was determined that 11.1% of the cases accompanied by OA-OB incompatibility were given IVIG. IVIG treatment was given to 17.85% of cases with only subgroup incompatibility that did not accompany Rh and OA-OB incompatibility. According to our study, there is a need for IVIG treatment in conjunction with Rh and subgroup incompatibility, especially in those who accompany with Rh and C incompatibilities. In OA-OB incompatibilities, it is seen that a lower rate of IVIG treatment is needed. There was no study in the literature on this subject, and in our study, especially in cases where Rh and C subgroup incompatibilities were observed, this Rh and C subgroup incompatibility was found due to the high probability of IVIG delivery indication. We believe that patients should be followed closely. In addition, we believe that new and comprehensive studies on this subject will be of great benefit.

Indirect bilirubin becomes harmful after exceeding a certain level in the blood. Bilirubin encephalopathy defines the clinical picture associated with damage to the central nervous system, causes neurological sequelae in the first days of life, ranging from mild impairment in hearing to severe clinical conditions that result in opistotonus, convulsion or even death (23, 24). For this reason, it is one of the most effective methods to decrease the blood bilirubin level with blood exchange in a short time (25). In hemolytic conditions, blood exchange is recommended when the blood bilirubin level increases rapidly, in severe anemia, and when the bilirubin level does not decrease despite intensive phototherapy treatment (23, 24, 26). Minor blood group incompatibility is rare, but severe hemolytic reactions that require blood exchange can be observed (15, 27). A case with direct antiglobulin positivity due to Anti E and requiring two blood exchanges has been reported from our country (28). Among these, it has been reported that the most severe hemolytic clinic is indicate by Anti c antibodies (27, 29, 30). The most common cause of blood exchange has been reported as ABO incompatibility (31%), Rh incompatibility (19%) and subgroup incompatibilities (SGU) (17%) (31). In his study, Deveci(21) reported that 19.6% of cases requiring blood exchange only constituted 26.7% of subgroup incompatibility and other blood group incompatibilities, while not only accompanying OA, OB and Rh incompatibility. It has been reported that these blood exchange values constitute only 39.2% of those whose subgroup suitability is found, and 42.8% of those whose subgroup and other blood group incompatibilities are detected. In this study, blood exchange was performed only 16.5% of cases with subgroup incompatibility. Blood exchange was performed in 40.9% of the incompatibility group with Rh and C, and this constituted 69% of all cases. In 13 cases of incompatibility with Rh, C + e, C + Kell, Rh + C + C^w, e and, c (unlike to previous studies) no blood exchanges procedure were performed. While blood exchange is applied to 50% (2/4) of the patients with Rh and C incompatibility, 46.7% (7/15) of the cases with Rh and C had this procedure. Blood change was performed in 33.3% (1/3) of the cases with OA + E + c. No detailed studies were found in the literature on this subject. According to our study, especially in Rh and C subgroup incompatibilities, there is a high

probability of blood exchange indication due to high bilirubin level. We also think that patients with Rh and C incompatibility that accompany other blood group incompatibilities should be followed closely. In addition, we believe that new and comprehensive studies on this subject will be of great benefit.

Although Rh incompatibility is the most important cause of serious jaundice causing mental and motor retardation in newborns, the incidence of severe hyperbilirubinemia due to Rh incompatibility has decreased significantly, especially with the widespread use of Rhogam. Importance of subgroup blood incompatibilities are increasing in worldwide. However, in many centers around the world, they are still not routinely screened because of technical impossibilities or lack of their importance. For this reason, it is especially important to identify the types of subgroup blood incompatibilities that cause serious hyperbilirubinemia, and to detect them early. We believe that complications and blood exchange rate of hyperbilirubinemia can be significantly reduced by knowing the risk groups in advance and early intensive phototherapy.

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