Neonatal exchange transfusion for hyperbilirubinemia in Guilan (the north province of Iran): a 3-year experience

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Exchange transfusion is the standard method for treatment of severe hyperbilirubinemia. Our goal was to determine the indications for exchange transfusion (ECT) and the rates of ECT-related adverse events.

A retrospective descriptive investigation was performed in newborns that underwent ECT at 17 Shahrivar Pediatric Hospital, Rasht, Guilan province during the period April 2008 to April 2011.

Of the 69 patients, 2 (2.9%) required more than one ECT. The mean total serum bilirubin before ECT was 21.55±5.12 mg/dl. The most common cause of ECT was ABO incompatibility (26.1%). ECT complications occurred in 9 neonates (13.0%), the most common being sepsis (7.4%). No case of ECT-related mortality was observed. All the adverse events resolved completely before discharge.

ABO isoimmunization was the most common cause of ECT in this study. The majority of adverse events associated with ECT are asymptomatic and reversible.

Key words: hyperbilirubinemia, exchange transfusion, complication.

Neonatal jaundice is a very common problem in the first week of life[1], and is defined as yellowish discoloration of the skin, sclera of the eyeball and mucous membranes caused by deposition of bilirubin in these tissues[2].

The most common cause of jaundice in the neonatal period is usually due to hemolysis from ABO incompatibility. Rhesus (Rh) incompatibility, glucose-6 phosphate dehydrogenase (G6PD) deficiency, polycythemia, cephalhematoma, sepsis, hypothyroidism, infections, metabolic disorders, congenital malformations, prematurity, and breast-feeding jaundice are the other causes[3,4].

Visible jaundice is seen in approximately 60% of term infants and 85% of preterm infants in the first 24-36 hours or beyond the first week of life[5,6]. Most of these cases are benign, but in some infants, serum bilirubin level may rise excessively, which can be a cause of concern because unconjugated bilirubin is a neurotoxin and can cause death and serious complications[7], such as acute bilirubin encephalopathy (including lethargy, convulsion, irritability, change in muscle tone and posture)[8,9] and kernicterus (including athetoid cerebral palsy, hearing loss, and visual and dental problems)[1], in newborns who survive.

For preventing kernicterus and other complications of hyperbilirubinemia, jaundice should be managed by phototherapy or exchange transfusion (ECT)[10]. Treatment is usually started with phototherapy. ECT is preferred when the bilirubin level continues rising, instead of declining, to a level that kernicterus is considered a threat.

Exchange transfusion (ECT) is the standard method for immediate treatment of severe hyperbilirubinemia and prevention of kernicterus[11,12]. ECT is the replacement of most or all of the recipient's red blood cell (RBC) mass and plasma with appropriately compatible RBCs and plasma from one or more donors[13,14]. It is commonly used to

remove antibody-coated RBCs and products of hemolysis in various immune or non-immune hemolytic anemias[15].

Although the value of ECT in the treatment of neonatal hyperbilirubinemia is recognized, the procedure is associated with serious adverse events[16] that carry a risk of both mortality (0.1-0.5%)[17] and morbidity (2.8-5.2%) in term neonates[18]. Complications of ECT may be increased by the amount of blood exchanged[16]. Most of these complications were asymptomatic and transient[19], such as severe thrombocytopenia, apnea, hypocalcemia, seizures, bradycardia, catheter malfunction, hyperkalemia, and necrotizing enterocolitis, which occurred within seven days after the exchange.

However, while the frequency of neonatal ECT has declined markedly in the last two decades[20], this procedure is still performed in many countries, especially in Asian countries with a high incidence of neonatal hyperbilirubinemia[21]. In Iran, hyperbilirubinemia is the cause of hospitalization in 32% of annually admitted neonates[22], and ECT is required in approximately 10% of hyperbilirubinemic hospitalized neonates[23].

In this study, we aimed to determine the indications for ECT and the rates of ECT-related adverse events in neonatal hyperbilirubinemia at 17 Shahrivar Pediatric Hospital, in Rasht, capital city of Guilan province, north of Iran.

Material and Methods

A retrospective descriptive investigation was performed by reviewing the medical records of 68 infants below one month of age who were admitted to the Department of Neonatology with hyperbilirubinemia and who received ECT at 17 Shahrivar Pediatric Hospital, in Rasht, capital of Guilan province, during the period April 2008 to April 2011.

All the neonates studied received phototherapy immediately after admission, and total serum bilirubin (TSB) was measured 4-6 hours after initiation of phototherapy. All data about the patient's demographic characteristics (birth week, birth weight, maternal age, feeding behavior, and history of sibling with jaundice), causes of hyperbilirubinemia, duration of ECT, frequency of exchange, and adverse events associated with ECT were collected from the registration medical records.

The cause of jaundice reported in the records was classified by etiology (Rh disease, ABO incompatibility, idiopathic hyperbilirubinemia, infection, and other hematologic diagnoses). ABO incompatibility was defined as an infant's blood type A or B with type O mother, regardless of the Coombs' test. Rh or minor blood group incompatibility was defined as different maternal-infant antigens and positive direct Coombs' test. We considered inadequate caloric intake as a predisposing factor for neonatal jaundice when the infant›s weight loss was more than 10% of birth weight.

The following investigations were performed on all neonates as a baseline: complete blood count, total and direct serum bilirubin, erythrocyte G6PD level, direct Coombs' test, thyroid hormone levels, blood culture, and pre- and post-exchange bilirubin, calcium, potassium, and blood glucose.

Exchange transfusion (ECT)-related adverse events were defined as any complication that was not present before ECT, which occurred within three days after the exchange. The following definitions were used: hypoglycemia: serum glucose <40 mg/dl; hypocalcemia: total serum calcium <8 mg/dl; hyperkalemia (serum potassium >5.5 mEq/L); thrombocytopenia: platelet count <100,000/mm^3; bradycardia: heart rate dropping to <80 beats per minute; apnea: cessation of respirations for >20 seconds; seizure: any tonic and/or clonic movement; bacteremia (detected colonization in the culture taken after ECT); necrotizing enterocolitis: defined according to Bell et al.'s criteria[24]. ECT–related mortality was defined as infant death within three days after exchange that was directly related to the ECT procedure.

All of this information was collected for each case and then statistical analysis of quantitative and qualitative data was conducted using the Statistical Package for the Social Sciences (SPSS) version 18 for Windows by use of t-test and Fisher's exact test, respectively. The results were presented through tables, cross-tabulation, graphs, and charts.

Results

During the three-year study period, of the

Table I. Baseline Demographic Characteristics

Characteristic	Value
Gestational age, mean ± SD, weeks	37.5 ± 2
Birth weightmean ± SD, g	2,945.38 ± 610.18
Age of ECT Mean ± SD, day	5.6 ± 3
ECT duration Mean ± SD, min	61.67 ± 10.73
Male gendern (%)	34 (49.3%)
Mother's age Mean ± SD, year	29.11 ± 5.18
Breast-feeding (%)	51 (73.9%)
History of jaundice in sibling (%)	13 (18.8%)
Method of delivery Cesarean section, n (%)	33 (47.8%)

SD: Standard deviation.

69 patients who underwent ECT, 2 (2.3%) required more than one ECT. The infants had a mean gestational age of 37.15±2.06 weeks and mean birth weight of 2945.38±610.18 g. The mean age at presentation was 5.59±3.05 days. The average duration of the ECT procedure was 61.67±10.73 minutes. Demographic characteristics of the newborns are shown in Table I.

Fifteen patients had bilirubin of >30 mg/dl at the time of admission. The mean TSB before ECT was 21.66±5.15 mg/dl and immediately after ECT was 10.42±3.18 mg/dl. Patients with ABO incompatibility had a higher bilirubin level as compared to Rh incompatibility.

The most common cause of ECT was ABO incompatibility (26.1%). The others were Rh incompatibility (8.7%), G6PD deficiency (11.6%), ABO and Rh incompatibility (5.8%), G6PD and ABO incompatibility (14.5%), G6PD and Rh incompatibility (2.9%), G6PD and ABO and Rh incompatibility (1.4%), and idiopathic (29%). The majority of neonates with ABO incompatibility in this study had blood group A followed by B, with the frequencies of 54.5% and 30.3%, respectively. In addition, 75.1% of their mothers had blood group O (Table II).

Weight loss of more than 10% of the birth weight was determined as a cause of hyperbilirubinemia in 22 patients (31.9%). ECT complications occurred in 9 neonates (13.0%), and the most common complication was sepsis (7.35%) (Fig. 1). No case of ECT-related mortality was observed. All of the adverse events had resolved completely before discharge.

Discussion

Hyperbilirubinemia is a common disorder during the neonatal period[25]. Long-term results of severe hyperbilirubinemia, including bilirubin encephalopathy and kernicterus, were thought to be rare since the advent of ECT, maternal Rh immunoglobulin prophylaxis and phototherapy[8,26]. ECT has remained the most rapid method for lowering serum bilirubin

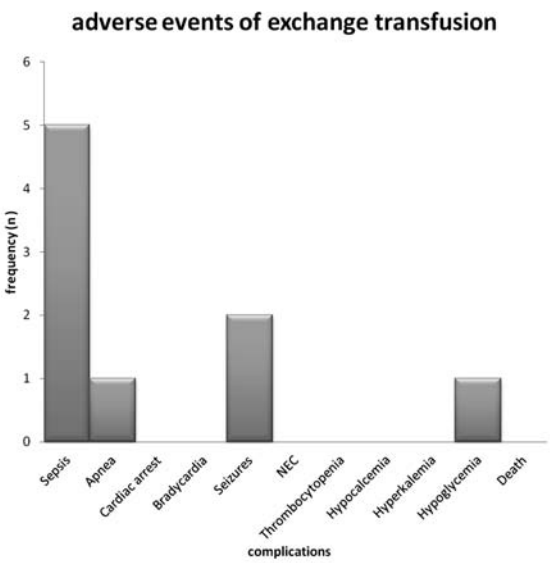

Figure 1. Frequency of adverse events associated with ECT in newborns.

Table II. Cross-Tabulation of Blood Groups of Neonates and Mothers in Patients with ABO Incompatibility

		Blood group of mothers						
		A-	A+	B-	B+	O-	O+	Total
Blood group of neonates	A-	0	0	0	0	1	0	1
	A+	0	0	0	0	1	16	17
	B-	0	1	0	0	0	1	2
	B+	1	2	0	0	0	5	8
	AB+	0	0	1	2	0	0	3
	O+	0	0	1	0	0	0	1
	Total	1	3	2	2	2	22	32

concentration, especially with higher levels of hyperbilirubinemia[27].

Hyperbilirubinemia is associated with a variety of physiologic and pathologic conditions[25]. Our study shows an association of hyperbilirubinemia with identified risk factors such as gestational age, weight loss of more than 10% of the birth weight, incompatibility of blood groups of neonates-mothers, and G6PD deficiency.

Isoimmune hemolytic disease has been identified as a pathologic cause of neonatal hyperbilirubinemia attributed to blood group incompatibility[26]. It has been reported that less than 0.1% of pregnancies with ABO incompatibility require treatment with ECT[27]. In our study, the most common cause of ECT was ABO incompatibility, and this finding is similar to those of other studies[28-30]. Rh incompatibility alone or concomitant with ABO incompatibility was observed in 11.7% and 7.3% of neonates, respectively. The reduction in Rh incompatibility may be due to the routine use of anti-Rh-globulin for Rh-negative mothers[4]. G6PD deficiency accounted for 37% of all causes of ECT in our study. This figure is higher than the estimated 19% prevalence of G6PD deficiency in term infants undergoing ECT in Badiee's study[19]. Abdul Wahid et al.[16] reported that no patient was found to have G6PD deficiency. This high prevalence of G6PD deficiency in our group of patients could be due to the racial differences in the prevalence of G6PD deficiency.

In the past decade, little information has been reported concerning the risks of adverse events related to ECT[31]. We observed a high rate of adverse events associated with ECT for neonatal hyperbilirubinemia, occurring in 9 newborns (13.0%). Most of these adverse events were asymptomatic and transient, and recovery is expected along with appropriate care and follow-up. The most common morbidities in our study included sepsis (7.4%), seizure (2.9%), apnea (1.4%), and hypoglycemia (1.4%), while in most of the previous studies, thrombocytopenia, hypoglycemia and hypocalcemia were commonly reported[15,19]. Patra et al.[32] showed that the most common adverse events following ECT were thrombocytopenia (44%) and hypocalcemia (29%). The rate of prolonged serious sequelae from ECT is also very low, approximately 1%, and prior reports indicate that necrotizing enterocolitis and bacteremia are the most common severe complications[14,19].

We observed no case of ECT-related mortality, while others have reported a mortality of 0.1-0.5%[17]. Since apnea, bradycardia and cyanosis can develop rarely during ECT, cardiorespiratory and oxygen saturation monitoring should be considered[19].

In conclusion, since ABO incompatibility was the most common cause of jaundice in neonates with ECT, it is recommended to establish a close follow-up program for isoimmune hemolytic disease from ABO incompatibility, especially in neonates born from mothers with blood group O. Although the severe complications with potential death in the neonate during

ECT are unusual, early diagnosis of infants at high risk before discharge[27,33], prevention of weight loss via appropriate nutrition selection[30] and application of an intensive phototherapy device in a suitable time[34] can considerably reduce the need for ECT.

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