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Exchange transfusion for neonatal hyperbilirubinemia: A multicenter, prospective study of Turkish Neonatal Society

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What is already known on this topic?

- *Exchange transfusion has declined in recent years but is still performed in many countries.*
- *The procedure is associated with considerable complications.*

What this study adds on this topic?

- *This is the first prospective, population-based study of infants with hyperbilirubinemia who underwent exchange transfusion in our country.*
- *Proper protocols for screening, follow-up, and management of hyperbilirubinemia need to be enforced.*

ABSTRACT

Objective: The frequency of neonatal exchange transfusion has declined in recent years, but is still performed in many countries. The procedure is associated with complications. The aim of the study was to determine the clinical features and etiologies of infants with hyperbilirubinemia who underwent exchange transfusion and evaluate the adverse events and clinical outcomes.

Material and Methods: We performed a secondary analysis of the multicenter Turkish Neonatal Jaundice Online Registry data. Otherwise healthy newborns born ≥35 weeks of gestation who were hospitalized for jaundice and underwent exchange transfusion were included.

Results: One-hundred thirty-two patients with a mean serum bilirubin level on admission of 24.9±9.1 mg/dL were enrolled in the study. The most common cause for exchange transfusion was hemolytic jaundice (63.6%), followed by lack of proper feeding (12.9%). It was found that the infants with lack of proper feeding were discharged earlier from the maternity ward (p=0.02), but they were admitted to hospital later (p<0.001) with a higher bilirubin level (p=0.001), and geater weight loss (p=0.04). The reported rate of adverse events associated with exchange transfusion was 11.4%. The most common complication was thrombocytopenia (40%). None of the infants died during the procedure. Acute bilirubin encephalopathy was reported in 13 (9.8%) patients.

Conclusion: Severe hyperbilirubinemia requiring exchange transfusion and acute bilirubin encephalopathy are still challenging problems in neonatal periodin our country. The policies including blood group analysis of pregnant women, programs informing parents about breastfeeding and jaundice, and monitoring bilirubin levels of high-risk newborns should be developed to reduce the necessitating for exchange transfusion and to avoid related complications.

Keywords: Complication, exchange transfusion, hyperbilirubinemia, newborn

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Introduction

Exchange transfusion (ET) is the removal of an infant's blood with high bilirubin levels and/or antibody-coated red blood cells (RBCs) and replacement with fresh donor blood. It is indicated when hyperbilirubinemia remains at high levels despite intensive phototherapy and is particularly useful when there is excessive hemolysis. Another indication for ET is moderate-severe acute bilirubin encephalopathy (ABE), regardless of the bilirubin level at the time (1, 2). Although the frequency of neonatal ET has declined markedly in the last two decades,

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which is associated with the widespread use of intensive phototherapy, anti-D prophylaxis use for Rh-negative mothers, intravenous immunoglobulin (IVIG) use in infants with hemolysis, and advances in prenatal and postnatal care, this procedure is still performed in many countries, especially in those with a high incidence of severe hyperbilirubinemia (3-5).

However, ET is not a risk-free procedure. Adverse events associated with ET have been reported even in settings with advanced clinical care. It may be associated with complications such as sepsis, electrolyte imbalance, air embolism, portal vein thrombosis, cardiac overload, thrombophlebitis, thrombocytopenia, necrotizing enterocolitis, the transmission of blood-borne diseases, and even mortality (6-10).

The aim of this study was to determine the clinical features and etiologies of infants with hyperbilirubinemia who required ET, to evaluate the complications related to the procedure, adverse clinical outcomes associated with hyperbilirubinemia, and to try to define new recommendations to prevent these.

Material and Methods

This study used the data of the 132 patients who were enrolled in the Turkish Neonatal Jaundice Online Registry, which was a multicenter prospective cohort study conducted between September 2015 and September 2016 at 50 neonatal intensive care units (NICUs) to evaluate neonatal jaundice in our country. The full details of this study have been published elsewhere (11).

Otherwise healthy newborns born ≥35 weeks of gestation who were hospitalized for jaundice and underwent ET were included in the study. The data of infants from 20 collaborating NICUs were evaluated. Patients were managed according to the unit protocols based on the guidelines for neonatal jaundice (2, 12).

A standardized electronic case form including details about the demographic and clinical findings of infants was created on an online registry database with a separate sheet for each patient. Basic patient characteristics including the gestational age (GA), birth weight (BW), sex, history of phototherapy or ET in siblings, age on admission to hospital, type of delivery, age of admission, weight loss on admission, maximum level of total bilirubin at the time of ET (mg/dL), hemoglobin (g/dL), reticulocyte count (%), and bilirubin/albumin ratio were recorded. The cut-off values for reticulocyte count and bilirubin/albumin were taken as 7% and 6.5, respectively, according to the data found in our published study (11).

The causes of hyperbilirubinemia were classified as follows: Rh incompatibility was defined as jaundice with the presence of hemolysis (direct Coombs positivity, low hematocrit and elevated reticulocyte count) in Rh-positive neonate from Rh-negative mother. Hemolytic disease due to ABO incompatibility was defined as the presence of jaundice, elevated reticulocyte count, a peripheral smear suggestive of hemolysis, anemia with or without direct Coombs positivity in a neonate with blood group A or B from a mother with blood group O. Minor blood group incompatibility was defined as alloimmunization due to minor erythrocyte non-D Rh antigens (c, C, e, E, Kell, Duffy, Kidd, and MNS) with direct Coombs positivity (13).

Lack of proper feeding was diagnosed by the physician with the following: weight loss ≥10% on the third day of life, diminished urine/stool output, and confirmed dehydration with laboratory tests. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was diagnosed by measuring the enzyme activity using quantitative spectrophotometric analysis (14). Polycythemia was defined as a venous hematocrit ≥65% in an infant without signs of dehydration (15).

The double-volume ET procedure (160-180 mL/kg) was generally completed by repeatedly removing and replacing small aliquots of blood (5-7 mL/kg) in about 60-120 minutes through a single catheter in the umbilical vein or a catheter each in the umbilical vein and umbilical artery or a catheter placed in a peripheral vessel. Whole blood or RBCs plus fresh frozen plasma (FFP) was used for ET according to the unit's preference and availability of the product. The ETs were performed by the attending neonatologists or neonatology fellow or by pediatric residents.

The adverse events associated with the procedure were defined as any complication occurring within 7 days of an ET. The following definitions were used for adverse events: thrombocytopenia for a platelet count of <100 000/mm^3, hypocalcemia for serum calcium level of <8 mg/dL, necrotizing enterocolitis defined according to the modified Bell's criteria (16).

Adverse clinical outcomes associated with hyperbilirubinemia were evaluated. The bilirubin- induced neurologic dysfunction (BIND) score was used to define ABE (17). All patients underwent auditory evaluations to determine the auditory brainstem response before discharge from NICUs, and repeat tests were performed in the following months. Prolonged jaundice was defined as persisting jaundice >14 days for term infants, >21 days for preterm infants (born <37 gestational weeks') (18). Readmission was defined as infants who returned to the hospital within 0-20 days of initial discharge (19).

The study was approved by Online Studies Scientific Steering Committee of Turkish Neonatal Society, and ethics committee approval was obtained from Ankara University Faculty of Medicine, Clinical Researches Ethics Committee (Approval No. 14-593-15). The study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all participants.

Statistical analysis

All data were analyzed using the IBM Statistical Packages for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA) Ver. 21.0 software package. Categorical data are presented as number (n) and percentage (%). Continuous variables are presented as mean±standard deviation. Student's t-test was used to compare the groups showed normal distribution. A *p*-value at the 0.05 level was considered statistically significant.

Results

During the study period, 5620 infants were recorded at 'Turkish Neonatal Jaundice Online Registry', and 132 of these infants (2.3%) underwent ET. The total number of admissions of the 20 collaborating NICUs was 24 899 during this period.

The infants had a mean GA and BW of 38±1.5 weeks and 3005±480 g, respectively. The male to female ratio was 1.4:1. All infants were hospital-born. The mean age of the infants at discharge from the maternity ward and on admission to the NICU for jaundice was 2.9±1.6 days and 3.7±2.5 days, respectively. The mean total serum bilirubin level on admission was 24.9±9.1 mg/dL, and almost half of the infants (49.3%) were admitted with a bilirubin level of >25 mg/dL. The demographic and laboratory findings of the patients are shown in Table 1.

Table 1. Demographic and laboratory findings of patients underwent exchange transfusion

	Number of patients (n=132)
Gestational age (w)*	38±1.5
Birth weight (g)*	3005±480
Sex (male), n (%)	77 (58.3)
Type of delivery (CS), n (%)	53 (40.1)
Sibling with history of phototherapy, n (%)	28 (21.2)
Sibling with history of ET, n (%)	6 (4.5)
Age at discharge from maternity service (d) *	2.9±1.6
Age on admission (d)*,§	3.7±2.5
	3.5 (1-9)
Weight loss rate on admission (%)*	4.5±5.2
≤10% loss, n (%)	112 (85)
>10% loss, n (%)	20 (15)
Bilirubin level on admission (mg/dL)*	24.9±9.1
<20 mg/dL, n (%)	35 (26.5)
20-25 mg/dL, n (%)	32 (24.2)
26-30 mg/dL, n (%)	27 (20.5)
>30 mg/dL, n (%)	38 (28.8)
Hemoglobin on admission (g/dL)*	14±4.2
Direct coombs positivity, n (%)	55 (41.7)
Reticulocyte count*	6.4±5.8
<7, n (%)	63 (47.7)
≥7, n (%)	37 (28)
Not recorded	32 (24)
Albumin level (g/dL) *	3.4±0.5
Bilirubin/albumin ratio <6.5, n (%)	39 (29.5)
Bilirubin/albumin ratio ≥6.5, n (%)	63 (47.7)
Not recorded	30 (22.8)

*Data reported as mean±standard deviation, §Data reported as median (range). CS, Cesarean section; ET, Exchange transfusion

Table 2. Causes of hemolytic jaundice

Causes	Number of patients (n=15)
ABO incompatibility, n (%)	37 (44)
Rh incompatibility, n (%)	34 (40.5)
Minor blood group incompatibility, n (%)	9 (10.7)
G6PD deficiency, n (%)	4 (4.8)

G6PD, Glucose-6-phosphate dehydrogenase

Table 3. Adverse events associated with exchange transfusion procedure

	No. of patients (n=15)
Thrombocytopenia, n (%)	6 (40)
Hypocalcemia, n (%)	3 (20)
Hypocalcemia+thrombocytopenia, n (%)	2 (13.3)
Necrotizing enterocolitis, n (%)	2 (13.3)
Hypocalcemia+thrombocytopenia+sepsis, n (%)	1 (6.7)
Sepsis, n (%)	1 (6.7)

The most common cause for ET was hemolytic jaundice (63.6%), followed by a lack of proper feeding (12.9%), prematurity (4.5%), polycythemia (3%), cephalohematoma (1.5%), and sepsis (0.75%). No underlying condition could be found in 13.6% of cases (Figure 1). Among the hemolytic jaundice cases, ABO blood incompatibility was the leading etiology (44%) (Table 2). Among the 80 infants with hemolytic jaundice due to ABO blood, Rh or minor blood group incompatibility, 39 infants received IVIG before ET.

The infants with a lack of proper feeding (n=17) were discharged earlier from the maternity ward after birth (2.4±0.9 vs. 3.1±1.7 days, p=0.02), but were admitted to the NICU later (5.9±2.2 vs. 3±2.3 days, p<0.001) with a higher mean weight loss (8.5±6.1 vs. 3.5±4.6, p=0.04) and a higher bilirubin level on admission (30.1±6.4 vs. 23±9.4 mg/dL, p=0.001) when compared with infants who had hemolytic jaundice (n=84). Almost half of the patients (47%) with a lack of proper feeding had severe dehydration (>10% weight loss).

Exchange transfusion was performed via a single catheter in the umbilical vein in 124 (94%) patients, a catheter each in the umbilical vein and umbilical artery in five (4%) patients, and a substitute catheter placed in a peripheral vein in three (2%) patients. Although whole blood was used in 59 (44.7%) patients, RBCs plus FFP was preferred in 73 (55.3%) infants for the ET procedure. Adverse events associated with ET were seen in 15 patients (11.4%) (Table 3). The most commonly observed complication was thrombocytopenia (40%). None of the infants died during the ET procedure.

Table 4. Adverse clinical outcomes of infants who underwent exchange transfusion

	Number of patients (n=132)
Acute bilirubin encephalopathy, n (%)	13 (9.8)
Prolonged jaundice, n (%)	12 (9.1)
Hearing loss, n (%)	7 (5.3)
Rehospitalization, n (%)	2 (1.5)
Without problem, n (%)	98 (74.2)

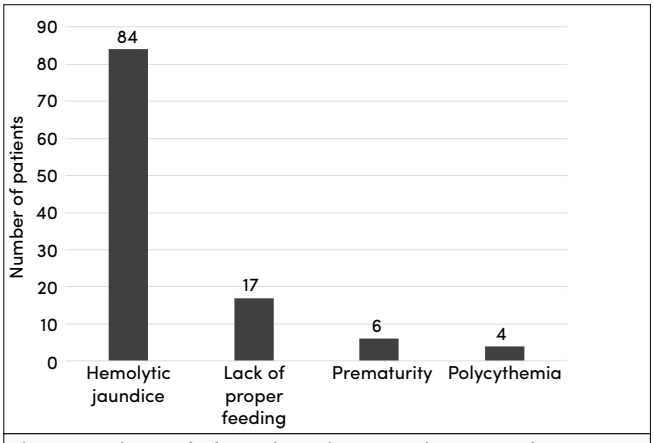

Figure 1. Etiologies of infants who underwent exchange transfusion

The adverse clinical outcomes reported in patients who underwent ET are listed in Table 4. ABE was reported in 13 infants (9.8%), 11 (84.6%) of whom were male. The median BIND score of infants who had ABE was 7 (range 4-9) days. Patients with ABE had a mean admission age as 4±1.2 days and mean serum bilirubin level of 35.9±5.7 mg/dL, whereas infants who did not develop ABE had a mean serum bilirubin level of 23.8±8.6 mg/dL ($p<0.001$). The etiologies of infants with ABE were reported as hemolytic jaundice in (n=8, 61.5%), lack of proper feeding (n=2, 7.7%), and unknown cause (n=3, 23.1%), respectively. Two of these patients died in the NICU on the postnatal 8th and 9th days of their lives.

Discussion

Exchange transfusion is a definitive and an effective therapy where intensive phototherapy is either lacking or proves to be ineffective in arresting rising bilirubin levels in infants with severe neonatal hyperbilirubinemia or symptoms of ABE (2, 20, 21). Through this study, we determined the incidence and the underlying causes of patients who underwent ET, adverse events associated with ET, and adverse clinical outcomes associated with hyperbilirubinemia. Although the findings presented here are already known about this procedure, some specific implications for our country were obtained with the data of this study.

ABO hemolytic disease of the newborn was the leading cause of hyperbilirubinemia in patients who underwent ET in our cohort, similar to that reported in many series (22-25). One the other hand, this study showed that rhesus disease was the second most common cause of hemolytic jaundice, responsible for 25.7% of all ETs. Despite anti-D prophylaxis being provided free by the state, rhesus disease is still a common cause of alloimmunization in our country. In a study from Turkey, the prevalence of Rh alloimmunization was found as 8.7% in the Rh-negative group (26).

One of the important results of the study was the lack of proper feeding, which was the second most common cause of ET. Cesarean section (CS) delivery in Turkey is above the suggested rate by the World Health Organization, which may contribute to a lack of proper breastfeeding with early discharge from maternity wards (27). Poor caloric intake, dehydration associated with decreased volume and frequency, and the secondary delayed passage of stools due to inadequate breastfeeding may contribute to the development of hyperbilirubinemia (3). Studies showed that woman who delivered by CS were less likely to breastfeed, or there was a delay in breastfeeding initiation (28, 29). Although it is recommended to discharge mothers after three days following CS by health organization, it is a common practice to discharge mothers on the second day after birth. It was demonstrated that discharge after 24 hours following CS resulted in higher neonatal admission with jaundice compared with the group discharged after 72 hours (30). Earlier discharge of neonates from maternity wards may result in infants leaving close supervision before breastfeeding was successfully established and before clinically apparent jaundice could become manifest (31). We believe that late initiation of effective breastfeeding, short hospital stay in the maternity ward after birth, inadequate establishment of breastfeeding, and inconsistent follow-up after discharge may all be factors in the high rate of severe hyperbilirubinemia requiring ET in our country.

The ET procedure is relatively safe when performed by experienced practitioners in newborns (8, 9). Central umbilical catheter or peripheral veins are used for ET to remove and replace the infant's blood (6). The pull-push technique through a central umbilical catheter (98%) was used mostly with RBCs and FFP (55.3%) in this study. Although Yigit et al. (32) demonstrated that the use of O group RBCs suspended in A or B plasma decreased the re-exchange risk compared with O group whole blood in cases of ABO hemolytic disease, the same efficiency was shown with using either reconstituted or fresh whole blood for ET (33). As whole blood contains natural anti-A or anti-B antibodies, group O Rh-specific RBCs reconstituted with AB plasma are recommended in ABO incompatibility. If mother and infant are ABO identical, group-specific RBCs or whole blood can be used (34). Adverse events associated ET were reported at different rates from centers. The reported adverse events in our study were similar to previous reports in the literature (5, 7-9). Although mortality was reported in a few series, we did not observe any deaths associated with ET in our study.

Most neonatal jaundice cases are benign, but in some cases, serum bilirubin level may rise excessively and can cause serious complications, such as acute encephalopathy. Cases of kernicterus continue to be reported worldwide. Neonates with hemolytic disease seem to be at higher risk of bilirubin-induced brain damage than non-hemolytic neonates (35-37). Lack of recognition and treatment of jaundice, and failure of the healthcare system could be represented with increased incidence of high bilirubin levels. Although our study was not designed to access the incidence of long-term neurologic problems, 13 (9.8%) infants developed ABE, and the most common cause of hyperbilirubinemia in these infants was hemolytic disease. It has been demonstrated that measuring bilirubin level before discharge is helpful to predict which infants will exhibit jaundice (38). We could likely prevent more severe hyperbilirubinemia requiring ET in addition to bilirubin encephalopathy if all centers performed a bilirubin test on all neonates before discharge and planned follow-up.

This study includes the first multicenter, online nationwide information on ET from our country. The data reported in a registry database was largely drawn from NICUs of tertiary centers across Turkey where neonatologists are aware of the situation, and therefore the information can be generalized to a national level. The limitation of this study is the dependence on self-reported data, which may lead to underestimating the exact incidence and data of severe hyperbilirubinemia and ABE.

The results of this study demonstrate that hyperbilirubinemia requiring ET and bilirubin encephalopathy are still problems in our country. Although hemolysis is the major cause of hyperbilirubinemia in infants needing ET, the other important factors are early discharge from maternity ward after birth without establishing appropriate breastfeeding, insufficient feeding, under-recognition of jaundice by parents, and late presentation to hospital. Simple policies for blood group analysis of pregnant women, breastfeeding consultations through postnatal care, bilirubin monitoring of newborns before discharge from

the maternity ward, and health education of the population about jaundice can identify infants with high risk and help to prevent severe hyperbilirubinemia related short and long-term complications.

Ethical Committee Approval: The study was approved by Online Studies Scientific Steering Committee of Turkish Neonatal Society, and the ethic committee approval was obtained from Ankara University Faculty of Medicine, Clinical Researches Ethics Committee (Approval No. 14-593-15).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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