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Original Article

Role of Subgroup Incompatibility in Newborn Jaundice Requiring Exchange Transfusion

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ABSTRACT

We aimed to determine the role of exchange transfusion related complications, treatment, and etiology as well as subgroup incompatibility in patients subject to ET (exchange transfusion) due to newborn jaundice. 82 patients hospitalized due to newborn jaundice and exposed to exchange transfusion between August 2007 and August 2011 were retrospectively studied. Before ET mean total serum bilirubin was 29,2±9,83. The most frequent cause of ET was ABO incompatibility (31%) followed by Rh incompatibility (19%) and subgroup incompatibility (17%), respectively. In 46% of all patients and in 71% of the patients presenting with subgroup incompatibility , direct combs test was detected to be (+). 49% of the patients were administrated with intravenous immunoglobulin. 5 of the patients who were exposed to ET presented with hydrops fetalis. Of these patients 3 had Rh, 1 had ABO while the other had subgroup incompatibility. Although ABO and Rh incompatibility are substantial underlying reasons of severe jaundice requiring exchange transfusion, particularly widespread use of RhoGAM thereby enabling the prior identification and precautions, ET need was reduced compared to previous cases. On the contrary, SGU related severe hemolytic jaundice relatively enhanced, however.

Key words: *Exchange transfusion, newborn jaundice, hyperbilirubinemia, subgroup incompatibility, minor blood group incompatibility*

Kan Değişimi Gereksinimi Olan Yenidoğan Sarılığında Subgrup Uyuşmazlığının Rolü

ÖZET

Bu çalışmada yenidoğan sarılığı nedeniyle kan değişimi (KD) yapılan hastalarda etiyoloji, tedavi, KD ile ilgili komplikasyonlar ve subgrup uyuşmazlığının rolünü belirlemeyi amaçladık. Dört yıl boyunca yenidoğan sarılığı nedeniyle yatırılarak 89 KD yapılan toplam 82 hasta retrospektif olarak değerlendirildi. KD öncesi ortalama total serum bilirubin düzeyi 29,2±9,83 mg/dl idi. En sık KD sebebi ABO uyuşmazlığı (%31), bunu Rh uyuşmazlığı (%19) ve subgrup uyuşmazlığı (SGU) (%17) izliyordu. Tüm hastaların %46'sında ve SGU olan hastaların %71'inde direkt coombs testi (+) idi. Hastaların %49'una İVİG verildi. KD yapılan hastalardan 5'inde hidrops fetalis tablosu mevcuttu. Bunların 3'ünde Rh, 1'inde ABO ve diğerinde SGU mevcuttu. KD gereksinimi gösteren ciddi sarılığın en önemli sebebi ABO ve Rh uyuşmazlığı olsa da özellikle Rhogamın yaygın kullanılması, bu risk nedenlerinin önceden tanımlanarak gerekli öneriler ve önlemler sayesinde KD ihtiyacı eskiye oranla azaltılmıştır. Ancak bunun aksine SGU'na bağlı ciddi hemolitik sarılık ve KD ihtiyacı rölatif olarak artmıştır. Kaldi ki SGU hidrops fetalis, kernikterus ve ölüme yol açabilmektedir. Riskli grupların önceden bilinmesi ve erken yoğun fototerapi sayesinde hiperbilirubineminin komplikasyonları ve KD oranı önemli ölçüde azaltılabilecektir.

Anahtar kelimeler: *Kan değişimi, yenidoğan sarılığı, hiperbilirubinemi, subgrup uyuşmazlığı, minör kan grubu uyuşmazlığı*

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INTRODUCTION

Hyperbilirubinemia is one of the most common problems in newborns. Although most of those babies presenting with jaundice do not have any other accompanying problems, potential toxic impacts on central nervous system cause substantial concern. Undoubtedly that the earliest and most effective treatment method of indirect hyperbilirubinemia in newborns is exchange transfusion (ET) (1-4). Common use of phototherapy, increasing the ET limits, widespread use of RhoGAM and IVIG treatment as well as increasing sensitivity in society reduced the ET need (1-6).

ABO and Rh incompatibility are the most common cause of serious indirect hyperbilirubinemia. In addition, erythrocyte defects, erythrocyte structural defects, infections, delivery traumas and prematurity are among other common causes. Minor blood group incompatibilities (such as anti-Kell, anti-C, anti-E) are held responsible for 3-5% of all newborn jaundices (1–4,7–13). We retrospectively studied the underlying cause of indirect hyperbilirubinemia, and the etiology, complication and surveillance of the patients undergoing exchange transfusion during 4 years. Moreover, we tried to work out the role of subgroup incompatibility (SGI).

MATERIALS AND METHODS

In this retrospective study, we evaluated patients who were exposed to 89 exchange transfusion procedures due to hyperbilirubinemia in Meram School of Medicine Neonatal Unit between August 2007 and August 2011.

For ET limits, the guidelines recommended by American Pediatric Academy were used (2,3). For ET indication, total bilirubin level was considered to be limit. Histories, delivery weeks, weights, place and genders of the patients were acquired from medical files. Mother blood groups, infant blood group, direct combs test, haemogram, reticulocyte count, total and direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), peripheric smear, whole urine test, serum calcium values, G6PD and osmotic fragility tests were evaluated. Intensive phototherapy was applied to all the patients before and after the ET. Despite ET and phototherapy, if the serum total bilirubin levels were detected to be critical or increased up to such level, ET was repeated. All the complications detected in patients exposed to ET were recorded. 0.5-1 g/kg/dose IVIG was administrated to infants who presented with indirect hyperbilirubinemia related to ABO, Rh and SGI. In all the infants who were exposed to ET, BAER (Brainstem Auditory Evoked Response) test was performed. As stated in the ET standard guidelines, double volume ET procedure was performed by using whole blood in a bag containing Acid Cytrate Dextrose (ACD) which was taken not more than 5 days ago as well as compatible blood group.

For the statistical analysis of the results, SPSS 16.0 (Statistical Package for Social Sciences) software was used. Demographic features were evaluated with descriptive statistic analysis. Student t test was used in the comparison of central tendency and transmission criteria means from the descriptive statistic methods.

RESULTS

In total 1038 patients were followed in our neonatal department due to newborn jaundice for four years. Of these patients 82 (7.9%) were exposed to 89 ET procedures. The characteristics of the patients who were exposed to ET were summarized in Table 1. We determined that the most frequent underlying reasons of hyperbilirubinemia included ABO (31%) blood group incompatibility between the mother and infant, Rh incompatibility (19%) and SGI (17%) (Table 2).

5 of 14 patients with SGI had anti-Kell, and 4 had anti-C, 3 had anti-E, and 2 had anti-c SGI. Of the 82 patients, one was exposed to 3 times, 5 were exposed to 2 and the remaining 76 patients were exposed to once ET. In 38 (46%) of the patients who were exposed to ET, direct combs test results were positive. Of these cases 15 had Rh, 12 had ABO, and 10 had SGI while one had no blood incompatibility. In 71% of the patients exposed to ET due

***Table 1**. Demographic characteristics of patients.*

Characteristic	
Gender	
Famale (n, %)	37 (%45)
Male (n, %)	45 (%55)
Term (n, %)	65 (%80)
Preterm (n, %)	17 (%20)
Gestational age (weeks)	37,1±1,3*
Body weight (gram)	2810±524*
Age of ET, (day)	4,4±2,8*
At admission, the level of total bilirubin, mg/dl	29,2±9,83*

*mean ± SD (Standard deviation)

Table 2. Causes of hyperbilirubinemia

Causes	n	%
ABO incompatibility	25	31
Rh incompatibility	16	19
Subgroup incompatibility	14	17
Prematurite	8	10
Sepsis	3	4
Herediter sferositoz	2	2
G6PD deficiency	1	1
Birth trauma	1	1
Idiopathic	12	15
Total	82	100

to SGI, direct combs test was detected to be positive.

IVIG was administrated to 40 patients (49%) who were exposed to ET. Of these patients 16 (40%) had Rh incompatibility, 10 (25%) ABO incompatibility, 10 25%) SGI, and 3 (7.5%) had sepsis and hyperbilirubinemia and exposed to ET and 1 (2.5%) patient had (+) direct combs results.

Mean total bilirubin value of the patients who were exposed to ET was detected to be 29.2 mg/dl. Kernicterus occurred in 4 patients who were exposed to ET (out of those two patients who died). Mean total bilirubin value of the patients presenting with kernicterus was 32.9 mg/dl. In these patients, the cause of hyperbilirubinemia was detected to be ABO incompatibility, Rh incompatibility, SGI and hereditary spherocytosis, as well. Of the four patients presenting with kernictus, the signs of kernictus were demonstrated in brain MRI. 5 of the patients who were exposed to ET were born with hydrops fetalis. Of these patients three had Rh and one had ABO while the other had SGI.

Table 3. Adverse Events of Exchange Transfusion

Complications	n	%
Thrombocytopenia	17	21
Anemia	10	12
Hypercalcemia	9	11
Sepsis	7	9
Hypocalcemia	7	9
Hipotermi	4	5
Hyperkalemia	4	5
Hypoglysemia	3	4
Catheter-related complications (vasospasm, bleeding, thrombosis)	2	4
Apnea	2	2
Cardiopulmonary arrest	1	1
Arrhythmia	1	1
Death	0	0

In our hospital, all the infants enrolled in natal and/or neonatal unit are exposed to routine hearing test (auto acoustic emission). However, additional BAER is applied to all the infants who are exposed to ET. Other than four patients presenting with kernictus, BAER test was normal in our patients who were exposed to ET. The complications occurring in the patients who were exposed to ET were summarized in table 3.

DISCUSSION

Indirect hyperbilirubinemia is the most widespread cause of hospitalization of the newborns (14). Approximately 5-10% of all the newborns need to be intervened due to pathological jaundice (15). In order to be protected from bilirubin encephalopathy, early diagnosis and treatment are significant. ET is one of the most effective methods in treating the serious newborn jaundice (1–4,15-17). In the literature ET ratio varies between 0.24% and 22.1 (1,4,18,19). In our study, ET ratio in the patients hospitalized due to jaundice was 7.9%.

In the studies on the etiology of the infants who were exposed to ET, the most frequent causes of ET need were detected to be ABO blood group incompatibility and Rh incompatibility respectively (1–4,11–13,18,20,21). On the other hand, despite being different in some regions, prematurity, hereditary anemia (such as lack of G6PD, hereditary spherocytosis), SGI and delivery traumas may lead to serious jaundice and ET need (1,4–7). In this study, we encountered ABO blood group incompatibility as the most common ET requiring case (31%). This ratio was followed by Rh incompatibility (19%), SGI (17%), blood incompatibility with indefinite cause (15%) and prematurity (10%). The jaundice etiology associated results in the patients who were exposed to ET in our study were complying with literature but not SGI. However, the prevalence of SGI patients were relatively higher compared to literature.

As known, SGI is responsible for 3-5% of newborn jaundice cases, it may also cause ET requiring serious jaundice (4,7,8,10,21). Blood incompatibility between mother and baby that leads to the most common minor blood group antigens D, C, c, E, and K antigen (8,10,21). In a study on SGI, antiKell was determined to be 22%, antiD 18.4%, anti-E 14%, anti-c 5.8%, anti-C 4.7% (22). Among these, particularly anti-c causes more serious hemolytic disease (23). If the direct combs test results are (+) in

the hyperbilirubinemic infants, isoimmune hemolytic disease between mother-infant should be considered. Therefore, the severity of hemolytic disease is generally parallel to reaction of combs test. However, the fact that combs test has (+) result does not mean the existence of essential severe hemolytic jaundice, while (-) results do not mean that incompatibility and serious jaundice do not occur (1–3,8–10,21,24,25). In our study, in most of the patients (15/16) presenting with Rh incompatibility and needing ET, direct combs test was positive in 71% of the SGI patients and in approximately half of the patients with ABO incompatibility (12/25). In the literature in all the infants presenting with SGI 33% positive results were acquired in direct combs test (21).

Recent developments in the treatment of newborn jaundice are used in the cases who were exposed to other treatment models but failed in order for controlling the bilirubin proliferation due to ET related mortality and morbidity. Phototherapy is most common and standard treatment model in case of jaundice (4). IVIG, albumin, Phenobarbital and other medications may be alternative of ET or may reduce the ET need (1,4,26). IVIG is routinely used in the treatment of Rh and ABO incompatibility associated newborn jaundice in European countries. IVIG is considered to inhibit the Fc receptors thereby reducing the bilirubin production and becoming effective (4,26,27). It is also found out that IVIG is effectively used in the treatment of SGI related jaundice and it reduces the severity and ET prevalence (8,27). Kernicterus (bilirubin encephalopathy) is the most frightening complication of hyperbilirubinemia. Indeed, the most substantial cause of applying ET procedure is to prevent the development of kernicterus (1–4). Among the major risk factors of kernicterus are serious hemolytic, early development of jaundice, prematurity, sepsis, dehydration, instant proliferation of hypoalbuminemia and bilirubin. In four patients (4.8%) who were exposed to ET procedure, kernicterus occurred.

It has been reported that in all the infants undergoing treatment due to high bilirubin level, hearing test should be performed (2). We performed BAER test in all the infants we applied ET procedure. Other than four patients with kernicterus, in all the infants BAER test was normal. It has been reported that all the infants should be followed for late anemia whether they were exposed to ET or underwent other treatment models due to hemolytic jaundice (2,9,21). In 17 of our patients, late anemia developed. One of them was hereditary spherocytosis and others were blood group incompatibility associated hemolytic jaundice. As in all medical procedures, ET has complications, too. These complications vary according to the weight, catheter insertion, exchange transfusion technique, blood products and experience of the medical staff (1,2,4). ET related mortality ratio varies between 0.79%-3.2% in each patient and 0.6%-1.9% in each procedure and mortality or severe sequel ratio was reported to be <1% if the procedure were performed according to rules (1,4). On the other hand, in the severe infants mortality was 8% while serious complications might reach up to 12% (1). Other complications include hypocalcaemia, hyperkalemia, thrombocytopenia, hypothermia, apnea, bradicardia, hypoglycemia, sepsis, portal vein thrombosis and most of these complications may be spontaneously recovered (1,4,11–13). None of our patients died due to ET. Most frequently detected complications in our study were transient thrombocytopenia (21%), anemia (12%), hypercalcaemia (11%), sepsis (9%) and hypocalcaemia (9%).

Consequently we can state that intensive phototherapies are used in treatment thereby reducing the prevalence of ET, it is still the most effective treatment method in the serious hemolytic jaundice in newborns. Although ABO and Rh incompatibility are leading factors in the etiology of ET need demonstrating serious jaundice, if these two hemolytic causes are known beforehand and if the required precautions are taken ET need was reduced compared to prior period with common use of RhoGAM. However, contrary to this reduction, SGI related serious hemolytic jaundice and ET need were relatively increased. Subjects, had been done within a day and certain time span. By this point of view, our study is contributing to the literature by establishing the long term alterations in the nasal cycle. The study has shown that nasal cycle patterns of the subjects may transform from one another. On the other hand, subjects showing non-cyclic pattern, can be detected nasal cycle on time. This can be due to the nasal cycle which is under control of the hypothalamus, could be affected by the environmental factors or occurrence of cyclic alterations in nasal cycle could be more than 6 h of time span.

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