Research Article / Araştırma Makalesi

Exchange Transfusion in Indirect Hyperbilirubinemia: A Single Center Experience

İndirekt Hiperbilirubinemide Exchange Transfüzyon Uygulanması: Tek Merkez Deneyimi

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Abstract

Background: Hyperbilirubinemia is a common clinical condition in newborn infants, and bilirubin encephalopathy remains an important health problem today. Decreased bilirubin anxiety and inadequate etiological evaluations lead to serious problems such as kernicterus. In this study, the development of bilirubin encephalopathy and its etiological causes were evaluated in patients who received exchange transfusion due to indirect hyperbilirubinemia for a period of one year.
Materials and Methods: Newborns admitted to the Neonatology clinic between September 2020 and August 2021 due to indirect hyperbilirubinemia and undergoing exchange transfusion were analyzed retrospectively. Demographic data, laboratory parameters, and incidence of complications related to exchange transfusion were investigated.
Results: A total of 62 infants, 61.3%(38) male and 38.7%(24) female, were included in the study. 53.2%(33) of the cases were delivered by cesarean section. Mean gestational age was 38(36-41) weeks and mean birth weight was 3063±478 grams. The median age at presentation was found to be 5 (1-22) days. In the etiological evaluation of the cases, 27.4%(44) Rh incompatibility, 50%(31) ABO incompatibility, 46.8%(29) Subgroup incompatibility were observed. More than one discrepancy was detected in 33.8%(21) of the cases. Glucose 6 phosphate dehydrogenase enzyme deficiency was detected in 21% (13) of the cases. No etiological cause was found in 4.8%(3) of the cases.
Conclusions: Indirect hyperbilirubinemia and related bilirubin encephalopathy still remain a serious problem and therefore exchange transfusion may be required. In order to reduce serious morbidity and even mortality due to indirect hyperbilirubinemia, bilirubin monitoring should be done closely and risky babies should be determined in advance with etiological evaluations.

Key Words: Bilirubin encephalopathy, Exchange transfusion, Indirect Hyperbilirubinemia

ÖZ.

Amaç: Hiperbilirubinemi yenidoğan bebeklerde sık görülen bir klinik durumdur ve bilirubin ensefalopatisi günümüzde hala önemli bir sağlık sorunu olmaya devam etmektedir. Bilirubin endişesinin azalması ve etyolojik değerlendirmelerin yeterince yapılamaması kernikterus gibi ciddi sorunlara yol açmaktadır. Bu çalışmada, bir yıllık sürede indirekt hiperbilirubinemi nedeni ile exchange transfüzyon yapılan hastalarda, bilirubin ensefalopatisi gelişimi ve etiyolojik nedenleri değerlendirilmiştir.
Materyal ve Metod: Eylül 2020-Ağustos 2021 tarihleri arasında neonatoloji kliniğine indirek hiperbilirubinemi nedeni ile yatan ve kan değişimi uygulanan yenidoğanlar retrospektif olarak incelendi. Demografik veriler, laboratuvar parametreleri, kan değişimine bağlı komplikasyonların gelişme sıklığı araştırıldı.
Bulgular: Çalışmaya %61.3(38)'ü erkek, %38.7(24)'si kız olmak üzere 62 bebek alındı. Olguların %53.2(33)'si sezaryen ile doğurtulmuştu. Ortalama gebelik yaşı median 38(36-41) hafta olup, doğum ağırlığı ortalama 3063±478 gram bulundu. Olguların ortalama başvuru yaşı median 5 (1-22) gün olarak bulundu. Olguların etyolojik değerlendirilmesinde %27.4(44)'ünde Rh uyuşmazlığı, %50(31)'sinde ABO uyuşmazlığı, %46.8(29)'unda Subgrup uyuşmazlıklarının olduğu görüldü. Olguların %33.8(21)'inde birden fazla uyuşmazlık tespit edildi. Olguların %21(13)'inde Glukoz 6 fosfat dehidrogenaz enzim eksikliği saptandı. Olguların %4.8(3)'inde etyolojik bir neden bulunamadı.
Sonuç: İndirek hiperbilirubinemi ve buna bağlı bilirubin ensefalopatisi halen ciddi bir sorun olmaya devam etmektedir ve bu nedenle de exchange transfüzyon uygulanması gerekebilmektedir. İndirek hiperbilirubinemiye bağlı ciddi morbidite ve hatta mortalitelerin azaltılması açısından bilirubin izlemi yakından yapılmalı ve etyolojik değerlendirmeler ile riskli bebekler önceden tespit edilmelidir.

Anahtar kelimeler: Bilirubin ensefalopatisi, Exchange transfüzyon, İndirek Hiperbilirubinemi

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Introduction

Indirect Hyperbilirubinemia (IHB) is generally within physiological limits and has a benign clinical course in the neonatal period (1,2). However, bilirubin levels rise to very high levels in some infants (1,2). When high bilirubin levels are not treated early and appropriately, they may cause irreversible brain damage and cause important neurological sequelae called bilirubin encephalopathy (2). Risk factors for severe hyperbilirubinemia; prematurity, breastfeeding, increased bilirubin in the first 24 hours of life, isoimmune hemolytic diseases (Rh, ABO, Subgroup incompatibility), immune hemolytic diseases (Glucose 6 phosphate dehydrogenase (G6PD), pyruvate kinase deficiency, etc.), galatosemia and cephal hematoma (3). Compared to developed countries, it is reported that there are 4-5 times more Exchange transfusions(ET) in our country (4). In case of high bilirubin level, early and rapid initiation of intensive phototherapy is important, but it is stated that performing blood exchange at the appropriate time prevents the development of neurotoxicity and reduces mortality and morbidity (4). However, since this procedure is an invasive procedure, serious side effects may occur (2). In order to reduce the risk of bilirubin encephalopathy and hospitalizations due to indirect hyperbilirubinemia, the American Academy of Pediatrics (AAP) recommends that health institutions should investigate the risk factors that may occur before the newborn discharge procedures, determine the rate of bilirubin increase, and establish a specific follow-up protocol in this regard(5). In our country, studies examining the risk factors that cause severe hyperbilirubinemia, possible outcomes after phototherapy and/or exchange transfusion therapy, and long-term neurodevelopmental follow-up of the cases are limited(6).

In this study, it was aimed to evaluate the demographic characteristics, etiological causes, indirect hyperbilirubin levels and risk factors for the development of acute bilirubin encephalopathy in infants who underwent exchange transfusion for one year in the neonatal intensive care unit (NICU) due to indirect hyperbilirubinemia.

Materials and Methods

In this study, 250 infants who were followed up and hospitalized with the diagnosis of indirect hyperbilirubinemia in the NICU between September 2020 and August 2021 were investigated retrospectively. Out of these cases, the results of 62 cases meeting the study criteria were evaluated. The study was approved by the Dicle University medical faculty ethics committee for non interventional studies (10.11.2021/442).

Newborns with clinical neonatal jaundice who were born between 36-42 weeks of gestation, birth weight above 1500 g, who underwent ET, and who were between 0-28 days after birth were included in the study. Babies with multiple congenital anomalies, born under 1500 g, cyanotic congenital heart disease, direct hyperbilirubinemia,

and babies born before 36 weeks of gestation and after 42 weeks of gestation were excluded from the study. Babies diagnosed with neonatal jaundice were identified from the archive files of the cases hospitalized in the NICU during the study period. Research data about the cases were obtained from the electronic records in the archive unit of the same hospital. A standard form was created for the data of each case. The blood group, subgroups, direct Coombs test (DCT), demographic characteristics, treatment modalities, treatment durations and hospitalization durations of the babies and their mothers treated with these forms were recorded. Complete blood count, biochemical tests, DCT, maternal and infant blood groups and subgroups of all cases were evaluated. G6PD levels were taken in patients with signs of hemolysis. Rh incompatibility if the blood group of the patients whose mother is Rh negative is Rh positive, the patients whose blood group is 0 but whose baby blood group is A, B or AB are ABO incompatibility, the mother is c, e, C, E, C^w, Kell subgroup antigen negative, infants with positive c, e, C, E, C^w, Kell antigen were evaluated as subgroup incompatibility.

Direct Coombs Test ; Positive or negative status was evaluated from the blood taken into the EDTA tube by agglutination method.

Determination of Blood Group ; Blood was drawn into a tube with EDTA . After centrifuging 25 microliters of 5% erythrocyte suspension on monoclonal cards (Ortho), they were evaluated.

Complete blood count (White blood cell count, red blood cell count, platelet count, hemoglobin, hematocrit , MCV, MCHC); Made with the CELL-DYN Ruby model.

Serum bilirubin level measurement; Total serum bilirubin from venous blood samples by enzymatic method with Architect c16000 autoanalyzer device, indirect bilirubin and direct bilirubin levels were measured and recorded.

The decision to apply phototherapy and/or exchange transfusion was made on the basis of the total serum bilirubin (TSB) values accepted in the APA recommendations. Ertunç Özcan brand Baby Led Force model led phototherapy device or Novos brand Bilisphere 360 LED versatile intensive phototherapy devices were used as phototherapy devices.

Exchange transfusion process; The procedure was performed in one hour using a 3.5, 5 or 8 Fr umbilical vein catheter selected according to the umbilical vein size of the baby, a triple tap, serum set and injector, with the method of drawing blood and giving transfusion blood. The hemodynamic status, respiratory rate, peak heart rate, blood pressure, and sPO_2 levels of the patients were recorded during and after ET.

Statistical analysis

Statistical Package for Social Sciences (SPSS) program version 21 was used in the statistical analysis of the data obtained from the subjects included in the study. In the evaluation of the data, descriptive statistical methods, mean and standard deviation, as well as the comparison of non-nor-

mally distributed parameters in the comparison of quantitative data were performed using Mann Whitney U test between groups, and Student's t-test was used in comparison of normally distributed parameters between groups. P<0.05 values for all tests were considered statistically significant.

Results

A total of 62 infants, 61.3%(38) of whom were male and 38.7%(24) were female, were included in the study. The rate of delivery by cesarean section/section(C/S) was 53.2%(33). Mean gestational age was 38(36- 41) weeks and mean birth weight was 3063±478 grams. The median age of the patients was 5 (1-22) days. (Table 1) Rh incompatibility was observed in 17 (27.4%) of the patients, ABO incompatibility in 31 (50%) and Subgroup incompatibility in 30 (46.8%). More than one discrepancy was detected in 21 (33.8%) of the patients. Glucose 6 phosphate dehydrogenase (G6PD) enzyme deficiency was detected in 13 (21%) of the cases, and different blood group incompatibilities were found in 10 of these patients. Isolated G6PD deficiency was detected in only 3 patients. No etiologic cause was found in 8 (12.9%) of the patients. When the mean total bilirubin values of the cases at the time of hospitalization were examined, it was found that 26.3±9.8 mg/dL and indirect bilirubin values were 24.5±9.4 mg/dL. It was found to be 26.7±10.2 mg/dL in male and 25.8±9.3 mg/dL in female, and there was no statistically significant difference between both genders (p=0.47) (Table 1). The mean serum total bilirubin value of those born by normal spontaneous vaginal delivery was 26.3±10.5 mg/dL, and the mean total bilirubin value of those born with C/S was 26.3±9.3 mg/dL, and there was no statistically significant difference between delivery method and total bilirubin levels (p=0.68) (Table 1).

Considering the etiological evaluations of all cases, it was found that ABO incompatibility was the most common (Table 2). DCT was positive in 18 (29%) of all cases. IVIG treatment was given to 8 (12.9%) of the patients with direct Cooms Test positivity and signs of hemolysis (Table 3).

Considering the treatments applied to the cases, exchange transfusion was applied to all patients and phototherapy was given. The rate of the cases who were treated with IVIG was found to be 8 (12.9%). The number of cases treated with IVIG was 13 and the most common etiology was ABO incompatibility with a rate of 46.1%.

Table 1. Comparison of the demographic characteristics

	Number n(%)	Total Bilirubin mg/ dL Mean±SD	*p*
Gender			
Female	**24 (38.7)**	**25.8±9.3**	**0.47**
Male	**38 (61.3)**	**26.7±10.2**	
Type of birth			
NSVD	**29 (46.8)**	**26.3±10.5**	**0.68**
C/S	**33 (53.2)**	**26.4±9.3**	
Gestational age (week) (Minimum -Maximum)	**38 (36-41)**		
Birth weight (grams) Mean±SD	**3063.1±478**		
Median age at admision (days) (Min. -Max.)	**5 (1-21)**		
Length of stay at the hospital (days) Mean±SD	**8.4±3.4**		

NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section, SD: Standard deviation

Table 2. Etiological evaluation of all cases

Etiology	n (%)
AB0 incompatibility	19 (30.8)
Rh incompatibility	2 (3.2)
Subgroup incompatibility	9 (14.5)
AB0 incompatibility + Rh incompatibility	1 (1.6)
AB0 incompatibility + Subgroup incompatibility	6 (9.7)
Rh incompatibility + Subgroup incompatibility	8 (12.9)
AB0 incompatibility + Rh incompatibility + Subgroup incompatibility	6 (9.7)
Isolated G6PD deficiency *	3 (4.8)
Other (such as urinary tract infection , Sepsis)	5 (8)
Etiology not determined	3 (4.8)
Total	62 (100)

** G6PD: Glucose 6-phosphate dehydrogenase*

Table 3. DCT, IVIG administration and mean total bilirubin values in cases with blood group incompatibility

Blood group incompatibility	Number (n)	DCT positivity* n	IVIG* n	Total bilirubin±SD (mg/ dL)
ABO incompatibility (Total)	32	13	6	25.4±10.5
ABO incompatibility (Alone)	8	0	0	22.4 ±8.4
ABO incompatibility + Subgroup incompatibility	6	8	0	23.8 ± 7.8
ABO incompatibility + Rh incompatibility + Subgroup incompatibility	6	1	1	20.4 ±6.1
Rh incompatibility (Total)	17	3	0	23.4±9.5
Rh incompatibility (Alone)	2	0	0	20.8 ±1.2
Rh incompatibility + Subgroup incompatibility	8	2	0	20.4 ±8.2
Subgroup incompatibility (Total)	29	9	one	26.7±8.9
Subgroup incompatibility (Alone)	9	3	0	21.5±5.8

** DCT: Direct Coombs test. IVIG: Intravenous Immunoglobulin , SD: standard deviation.*

Discussion

Acute and chronic bilirubin encephalopathy due to indirect hyperbilirubinemia still remains an important health problem. In this study, we tried to explain the characteristics, etiology and complications of patients who underwent exchange transfusion due to indirect hyperbilirubinemia in a single center within a year.

Exchange transfusion is a type of blood transfusion in which the patient's blood or its components are exchanged with other blood or blood products, and the aim is to lower the serum bilirubin level to reduce the risk of kernicterus(7). The ET technique was applied for the first time by Diamond et al.(8) in 1951 to control hyperbilirubinemia due to Rh incompatibility and to prevent kernicterus, which is a chronic bilirubin encephalopathy. In addition to reducing the level of bilirubin in exchange transfusion, it is also possible to correct anemia caused by hemolysis, to remove maternal antibodies, to remove antibody-bound erythrocytes and other toxic substances(9). Exchange transfusion is recommended in cases of lysis of erythrocytes due to hemolysis, in cases where the TSB value rises rapidly above the threshold values, in cases of severe anemia and in cases where indirect bilirubin value does not decrease despite intense phototherapy (9).

Tıraş et al.(10) found the blood exchange rate to be 6.8% and 13.3% by Narlı et al.(11) in patients followed up for indirect hyperbilirubinemia, and it was seen that the most common cause was ABO blood group incompatibility. In our study, ET was performed in 62 (18.5%) of the cases, and it was seen that the most common reason was ABO and Subgroup incompatibility.

Various complications such as sepsis and necrotizing enterocolitis are seen in patients undergoing exchange transfusion due to acute bilirubin encephalopathy. The increase in the rate of neurological sequelae after hyperbilirubinemia both impairs the patient's quality of life and imposes serious economic and social burdens on the society. There are major and minor risk factors in hyperbilirubinemia (12). The emergence of jaundice in the first 24 hours, DCT positivity, enzyme disorders such as G6PD deficiency, blood group, Rh and subgroup incompatibility, history of phototherapy and/or exchange transfusion in a previous sibling, and East Asian race are considered major risk factors (12). Advanced week of gestation, jaundice before discharge, history of jaundice in a previous sibling, maternal age over 25, and male gender are minor risk factors (12).

Neonatal hemolytic disease is a reaction formed by the antibodies formed in the mother due to blood incompatibility against the antigens in the erythrocytes of the newborn. ABO, Rh and subgroup incompatibilities can cause this(13). The incidence of indirect hyperbilirubinemia due to Rh sensitization is gradually decreasing with the widespread use of Anti-D gamma globulin, which is applied in the case of Rh antigen testing during pregnancy and if Rh-negative mother has a Rh-positive spouse. However, the rate of minor blood group incompatibility other than Rh (D) antigen such as Kell, c, C, E, e, duffy is increasing (14).

Subgroup incompatibility should be considered in the presence of severe hemolysis with indirect hyperbilirubinemia, and/or in newborns with DCT positive and profound anemia (15). Newborns with subgroup blood group incompatibility may present with a clinical spectrum ranging from asymptomatic to severe hydrops fetalis (16).

In our study, the rate of cases with ABO incompatibility was 32 (51.6%), while those with ABO incompatibility alone were found to be 19 (30.6%). The rate of patients with Rh incompatibility is 9 (14.5%) and those with Rh incompatibility alone are 2 (3.2%). We think that this is due to the fact that obstetricians, family physicians and pediatricians are aware of this situation and that Rhogam administration and bilirubin follow-up are more serious. The rate of patients with subgroup incompatibility was 29 (46.7%) and 9 (14.5%) with subgroup incompatibility alone. The fact that subgroup incompatibility is more common than known suggests that there may be subgroup incompatibility among cases of unknown cause and that there may be a proportional increase due to the decrease in exchange transfusion due to Rh incompatibility. For this reason, subgroup incompatibility should be investigated in patients undergoing exchange transfusion.

Antibodies detected by direct Coombs test are in IgG structure. Because all of the anti-D antibodies and some of the anti-A antibodies are in the IgG structure, DCT is seen with a high rate of Rh incompatibility (17). In our study, DCT was positive in 18 (29%) of the patients hospitalized due to hyperbilirubinemia, and it was found in 13 (72%) of them with ABO incompatibility.

The most common enzyme defect in the world is G6PD enzyme deficiency (18). G6PD enzyme deficiency, which is X-linked recessively inherited, is highest in Africa, Asia, the Middle East, Latin America and the Mediterranean region and affects approximately 400 million people (5,14). In our study, 3 patients had to undergo exchange transfusion due to G6PD deficiency, and G6PD deficiency was accompanied by other incompatibilities in 10 patients. In patients presenting with hyperbilirubinemia in countries with risk for G6PD enzyme deficiency, G6PD enzyme deficiency should be investigated and bilirubin follow-up should be planned accordingly.

In some studies on IHB seen in the neonatal period, the proportion of cases without any etiologic cause varies. No cause was found in 64% of the cases in a study conducted in Canada, in 50.7% in a study conducted in Iran, and 18.4% in a multicenter study from Turkey (18-20). In our study, no cause was found in 3 (4.8%) of the cases who underwent exchange transfusion due to IHB. The reason why the rate was found to be lower than other studies was thought to be due to the fact that many tests for hyperbilirubinemia could be performed in our unit. As seen in our study, the etiology of exchange transfusion due to hyperbilirubinemia

can be clarified when extensive etiological studies are conducted for neonatal hyperbilirubinemia. Thus, undesirable adverse effects due to bilirubin encephalopathy will be reduced, and the frequency of kernicterus will decrease, both in the patient and in the next child.

Many studies have shown that male gender is a risk factor for hyperbilirubinemia, and it is among the minor risk factors by the AAP (5). In a multicenter study conducted by Erdeve et al., 53.3% of hyperbilirubinemia cases were found to be male (18). In our study, 38 (61.3%) of the cases were male, and the male/female ratio was found to be 1.58. In our study, it was shown that there was no significant relationship between exchange transfusion and gender, although it was more common in males in patients undergoing exchange transfusion (p=0.47).

Limitations

The most important limiting factor is that it was done in a single center and with a limited number of patients. In the continuation of the study, the fact that the patients were not evaluated clinically and neurologically was considered as another limiting factor.

Conclusion

Prevention of hyperbilirubinemia and consequent exchange transfusion is based on the identification of babies at risk and the effective use of early diagnosis and treatment methods, identifying the risk factors necessary to reduce total bilirubin levels. In neonatal hyperbilirubinemia, if early diagnosis and treatment is not performed, exchange transfusion is performed. Both brain damage due to encephalopathy and complications related to exchange transfusion have high morbidity and mortality. Today, while ABO and Rh incompatibilities, which have an important etiological place, are closely followed, other etiological conditions such as subgroup incompatibility, infections, G6PD deficiency, hypothyroidism, metabolic diseases should be kept in mind, bilirubin concerns should not be ignored, and early diagnosis and treatment should be performed. In order for this method to be applied as a standard, extensive studies with large numbers of patients are needed.

Ethical Approval: The study was approved by the Dicle University medical faculty ethics committee for non interventional studies (10.11.2021/442).

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