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Adverse events associated with exchange transfusion and etiology of severe hyperbilirubinemia in near-term and term newborns

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Aim: To assess clinical features, etiology, and complications in term and near-term newborns who received exchange transfusion.

Materials and methods: Infants with ≥35 gestational weeks admitted to our neonatal intensive care unit in the first 30 days of life and underwent exchange transfusion due to severe hyperbilirubinemia between 2002 and 2008 were included. Clinical features, etiology of hyperbilirubinemia, and complications of exchange transfusion were assessed.

Results: Exchange transfusion was performed 86 times in a total of 73 patients. Eleven patients received exchange transfusion twice, and 1 patient 3 times. A great proportion of the patients (61.6%) were male, and mean (± standard deviation) gestational age and birth weight of the patients were 38.0 (1.4) weeks and 3249 (619) g, respectively. While the admission, mean total serum bilirubin levels were 27.5 (7.4) mg/dL. Hemolytic disease was found in 56.1% of the newborns (n = 41). The most common causes of hemolysis were ABO incompatibility (23.2%) and Rh sensitization (12.3%). The underlying cause was not able to be identified in 29 (39.7%) cases. The most common 2 complications were hypocalcemia (n = 7) and thrombocytopenia (n = 5).

Conclusion: This study implies that no etiology was defined in nearly half of the term and near term newborns who received exchange transfusion. Despite technological advances in neonatal care units in the last decade, the blood exchange-related complication rates remained the same.

Key words: Hyperbilirubinemia, exchange transfusion, newborn

Kan değişimi uygulanan yenidoğanlarda ciddi hiperbilirubineminin nedenleri ve kan değişimi uygulamasının yan etkileri

Amaç: Ciddi hiperbilirubinemi nedeniyle kan değişimi uygulanan term ve sınırda term bebeklerde, klinik özelliklerin, hiperbilirubinemi nedenlerinin ve kan değişimi uygulaması sonucu saptanan yan etkilerin değerlendirilmesi.

Yöntem ve gereç: 2002-2008 yılları içerisinde yaşamın ilk 30 gününde, ciddi hiperbilirubinemi nedeniyle kan değişimi uygulanan, gebelik haftası ≥35 olan bebekler çalışmaya alındı. Hastaların klinik özellikleri, hiperbilirubinemi nedenleri ve kan değişiminin yan etkileri incelendi.

Bulgular: Bu dönemde on bir hastaya 2 kez, bir hastaya 3 kez olmak üzere 73 hastaya toplam 86 kez kan değişimi yapıldı. Hastaların % 61,6'sı erkek, ortalama gebelik haftası 38,0 ± 1,4 hafta ve doğum ağırlığı 3249 ± 619 g olarak saptandı. Yatış esnasında ortalama serum bilirubin değeri 27,5 ± 7,4 mg/dL idi. Bebeklerin % 56,1'inde (n = 41) hemoliz saptandı. En sık saptanan hemoliz nedenleri ABO uyuşmazlığı (% 23,2) ve Rh Uyuşmazlığı (% 12,3) idi. Yirmi dokuz hastada (% 39,7) hiperbilirubineminin nedeni saptanamadı. Kan değişiminin en sık saptanan iki yan etkisi hipokalsemi (n = 7) ve trombositopeni (n = 5) idi.

Sonuç: Çalışmamızda kan değişimi uygulanan bebeklerin yarısında ciddi hiperbilirubineminin nedeninin saptanamadığı ve son 10 yılda yenidoğan ünitelerindeki gelişmelere rağmen kan değişimi ile ilgili yan etkilerin değişmediği belirlendi.

Anahtar sözcükler: Hiperbilirubinemi, kan değişimi, yenidoğan

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Introduction

The bilirubin level at which exchange transfusion (ET) is indicated remains controversial (1,2). This is because it is very difficult to define the risk of bilirubin encephalopathy in various categories of the patients, such as patients with or without hemolysis, term or premature, or even healthy or ill. Kernicterus has become uncommon due to the advantage of effective prevention from rhesus (Rh) incompatibility and the treatment of elevated bilirubin levels with phototherapy (3-6). Most reported kernicterus patients in the world are from the United States (27%), Singapore (19%), and Turkey (16%) (4). Considering the high frequency of kernicterus in Turkey, it is clear that further studies concentrating on the etiology and treatment outcomes of neonatal jaundice are necessary and important.

Intensive phototherapy and ET are the main treatment methods in prevention from kernicterus (2,4). Though ET is effective, the method can give rise to numerous complications including transient hypocalcemia, hypoglycemia, hyponatremia and thrombocytopenia, rare life threatening infections, catheter break off, renovascular hypertension, thrombosis and embolism, and even death (4,7,8). In this study we aimed to assess the clinical features, etiology, and complications in term and near-term newborns who received exchange transfusion because of severe hyperbilirubinemia, which is one of the most important neonatal health problems in Turkey.

Materials and methods

Patients

The subjects were newborns with ≥35 gestational weeks admitted in the first 30 days of life with severe hyperbilirubinemia to the neonatal intensive care unit of Şişli Children's Hospital and received ET between 2002 and 2008. Decision of ET was made according to the guidelines proposed by the American Academy of Pediatrics (AAP) (2,9). Files of all patients who received ET, except partial ET, were reviewed retrospectively, and 116 patients were determined.

Demographic features, physical examination findings, nutrition types (breast milk only, formula, and mixed), birth of place, the age of the newborns when jaundice was noticed, the age on the first admission, the period between admission and ET, and duration of hospitalization were recorded.

Exchange transfusion procedure and monitoring complications

According to the standard protocol of ET at our unit, all the patients were given intensive phototherapy and enteral nutrition followed till ET process. Gastric contents were drained via orogastric catheter just before ET. The procedure was performed in using a single line (umbilical vein), and the umbilical catheter was withdrawn soon after the ET ended. No calcium supplementation was given during the procedure. The newborns were followed up in terms of heart rate, respiratory rate, peripheral oxygen saturations, and blood pressure by means of a cardio-pulmonary monitoring during at least 8 h after the procedure.

All the blood products used for exchange transfusion were obtained from the Şişli Children's Hospital Blood Center. The blood products withdrawn from volunteer donors were anticoagulated with citrate phosphate dextrose adenosine-1 and were <5 days old. Whole blood ABO compatible between the baby and mother were used. The double volume ET was completed in about 1.5-2 h by repeatedly removing and replacing small aliquots of the blood (<5 mL/kg) according to our protocol.

An adverse event was defined as any complication occurring within 1 week after ET (10). The following definitions were used; hypoglycemia (serum glucose <45 mg/dL), hypocalcemia (total serum calcium <8 mg/dL), hyponatremia (serum sodium <135 mEq/L), hyperkalemia (serum potassium >5.5 mEq/L), thrombocytopenia (platelets below 50,000/mL), bradycardia detected during and 2 h after ET (heart rate dropping to <100 beats per min), apnea (cessation of respirations for >20 s), seizure (any tonic and/or clonic movement), bacteremia (detected colonization in the culture taken after ET), and necrotizing enterocolitis defined according to Bell's criteria (11). The records of adverse events, possibly related to ET, were classified according categories as defined by Jackson: asymptomatic untreated, asymptomatic treated, serious transient, serious prolonged, permanent serious sequel, and dead (8).

Etiologic investigations

According to our ET protocol, following etiologic investigations were performed in all the newborns at

baseline: mother-baby blood type, complete blood count, total and direct serum bilirubin, peripheral blood smear, reticulocyte count, direct Coombs' test, thyroid hormone levels, blood culture before ET, and serum levels of calcium, sodium, potassium and glucose.

Conditions with a minimum of 2 following findings were defined as hemolysis: reticulocyte count >7%, positive direct Coombs' test, hematocrit level <45%, spherocytosis in peripheral blood smear, and increase in total serum bilirubin level >0.5 mg/dL per hour. The cause of hemolytic jaundice reported in the records was classified in the following way: "Rh sensitization" was defined as jaundice in Rh-positive newborns who were born to Rh-negative mothers and evidence of hemolysis. ABO disease was defined as jaundice in newborns who were born to type O mothers with positive direct Coombs' test against the A or B antigens and evidence of hemolysis. Existence of Kell, C, and E subgroup incompatibilities were investigated in patients with hemolysis and without any previously mentioned hemolytic conditions according to our ET protocol.

All the newborns with hyperbilirubinemia, the etiology of which was not able to be clarified by the above mentioned analyses, were analyzed before ET for serum levels of glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase, tandem mass spectrometry (MS) and "TORCH"; and for urinalysis, culture and reducing substances. Abdominal ultrasonography was performed to eliminate hematoma in subjects without hemolysis. Blood and/or urine culture positivity were assessed as proven sepsis or urinary tract infection.

Statistics

The demographic features of the study were assessed via descriptive statistical analyses. Values were presented as mean ± standard deviation (range).

Results

During the study period, there were 6192 neonatal intensive care unit admissions, 782 of which were jaundiced, and 116 newborns received ET. Of these, 33 newborns had prematurity, and 10 newborns had deficient data in records, so both groups were excluded. The remaining 73 newborns, who received 86 ET procedures, were enrolled in the study. Overall, 11 patient had 2, and one had 3 sessions of ET.

Demographic characteristics of the newborns are shown in Table 1. Among all the newborns, 67 (91.8%) were admitted because of hyperbilirubinemia and/or any other reasons, and 6 (8.2%) were detected to have significant jaundice when were followed up by the well-baby nursery.

Table 2 shows the common etiologic factors of the patients who received ET and the most 2 of which were Rh sensitization and ABO incompatibility. No etiologic factor was found in 4 hemolytic patients and 25 nonhemolytic patients. One of the nonhemolytic patients had a history of a sibling with kernicterus despite ET. Pathological weight loss (>10% than birth weight) was detected in 14 of the entire group (19.1%), only 3 had dehydration alone, without any other risk factors (Table 2). No thyroid dysfunction or any other abnormality was detected in Tandem MS, TORCH analyses, and abdominal ultrasonographic examinations. Three patients whose urine samples had reducing substances were negative in further analyses. Ten patients were given intravenous immunoglobulin prior to ET for hemolysis and direct Coombs positivity.

Total serum bilirubin levels according to the day on which ET was performed are given in Table 3. ET was most often performed between days 3 and 6. The maximum TSB level before ET was 46 mg/dL.

ET related complications are given in Table 4. According to Jackson's classification (8), 2 asymptomatic patients were administered a dose of 75 mg/kg per day intravenous calcium when serum levels decreased to < 6mg/dL. Hypoglycemia persisted in another asymptomatic patient's 2-h follow-up, who was immediately supported with 6-8 mg/kg per min iv glucose for 24 h. Two infants were given erythrocyte suspension soon after ET since their hematocrit levels decreased below <30%. ET was ended in 2 cases because of bradycardia, whose heart rates recovered after oxygen therapy using hood. In these 2 patients, the second ET was not performed since control TSB levels were below ET indication levels. One newborn had apnea responding to positive pressure ventilation. Two additional patients with agitation and tremor had hypocalcemia, and thereafter were given intravenous calcium. Petechial rash due to thrombocytopenia was detected in a newborn; however, thrombocyte

Table 1. Baseline demographic characteristics.

	Value, mean ± SD	Range
Number of patients, n	73	-
Mean gestational age, weeks	38.0 ± 1.4	35-41
Birth weight, g, range, g	3249 ± 619	2030-5195
Body weight on admission, g	2983 ± 569	1740-5110
Gender		
Male, n (%)	45 (61.6)	
Female, n (%)	28 (38.4)	
Delivery		
Spontaneous vaginal, (%)	76.7	
Cesarean section, (%)	23.3	
Birth place		
Our hospital, n (%)	15 (20.5)	
Other center, n (%)	51 (69.9)	
Home, n (%)	7 (9.6)	
The day family noticed jaundice, day	2.9 ± 1.7	1-8
Postnatal age at the time of admission, day	4.6 ± 2.3	1-13
Mode of feeding before ET		
Breastfeeding, n (%)	42 (57.5)	
Formula, n (%)	8 (11.0)	
Mixed, n (%)	23 (31.5)	
Causes of admission		
Jaundice, n (%)	43 (58.9)	
Feeding difficulties, n (%)	12 (16.4)	
Respiratory distress, n (%)	7 (9.6)	
Irritability, n (%)	6 (8.2)	
Excess sleep, n (%)	5 (6.8)	
Admission TSB, mg/dL	27.5 ± 7.4	12-46.5
TSB before ET, mg/dL	29.4 ± 7.2	12.5-46
Time between admission and ET, h	2.5 ± 1.4	1-6
Duration of phototherapy, h	70.5 ± 33.7	24-144
Hospitalization duration, day	7.9 ± 5.6	2-24
The rate of readmission for phototherapy, n (%)	5 (6.8)	

ET: exchange transfusion, TSB: total serum bilirubin, SD: standard deviation

suspension was not given since no signs of bleeding were seen, anyhow thrombocyte levels recovered after 24 h. A patient was detected to have bacteremia because blood culture positivity for methicillin-resistant coagulase-negative staphylococci was detected after ET, and then he was treated with vancomycin for 14 days. An infant was transferred to our unit with respiratory distress and jaundice, underwent ET and was supported by mechanical ventilation due to a TSB level of 26 mg/dL, and Hct 17%. Unfortunately this patient died at the 6th h on the first day. Etiology for hemolysis could not be ruled out. Though we consider that the reason of death was primarily associated with respiratory distress, ET might have probably contributed. Total complication rate was 17.8% (n = 13) when those not requiring treatment were excluded.

On admission, 11 patients had irritability and excess sleep, and another 12 newborns showed feeding difficulty. Furthermore, clinical findings of acute encephalopathy were present in 6 patients. Symptoms of 3 patients vanished after ET, but the others manifested signs of kernicterus during their 3 month-follow-up. Two of the latter were home-born, and hospitalized on days 7 and 13 with TSB levels of 36.5 mg/dL and 36 mg/dL, respectively. The other one had G6PD deficiency with a TSB level of 41.4 mg/dL, and underwent ET twice.

Table 2. Etiology of hyperbilirubinemia in newborns performed exchange transfusion.

Causes of hyperbilirubinemia	**n**	**%***
with hemolysis	**41**	**56.1**
ABO incompatibility	17	23.2
Rh sensitization	9	12.3
ABO incompatibility + Rh sensitization	4	5.5
Other blood antigen sensitization	2	2.7
Proven sepsis	1	1.4
Urinary tract infection	1	1.4
G6PD deficiency	3	4.1
No hemolytic etiology determined	4	5.5
Without hemolysis	**32**	**43.9**
Proven sepsis	3	4.1
History of a sibling with ET performed	1	1.4
Severe dehydration	3	4.1
No etiologic factor determined	25	34.3
Total unknown etiology	**29**	**39.7**

% ratio is given regarding to total patient number.
G6PD: Glucose-6-phosphate dehydrogenase

Table 3. Day of life when ET was performed and mean total serum bilirubin levels.

Day of life when ET was performed	**N**	**%**	**TSB,* mean ± SD (range) mg/dL**
Day 1 (0-24 h)	6	8.2	22.9 ± 4.1 (18.0-26.0)
Day 2	8	11.0	19.0 ± 8.0 (12.5-34.0)
Day 3	11	15.1	28.5 ± 5.9 (21.5-38.8)
Day 4	12	16.4	32.3 ± 5.1 (18.7-38.3)
Day 5	11	15.1	34.2 ± 4.6 (29.2-40.0)
Day 6	10	13.7	31.9 ± 6.6 (25.5-46.0)
Day 7	9	12.3	31.8 ± 2.9 (28.7-36.5)
≥8 Days	6	8.2	28.9 ± 7.7 (20.5-37.0)
Total	73	100	29.4 ± 7.2 (12.5-46.0)

* Total serum bilirubin levels when ET was started.
ET: exchange transfusion, TSB: total serum bilirubin, SD: standard deviation

Discussion

ABO incompatibility, Rh sensitization, and G6PD deficiency were found as reasons for severe hyperbilirubinemia in this large study carried out in Turkey, where kernicterus and ET appliances are common. Forty percent of the patients in the study had no apparent etiologic reason. The literature search reveals common reasons for severe jaundices requiring ET, such as hereditary spherocytosis, urinary tract infections, hypothyroidia, hemolysis due to blood subgroup incompatibilities, pyruvate kinase enzyme deficiency, hemoglobinopathies, subdural hematoma, and adrenal gland hemorrhage (4,5,8,12-14). In a study carried out in Canada between 2002 and 2004 in which Rh sensitization newborns were not included since follow-up, most common causes for

Table 4. Adverse events associated with ET.

	n	%
Asymptomatic untreated		12.3
Thrombocytopenia	4	
Hypocalcemia	3	
Hypoglycemia	**2**	
Asymptomatic treated		6.8
Hypocalcemia	2	
Hypoglycemia	1	
Anemia	2	
Serious, transient		8.2
Apnea (requiring resuscitation)	1	
Bradycardia	2	
Hypocalcemia	2	
Petechial rash from thrombocytopenia	1	
Serious and prolonged /permanent		1.4
Bacteremia	1	
Dead	1	1.4

hyperbilirubinemia in 258 babies were ABO incompatibility and G6PD deficiency whereas 64% had no known etiology. ET was performed on these newborns with a rate of 22.1% (5). Reasons for hyperbilirubinemia in ET performed term and preterm infants were reported as follows: Rh sensitization 21.4%-48.1%; ABO incompatibility 19.8%-34%; Rh sensitization and ABO incompatibility association 4%-6.7%; G6PD deficiency 9%-34.4%; prematurity, 5.6%-7.4%; subgroup incompatibilities 5.6%; and other reasons 3.7%-22.2% (4,5,7,8,15-17). We were unable to find a reason in 40% of the subjects in our study. This rate was reported previously as 17%-37% (4,7,8,13,14). It is considered that more novel wider studies investigating enzymes in bilirubin metabolism like glucuronyl transferase are required for enlightening the etiology of these patients, rates of which were reported to be as high as 40%, whether as in the present study or previous ones, with the note that the present study has a privilege to include the maximum number of patients amongst the studies performed in Eastern Europe and Middle East Region in the last decade (7,12,15,16).

It is well known that the reasons for hyperbilirubinemia alter with respect to genetics and geographical distribution (2). G6PD deficiency is an important factor in this distribution. Johnson et al. reported that G6PD deficiency accounted for 31.5% of kernicterus; and the rate is 34.4% for all infants undergone ET according to Owa et al. (17,18). Eastern Mediterranean region is said to be the area where G6PD deficiency is seen common (15). G6PD deficiency is reported to account for 18% in term infants undergone ET in south-eastern Turkey (12). The rate found in this study is 4.1% in ET required newborns. The city where the study was conducted is a metropolis with a cosmopolitan structure. Another study conducted in İstanbul, Turkey was carried out by Atay et al., and G6PD deficiency was similarly reported to account for 3.8% of all the term babies admitted for hyperbilirubinemia (19). Pathological weight loss is a risk factor for serious hyperbilirubinemia (2,20,21). This sign indirectly indicates insufficient nutrition and an increase in enterohepatic bilirubin cycle. Hyperbilirubinemia development risk is said to increase whenever the loss gets over 10% according to AAP (2). Sgro et al. (5) reported that the rate of weight loss more than 10% accounts for 10.9% as found in 19.1% in our study. This result of ours suggests that weight loss more than 10% appears as a serious risk factor for hyperbilirubinemia and ET as well.

It is suggested that if the healthy newborn and early discharged term and near-term infants with a risk of jaundice are not on close follow-up, they are re-admitted to hospitals for hyperbilirubinemia and they develop kernicterus more often (22). The recommendation about this condition is that bilirubin levels should be assessed before discharge and they should be followed-up according to the analyses; this would provide early notice of severe hyperbilirubinemia (23,24).

In this study, only 6 infants with high risk for severe hyperbilirubinemia developed jaundice while they stayed at rooming-in, and thus were transferred to the neonatal unit. The remaining 67 newborns were admitted to our center from home due to jaundice or another problem. Furthermore, in this study approximately 90% of ET performed patients were born in hospital and the other 10% were born at home. Although most of the patients were born in institutional conditions, they all returned back to hospital with ET requiring bilirubin levels, which suggest that this is a problem about postpartum follow-up of term and near-term infants. Two of 3 infants with kernicterus were born at home and admitted first to

the hospital between 7 and 13 days, which impedes the early notice and increases the risk of kernicterus.

Another interesting result of our study is approximately 40% patients were brought to the hospital by parents for complaints other than jaundice. Moreover, infants were brought to our hospital approximately 2 days after when their families noticed the jaundice. These results show that inadequate information about jaundice is given to families. As in AAP (2) suggestions, families should not only be verbally informed, but also a detailed acknowledgement should be made via written documents contributing to early diagnose, and perhaps cutting back the need for ET.

Overuse of ET may reduce the incidence of bilirubin encephalopathy but adverse events remain common following ET (8,10). Some complications are as severe as the bilirubin encephalopathy. There are few recent reports of complications of ET or attempts to stratify the risk of adverse events based on clinical condition. Causes of death ascribed to ET include cardiovascular collapse during the transfusion and the subsequent complications of necrotizing enterocolitis, bacterial sepsis, and pulmonary hemorrhage (8). Mortality rates attributable to ET ranged from 0.65% to 3.2% in studies performed in the 1960s (25-27), and from 0.4% to 3.2% during the 1970s and 1980s (28-30). Mortality rate of ET in recent years is reported as 0.3%-1.5% (4,7,8,16). One of the 73 patients in this study (1.3%) died because of complications probably attributable to ET, similar to previous reports (4,7,8,16,31). The rate of prolonged/permanent serious sequel from ET is also very low, approximately 1%, and prior reports indicate that necrotizing enterocolitis and bacteremia are the most common severe complications (7,8). Bacteremia was detected only in 1 infant in the present study due to ET. The most common serious and transient morbidities include symptomatic hypocalcemia, hypoglycemia, bleeding due to thrombocytopenia, catheter-related complications, apnea, and bradycardia with cyanosis requiring resuscitation; all were reported as 5.2%-17% (7,8,31). The rate of serious and transient morbidities in our study was 8.2%. In a hypocalcemic newborn, calcium support was not performed during ET because it was not recommended (32). Similarly, the protocol in our unit also does not recommend calcium support. Asymptomatic untreated complications about laboratory findings were detected after ET, and recovered within 24-72 h without any treatment (8,33). In previous studies, thrombocytopenia, hypoglycemia, and hypocalcemia were commonly reported (8,10,33). The asymptomatic untreated complications in our study were in concordance with the literature. Most of the complications of ET are usually transient and mild and recovery is expected along with appropriate care and follow-up. Notwithstanding apnea, bradycardia and cyanosis can develop rarely, therefore cardio-respiratory and oxygen saturation monitoring appears to be indicated. Since many of the complications of ET are probably unavoidable, the best way to reduce complications is to prevent the need for ET (8). A close follow-up for discharged infants (2,4), early diagnose of infants with high risk before discharge (23,24), prevention from weight loss via appropriate nutrition selection (2,5), and intensive phototherapy appliance in convenient time (18) can greatly reduce the need for ET.

Conclusions

In conclusion, hyperbilirubinemia continues to hold the potential threat of complications for bilirubin encephalopathy and kernicterus apparently in healthy term and near-term newborn infants. This study shows that there was no etiologic reason in almost half of the infants requiring ET. Thus, it suggests that there is a risk for severe hyperbilirubinemia requiring ET in healthy term and near-term infants; and also healthy ones without any risk should be followed-up for jaundice as well as the newborns with high risk. Despite technological advances in neonatal care unit in the last decade, the blood exchange related complication rates remained the same. Though ET appears to prevent from bilirubin encephalopathy and kernicterus, the complications of ET, follow-up of these patients should be considered with this regard.

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