Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2022;47(1):111-119
DOI: 10.17826/cumj.1020238

ARAŞTIRMA / RESEARCH

Outcomes of rescue exchange transfusion in severe neonatal hyperbilirubinemia

Şiddetli neonatal hiperbilirubinemide kurtarma değişimi transfüzyonunun sonuçları

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Cukurova Medical Journal 2022;47(1):111-119

Abstract

Purpose: Urgent treatment in newborns with severe hyperbilirubinemia is the removal of bilirubin from the body by exchange transfusion (ET) as the main treatment modality. The aim of this study was to evaluate the outcomes of newborns with severe hyperbilirubinemia who underwent ET in two neonatal ıntensive care units (NICUs).

Materials and Methods: The clinical data were collected of 28 newborns who had undergone rescue exchange transfusions after hospitalization with a diagnosis of severe hyperbilirubinemia in NICUs of a university hospital and a state hospital.

Results: Evaluation was made of 28 newbons with a median serum bilirubin level on admission of 31.2 (20.3-36.8) mg/dL. The leading cause for exchange transfusion was hemolytic jaundice (67.8%), followed by inadequate feeding (14%). The most common cause of hyperbilirubinemia was Rh incompatibility. The reported rate of adverse events associated with exchange transfusion was 71%. The most common complications due to ET were thrombocytopenia and anemia. Four infants died after the ET therapy. Acute bilirubin encephalopathy (ABE) was detected in 39% of the newborns. Serum bilirubin and bilirubin/albumin ratios were found to be high in newborns with ABE.

Conclusion: Newborns with severe hyperbilirubinemia, especially when related to hemolytic jaundice, may need rescue ET. As newborns with severe hyperbilirubinemia with a high bilirubin/albumin ratio are at risk of ABE, ET should be considered in these cases

Keywords:. Newborn, exchange transfusion, hyperbilirubinemia, acute bilirubin encephalopathy

Öz

Amaç: Şiddetli hiperbilirubinemili yenidoğanlarda bilirubinin vücuttan uzaklaştırılabilmesi için, kan değişimi (KD) acil bir tedavi yöntemidir. İki yenidoğan yoğun bakım ünitesinde (YYBÜ) KD uygulanan şiddetli hiperbilirubinemili yenidoğanların sonuçlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bir üniversite hastanesi ve bir devlet hastanesinin YYBÜ'lerinde ağır hiperbilirubinemi tanısı ile hastaneye yatırıldıktan sonra kan değişimi yapılan 28 yenidoğanın klinik verilerini topladık.

Bulgular: Başvuru sırasında medyan serum bilirubin düzeyi 31,2 (20,3-36,8) mg/dL olan 28 yenidoğan çalışmaya alındı. En sık kan değişimi nedeni hemolitik sarılık (%67.8) ve bunu uygun beslenememe (%14) takip ediyordu. Hiperbilirubineminin en sık nedeninin Rh uyuşmazlığı olduğu bulundu. Kan değişimi ile ilişkili bildirilen advers olay oranı %71 idi. KD'ye bağlı en sık görülen komplikasyonlar trombositopeni ve anemi idi. İşlem sonrası 4 bebek hayatını kaybetti. Yenidoğanların %39'unda akut bilirubin ensefalopatisi (ABE) tespit edildi. ABE'li yenidoğanlarda serum bilirubin ve bilirubin/albümin oranları yüksek bulundu.

Sonuç: Özellikle hemolitik sarılıkla ilişkili ciddi hiperbilirubinemisi olan yenidoğanların kurtarma ET'sine ihtiyacı olabilir. Bilirubin/albümin oranları yüksek, şiddetli hiperbilirubinemisi olan yenidoğanlar ABE açısından risk altında olduğundan bu olgularda ET düşünülmelidir.

Anahtar kelimeler: Yenidoğan, kan değişim transfüzyonu, hiperbilirubinemi, akut bilirubin ensefalopatisi.

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Geliş tarihi/Received: 07.11.2021 Kabul tarihi/Accepted: 19.01.2022

INTRODUCTION

Neonatal hyperbilirubinemia is the most common reason for hospital admission in the first week of life[1,2]. Appropriate phototherapy or exchange transfusion (ET) is effective in controlling excessively high bilirubin in affected newborns[3]. Otherwise, untreated severe hyperbilirubinemia may cause acute bilirubin encephalopathy (ABE), and kernicterus[4,5] Severe hyperbilirubinemia, can also lead to long-term neurological sequelae such as sensorineural hearing loss and kernicterus[6,7].

Kernicterus can be prevented with the use of phototherapy, intravenous immunoglobulin (IVIg) therapy, or ET to lower serum bilirubin levels[8]. Phototherapy is an effective, non-invasive, first-line treatment that reduces bilirubin levels. IVIg is adjuvant therapy for hyperbilirubinemia in cases of hemolytic diseases, but the effectiveness of this treatment is controversial[7,9]. Although ET is more efficient at reducing bilirubin levels which cause severe hyperbilirubinemia due to hemolysis[10], it is also known to cause side-effects such as vascular events, and cardiovascular, electrolyte, and hematological disorders[11].

The incidence of severe hyperbilirubinemia has been reduced with the implementation of standardized and harmonized guidelines in high-income countries (HICs)[12]. However, it is still a major health problem resulting in significant disability and mortality in low and middle income countries (LMICs)[13].

Turkey is classified as a middle income country (MIC)[14], and the incidence of severe neonatal hyperbilirubinemia and ABE has been reported to be higher than in HICs and lower than in LMICs[1,12]. The aim of this study was to evaluate the outcomes of newborns with severe hyperbilirubinemia who underwent ET in two neonatal intensive care units (NICUs). It was thought that the presentation of our experience with ET due to severe hyperbilirubinemia may be helpful in the optimization of neonatal care strategies in Turkey.

MATERIALS AND METHODS

Study design and participants

This multicenter retrospective cohort study to evaluate the causes of severe hyperbilirubinemia used the data of 28 newborns who underwent exchange transfusion between December 2017 and December 2020 in two NICUs. The newborns included were those hospitalized for jaundice and undergoing ET in the NICUs of two hospitals. Infants with severe hyperbilirubinemia on presentation, defined as serum bilirubin level at or above the exchange transfusion threshold according to the American Academy of Pediatrics (AAP) exchange transfusion guidelines, were included in the study[3,7]. Six newborn infants with direct hyperbilirubinemia (n=1), TORCH infection (n=1), neonatal hepatitis (n=1) and lack of sufficient data (n=3) were excluded from the study.

The study was conducted in accordance with the principles of the Declaration of Helsinki and approval was granted by the Non-Interventional Clinical Research Ethics Committee of Sivas Cumhuriyet University (Decision no: 2020-09/09).

Variables of interest

Basic patient data were recorded, including the gestational age (GA), gestational birth weight (BW), gender, delivery mode, sibling with history of phototherapy, age at onset of jaundice, postnatal age on admission, weight loss during hospitalization, total bilirubin level (mg/dL), hemoglobin on admission (g/dL), Direct Coombs positivity (%), reticulocyte count (%), albumin level (g/dL), bilirubin/albumin ratio, length of hospital stay, IVIG therapy, mortality, cause of hyperbilirubinemia, Rh isoimmunization, ABO incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and sepsis. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was confirmed by measuring enzymatic activity through quantitative spectrophotometric analysis [15].

Lack of nutrition was diagnosed by the physician from the following: weight loss ≥10% on the third day of life, decreased urine/stool output, and dehydration confirmed by laboratory tests.

Set-Up and procedure

Fresh red blood cells with reduced leukocytes (within 7 days of collection), irradiated for ABO and Rh compatible with both the infant and mother, were remixed in the appropriate plasma (usually AB). Bags containing packed red blood cells and citrate as anticoagulants were reconstituted to a final hematocrit of 45%. The replacement volume was twice the blood volume of the newborns. Each newborn underwent the ET procedure using disposable equipment under aseptic technical

conditions using the umbilical vein. The double-volume exchange procedure was usually completed in 60-90 minutes, according to published standard guidelines of repeated removal and replacement of small blood aliquots (5 mL/kg) [16].The infants who presented with the complaint of neonatal jaundice and were planned to undergo exchange transfusion according to the AAP guideline, were administered the ET by the same neonatologists (FK, GT). The data of the infants who underwent exchange transfusion were recorded.

Therapeutic method

The neonates were managed using unit protocols based on AAP proposals for the treatment of hyperbilirubinemia. Accordingly, newborns with findings of ABE or serum bilirubin levels of 5 mg/dL above the exchange transfusion cut-off value underwent emergency exchange transfusion. For newborns with total serum bilirubin level slightly above the exchange cutoff value, 3-4 hours of intensive phototherapy was applied first, then exchange transfusion if the serum bilirubin level remained above the exchange transfusion threshold levels. Hemolytic icterus was confirmed as anemia, hyperbilirubinemia, and hemolysis findings in a peripheral smear. The threshold values for reticulocyte count and bilirubin/albumin were taken as 7% and 6.5%, respectively[1]. Direct Coombs test (DCT) positivity was accepted as a contributory finding for hemolytic icterus. IVIG was used in newborns with DCT positivity and hyperbilirubinemia close to the exchange transfusion level. Neurological evaluation was performed for newborn infants at the time of admission or in the first 6 hours of admission. The bilirubin-induced neurological dysfunction (BIND) score was used to evaluate ABE. According to the BIND score, ABE was graded as mild, moderate, or severe [17]. It was originally proposed as a scale from 0-9 where zero is normal and nine is the most abnormal [18]. Newborns with seizures and abnormal neurological signs such as irritability, sucking, and decreased muscle tone were enrolled to determine the BIND score.

Exchange transfusion complications

Procedural adverse events were defined as any adversity occurring within seven days of an ET. The following definitions were used for adverse events: thrombocytopenia for a platelet count of <100,000/mm3, hyperkalemia (serum potassium >6 mmol/L), anemia (Hb <15 mg/dL), arrhythmia, bradycardia, feed intolerance hypocalcemia for serum calcium level of <8 mg/dL, and necrotizing enterocolitis defined according to the modified Bell's criteria[19,20]. Sepsis criteria were defined as a positive blood culture for proven sepsis, and for suspected sepsis, elevated C-reactive protein, a total leukocyte count of >25,000/mm3, and band count of >10%[21].

During and after the ET procedure, all the newborns were monitored and complications were assessed. If observed, catheter-related events such as hemorrhage, infection, hemodynamic (related to excess removal or injection of blood), and hypo-or hypertension were recorded.

Statistical analysis

Data obtained in the study were analyzed statistically using IBM SPSS 23 software (USA). Data were examined with descriptive statistical tests. The normality of numerical variables was examined with the Shapiro-Wilk test. Non-parametric tests were applied to the data that did not conform to normal distribution. Descriptive measures were expressed as number and percentage for categorical variables, and as median and minimum-maximum values for data that did not show normal distribution. The Mann-Whitney-U test was used for numerical data that did not show normal distribution. The Chi-square test was used for categorical data that did not show normal distribution. The paired Wilcoxon test was used to compare pre and post exchange values. A value of $p<0.05$ was considered statistically significant.

RESULTS

The total number of admissions in the two NICUs was 3600 infants between December 2017 and December 2020. Of these cases, 945 newborns were hospitalized due to hyperbilirubinemia and ET was applied to 28 (2.9%) of these infants. The newborns had a median GA and BW of 38 (38-39) weeks and 3200 (2747-3400) g, respectively. From the total 28 infants included in the study, 15 (53.6%) were male, and 19 (67.9%) were delivered by normal vaginal delivery (NVD). Twenty-five of the infants were born in the hospital, and 3 were born at home.

The median age of the infants at the onset of jaundice and on admission to the NICU for jaundice was 2 (1-3.7) days and 3 (1-6) days, respectively. The median

total serum bilirubin level on admission was 30.01 (19.22-36.82) mg/dL. The demographic and laboratory findings of the patients are shown in Table 1. The most common cause of ET was hemolytic jaundice (67.8%), followed by a lack of proper feeding (14.4%), sepsis (7.1%), cephalhematoma (3.5%), and no underlying condition could be found in 10.7% of newborns (Table 2). In the hemolytic jaundice cases, Rh incompatibility was the leading etiology (32.1%) (Table 2). Of the 19 infants with hemolytic jaundice due to ABO blood, Rh, or minor blood group incompatibility, 16 (57.1%) infants received IVIG before ET.

Table 1. Clinical and laboratory characteristics of the severe neonatal hyperbilirubinemia group.

Variables	n=28 (%)
Gestational age (w) *	38 (38-39)
Birth weight (g) *	3200 (2747-3400)
Sex (male) n,(%)	15 (53.6%)
Type of delivery (NVD) n, (%)	19 (67.9%)
Sibling with history of phototherapy, n (%)	4 (14%)
Age at onset of jaundice (d)	2 (1-3.75)
Age on admission (d)	3 (1-6)
Weight loss rate on admission (%)*	4 (14.3%)
Bilirubin level on admission (mg/dL)*	30.01 (19.22-36.8)
Hemoglobin on admission (g/dL)*	14.4 (11.02-16.7)
Direct Coombs positivity, n (%)	14 (50%)
Reticulocyte count*	6.8 (4.01-13.07)
<7, n (%)	9 (32%)
≥7, n (%)	9 (32%)
Not recorded	10 (35%)
Albumin level (g/dL) *	3.9 (3.4-4.17)
Bilirubin/albumin ratio <6.5, n (%)	9 (32%)
Bilirubin/albumin ratio ≥6.5, n (%)	19 (67%)
Hospital stay (d)*	8 (5.2-11.7)
IVIG Yes n, (%)	16 (57.1%)
Mortality	4 (14.2%)

*Data reported as median with interquartile range. NVD: Normal vaginal delivery; IVIG, intravenous immunoglobulin

Table 2. Causes of jaundice requiring exchange transfusion.

Causes	n=28 (%)
Rh incompatibility	9 (32.1%)
ABO incompatibility	5 (17.9%)
Lack of proper feeding	4 (14.4%)
Blood subgroup incompatibilities	3 (10.7%)
G6PD deficiency	2 (7.1%)
Sepsis	2 (7.1%)
Cephalhematoma	1 (3.5%)
Undetermined	3 (10.7%)

G6PD, Glucose-6-phosphate dehydrogenase

The age on detection of signs of jaundice [5 (3.5-6.5) days] and the age on hospital admission [6 (5.25-8.25) days] were higher in newborns with weight loss compared to neonates with hematological jaundice (p=0.012). There was no significant difference between newborns with pathological weight loss and those with hematological jaundice in respect of bilirubin levels [36.75 (30.9-38.47) mg/dL; p>0.05].

The serum total bilirubin, direct bilirubin, electrolytes, platelet count, albumin, alanine aminotransferase (ALT), and aspartate transaminase (AST) values and blood Hb levels of newborns who underwent ET therapy are shown in Table 3. With the exception of the serum total bilirubin levels, there was no significant difference between laboratory variables measured before ET therapy and two hours

later, after ET therapy (p>0.05). ET therapy significantly reduced the serum total bilirubin level of the newborns (p<0.05). The serum albumin, thrombocyte count, and AST level were reduced significantly by ET therapy (p<0.05). Newborns with a high reticulocyte count at the rate of 11/28 (39%) before ET had low hemoglobin values (p<0.05).

The most commonly observed complications were thrombocytopenia (39.2%), anemia (32.1%), hypernatremia (17.8%), sepsis (14.2%), hypocalcemia (14.2%), bradycardia (3.5%), apnea (3.5%), and hypothermia (3.5%). Catheter-related events were not observed (Table 4).

Table 3. Laboratory findings of newborns before ET therapy and two hours later after ET therapy.

Lab parameters	Before ET therapy n=28	After ET therapy n=28	P value
Total bilirubin (mg/dL)*	31.2 (20.3-36.8)	15.35 (11.26-20.27)	**0.000**
Indırect bilirubin (mg/dL) *	29.5 (19.4-31.6)	14.05 (10.56-17.57)	**0.000**
Direct bilirubin (mg/dL)*	1.7 (0.9-5.2)	1.3 (0.7-2.7)	0.071
Hemoglobin (g/dL)*	14.1 (12.7-16.9)	13.4 (11.9-14.7)	0.051
Serum sodium (mmol/L)*	140.5 (139-143)	141 (135-144)	0.368
Serum potassium (mmol/L)*	4.7 (4.4-4.7)	4.4 (4.0-4.9)	0.110
Serum calcium (mg/dL)*	9.4 (8.9-10)	9.5 (8.8-10.4)	0.788
Platelet (10^9/L)*	297000 (159000- 358000)	153000 (76000-244000)	**0.005**
Albumin (g/L)*	3.9 (3.4-4.1)	3.2 (2.8-3.7)	0.002
ALT (U/L)*	14 (10.2-18)	14 (10.2-23.5)	0.753
AST (U/L)*	48.5 (31-66.7)	28.5 (19-46.2)	**0.010**

*Data are shown as median with interquartile range.; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

Table 4. Adverse events during and after exchange transfusion.

Adverse events	No.of patients n:28 (%)
Thrombocytopenia n (%)	11 (39.2%)
Anemia n (%)	9 (32.1%)
Hypernatremia n (%)	5 (17.8%)
Sepsis n (%)	4 (14.2%)
Hypocalcemia n (%)	4 (14.2%)
Bradycardia n(%)	1 (3.5%)
Apnea n(%)	1 (3.5%)
Hypothermia n(%)	1 (3.5%)

Table 5. Demographic and clinical characteristics of infants with and without ABE.

	ABE (n =11)	No ABE (n=17)	P value
Birth weight (g)*	3200 (2700-3300)	3300 (2745-3450)	0.487
Gestational age (w)*	38 (38-39)	38 (38-39)	0.677
Male n(%)	7 (63.6%)	8 (47.1%)	0.320
NVD n(%)	7 (63.6%)	12(70.6%)	0.507
Postnatal age on admission, (d)*	5 (2-8)	2 (1-5.5)	0.082
Total serum bilirubin (mg/dL)*	36.6 (31.6-39)	23.0 (17.8-31.2)	**0.004**
Bilirubin/albumin (ratio)*	8.7 (8.3-10)	6.4 (4.6-8.8)	**0.005**
G6PD deficiency n(%)	1 (9%)	1 (5%)	0.651
Rh isoimmunization n(%)	3 (27%)	7 (41%)	0.952
ABO incompatibility n(%)	2 (18%)	3 (17.6%)	0.419
BIND score	9 (8-9)	4 (3,5-5,5)	**0.000**
Mortality n(%)	3 (27%)	1 (5%)	0.153

G6PD: Glucose-6-phosphate dehydrogenase, ABE: Acute bilirubin encephalopathy, NVD: Normal vaginal delivery BIND: Bilirubin-induced neurological dysfunction ; *Data are expressed as median with interquartile range.

The mortality rate was 14.2% (n:4). Two of these four patients died on the 2nd postnatal day, and the other 2 on the 3rd and 6th days of life in the NICU. These patients who developed mortality after ET were determined to have died as a result of metabolic acidosis, heart failure, and respiratory failure due to gram-negative neonatal sepsis. None of the infants died during the ET procedure (Table 1,5).

The characteristics of infants with and without ABE are outlined in Table 5. ABE developed in 11 (39%) newborns. The median BIND score of infants with ABE was 9 (range 8-9) ($p<0.05$). Patients with ABE had a median age on admission of 5 (2-8) days and a median serum bilirubin level of 36.6 (31.6-39) mg/dL, and the infants who did not develop ABE had a median serum bilirubin level of 23.03 (17.8-31.2) mg/ dL ($p<0.05$). The serum total bilirubin level and bilirubin/albumin ratio were significantly higher in the newborns with ABE ($p<0.05$). The etiologies of infants with ABE were reported as hemolytic jaundice in 8 (72.7%), and lack of proper feeding in 3 (27%). No significant difference was observed between the newborns with and without ABE in respect of other clinical and laboratory parameters ($p>0.05$).

DISCUSSION

The main findings of the study were as follows; Rh incompatibility was the most common cause of hyperbilirubinemia in newborns requiring ET. The most common complications related to ET were thrombocytopenia and anemia. Acute ABE was detected in 39% of the study group. The significant risk factors for ABE were found to be a high level of serum bilirubin and bilirubin/albumin ratio.

Hyperbilirubinemia is a very common problem in the neonatal period with high morbidity and mortality. Phototherapy or exchange transfusion are accepted as effective therapies in reducing excess bilirubin in newborns admitted to the NICU[3]. The therapy of ET for severe neonatal hyperbilirubinemia was first published in the early 1950s[22]. In the current study, ET was applied to 28 (2.9%) of the infants hospitalized due to hyperbilirubinemia, and the most common cause was found to be Rh incompatibility (32%).The most common cause of severe hyperbilirubinemia in newborn infants has been previously reported to be Rh incompatibility, requiring ET over a range of 20% to >70%. Most treatments (88%) are performed within the first twelve hours after birth. After the American Academy of Pediatrics guidelines for the treatment of hyperbilirubinemia began to be used in HICs, the use of ET decreased to <20% [23]. The majority (21-38%) of ET therapy is administered due to acute hemolysis resulting in ABO and Rh incompatibilities. Blood subgroup incompatibilities, G6PD, and hypothyroidism have been reported to be the causes of 9-21% of the cases of serious hyperbilirubinemia, and 3.7-22% were due to other risk factors[24]. In the literature, hypothyroidism, urinary tract infections, hereditary spherocytosis, incompatibilities between blood subgroups, pyruvate kinase enzyme deficiency, hemoglobinopathies, and subdural hematoma have been reported as the causes of severe hyperbilirubinemia[24,25]. Similar outcomes were published in a study from Turkey for the years 2017-2018, in which it was shown that ABO and Rh incompatibilities were the most frequent causes of hyperbilirubinemia in 115 newborns who required ET (48%). In that study, the etiology could not be determined in 20% of the newborns[12]. Similarly, in the current study, the rate of hyperbilirubinemia due to ABO and Rh incompatibility was found to be 53%. The results of this study are consistent with previous findings in literature reporting that the etiology of hyperbilirubinemia could not be determined at a rate varying between 17% and 37%[24].

In other studies, it has been reported that G6PD deficiency is 31.5% to 34.4% in newborns with kernicterus[26,27]. G6PD deficiency is usually associated with serious hyperbilirubinemia requiring ET in newborns with lower levels of bilirubin. In a previous study from Turkey, the prevalence of G6PD deficiency was determined as 1%– 5% of the population with a male to female ratio of 3:1, and 3.8% of neonatal indirect hyperbilirubinemia infants were seen to be G6PD deficient[28]. In the current study, G6PD deficiency was determined as 7%, but this was not statistically significant. The disease is mainly prevalent in the Mediterranean region and the Middle East. Therefore, Turkey, due to both the geographical location and the fact of harboring immigrants from the Middle East, is expected to have a high prevalence of G6PD deficiency. The lack of data to investigate the effect of G6PD deficiency on the development of serious hyperbilirubinemia may be a limitation of this study. This also indicates that more newborns should be screened for G6PD.

It has been reported that weight loss and dehydration are important risk factors for hyperbilirubinemia in

newborns [29]. Before bilirubin levels return to normal, weight loss of >10% increases the likelihood of developing hyperbilirubinemia and kernicterus[30]. The AAP has reported weight loss of >12% as a risk factor in the development of severe hyperbilirubinemia[3]. In the current study, pathological weight loss was detected in 14% of newborns due to insufficient breast milk intake, but this was not statistically significant for the development of hyperbilirubinemia. Inadequate caloric intake, dehydration associated with volume and frequency reduction, and delayed stool transit secondary to inadequate breastfeeding may contribute to the development of hyperbilirubinemia[31]. It is common practice for mothers to be discharged on the second day after delivery, although healthcare providers recommend that mothers be discharged three days after cesarean section. It has been shown that being discharged 24 hours after CS is more likely to result in newborns presenting with jaundice compared to those discharged after 72 hours[32]. Therefore, the American Academy of Pediatrics and the Canadian Pediatric Association recommend a follow-up period of 48-72 h after hospital discharge of newborns[3].

Despite the increased experience of ET and technical improvements, ET remains an invasive procedure with a high risk of adverse effects. Morbidity rates associated with exchange transfusion (bacteremia, NEC, catheter-related complications) can reach 24%[33]. The most common side-effects of ET have been reported to be hematological and biochemical including thrombocytopenia, hypocalcemia, and metabolic acidosis. Patra et al. stated that the most common complications due to ET were thrombocytopenia (44%) and hypocalcemia (29%)[34]. Complications including hypocalcemia, hypoglycemia, apnea, and bradycardia with cyanosis may occur in the range of 5.2% to 17% in the early period[35]. In a multi-center study conducted in Turkey, the most common complication associated with exchange transfusion was thrombocytopenia (40%)[36]. In the current study, similar to the literature, complications due to ET were found to include thrombocytopenia, anemia, hypernatremia, hypocalcemia, and sepsis (Table 4).

Severe hyperbilirubinemia and ABE are mostly due to health system deficiencies and insufficient follow up of newborns in the first week of life[37]. Acute and chronic bilirubin encephalopathy is highly preventable if serious hyperbilirubinemia is detected early and treated by phototherapy or exchange therapy. Once the bilirubin level is elevated above 30 mg/dL or the bilirubin/albumin ratio is >8.6, advanced ABE that profits little from therapy is often present and mortality is increased[12]. In the current study, the serum total bilirubin level and bilirubin/albumin ratio were significantly higher in the newborns with ABE (36.6 (31.6-39) mg/dL; 19 (67%), $p<0.05$).

Four newborns (14.2%) in this study died after ET as a result of metabolic acidosis, heart failure, and respiratory failure due to gram-negative neonatal sepsis. Wolf MF et al. reported a 4% mortality rate within 7 days due to ET [8]. In another study by Chitty et al., mortality due to ET was found to be 8%[38]. Since the current study examined a smaller newborn population, the observed mortality differences between these two studies could be attributed to the study sample size. Moreover, the current study patients died from gram-negative sepsis, and this situation was not statistically significant.

This study had some limitations, primarily that the study was retrospective and relied on self-reported data. The dependence on self-reported data may have led to underestimation of the exact incidence and data of severe hyperbilirubinemia and ABE.

In conclusion, newborns with severe hyperbilirubinemia, especially when related to hemolytic jaundice, may need rescue ET. As newborns with severe hyperbilirubinemia with a high bilirubin/albumin ratios are at risk for ABE, ET should be considered in these cases.

Yazar Katkıları: Çalışma konsepti/Tasarımı:FK,AT,GT; Veri toplama: FK,AT, ; Veri analizi ve yorumlama:FK,AT,GT ; Yazı taslağı: FK; İçeriğin eleştirel incelenmesi:AT;GT ; Son onay ve sorumluluk: FK; Teknik ve malzeme desteği:AT -; Süpervizyon:FK,GT ; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Sivas Cumhuriyet Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulundan 23.09.2020 tarih ve 2020-09/09 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design:FK,AT,GT Data acquisition: FK,AT; Data analysis and interpretation:FK,AT,GT ; Drafting manuscript:FK ; Critical revision of manuscript:AT;GT ; Final approval and accountability:FK ; Technical or material support:AT -; Supervision:FK,GT ; Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee with the decision dated 23.09.2020 and numbered 2020-09/09.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

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