Exchange transfusion in severe hyperbilirubinemia: an experience in northwest Iran

Seddigheh Hosseinpour Sakha, Manizheh Mostafa Gharehbaghi
Tabriz University, Medical Science, Tabriz, Iran

SUMMARY: Hosseinpour Sakha S, Gharehbaghi MM. Exchange transfusion in severe hyperbilirubinemia: an experience in northwest Iran. Turk J Pediatr 2010; 52: 367-371.

Our goal was to determine the indications for exchange transfusion (ECT) and the rates of ECT-related adverse events in neonatal hyperbilirubinemia. We reviewed retrospectively the medical charts of all newborns that had undergone ECT over three years from January 2006 to December 2008. Causes of jaundice, demographic data of the patients, and details of ECT and ECT-related adverse events were recorded. A total of 176 ECT procedures were performed in 150 neonates in the three-year study period. The mean total serum bilirubin before ECT was 29.59±6.88 mg/dl. Those infants requiring more than one ECT had higher total serum bilirubin than neonates with single ECT, but the difference was not significant (35.66±12.21 vs. 29.12±6.30 mg/dl, p=0.09). The most common cause of ECT was ABO incompatibility (49.3%), Rh disease (7.3%) and idiopathic (28%). Among the adverse events related to ECT, thrombocytopenia (36.4%), hypocalcemia (25.5%), apnea (20%), and infection (10.9%) were noted commonly. No case of ECT-related mortality was observed. All of 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, neonate, exchange transfusion, complication, indication.

Neonatal jaundice due to indirect hyperbilirubinemia remains a continuous problem for hospital admission of newborns. Early detection and treatment are important in the prevention of bilirubin-induced encephalopathy[1-4]. Exchange transfusion (ECT) is the standard method of therapy for immediate treatment of severe hyperbilirubinemia and prevention of kernicterus. Although the frequency of neonatal ECT has declined markedly in the past two decades, this procedure is still performed in many countries, especially in those with a high incidence of neonatal hyperbilirubinemia[1].

The level of bilirubin at which ECT should be initiated has been a controversial issue. The neonatal hyperbilirubinemia practice guidelines of the American Academy of Pediatrics (AAP) define the identification and management of hyperbilirubinemia[5].

The procedure of ECT is relatively safe when performed by experienced practitioners in term newborns; nevertheless, it carries a risk of both mortality (0.1-0.5% in term neonates)[6] and morbidity (2.8-5.2%)[7]. Because of the high incidence of hyperbilirubinemia in Azerbaijan and Iran (hyperbilirubinemia is the cause of hospitalization in 32% of annually admitted neonates[8]), ECT is needed in approximately 10% of hyperbilirubinemic hospitalized neonates. We thus conducted this study to determine the underlying causes of ECT and the incidence of ECT-related mortality and morbidity.

Material and Methods

All neonates who had undergone ECT for neonatal hyperbilirubinemia in the neonatal intensive care unit (NICU) at Children's Hospital, Tabriz, Iran from January 2006 to

December 2008 were included in this study. The hospital's ethics committee in medical research approved this study. It is routine to use the 2004 AAP hyperbilirubinemia guidelines[5] for the management of admitted newborn infants in our Neonatology Department.

All of the studied neonates with severe hyperbilirubinemia received phototherapy immediately after admission and total serum bilirubin (TSB) was measured 4-6 hours after initiation of phototherapy. Infants with unresponsive hyperbilirubinemia underwent urgent ECT. Intravenous immunoglobulin (IVIG) was administered to infants with isoimmune hemolytic disease who had TSB 2-3 mg/dl below exchange level. Thus, IVIG was not used before the first ECT and was administered to reduce the need of repeated ECT.

The medical records of patients were reviewed and the following data were collected through detailed questionnaires: patients' demographic characteristics, causes of hyperbilirubinemia, duration of ECT, frequency of exchange, feeding behavior, and adverse events caused by ECT. The exclusion criterion was partial ECT for conditions other than hyperbilirubinemia such as severe anemia and polycythemia.

The laboratory investigations included the measurement of baseline complete blood count, total and direct serum bilirubin, glucose-6-phosphate dehydrogenase (G6PD), direct Coomb's test, and blood group of infants and mothers.

The causes of hyperbilirubinemia identified by laboratory investigations included the following: Rh isoimmunization, ABO incompatibility, G6PD deficiency, infection (proven by positive blood culture and/or signs and symptoms consistent with sepsis), and idiopathic hyperbilirubinemia. 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.

In this study, isovolemic double-volume fresh whole blood was used for ECT in 115 neonates. Stored red blood cells collected on citrate-dextrose phosphate adenosine (CDPA) anticoagulant with fresh frozen plasma (FFP) were used for ECT in the remaining patients. The umbilical vein method ECT was performed by inserting an umbilical venous catheter under aseptic conditions.

Removal and infusion of blood were done according to standard published guidelines with intermittent infusions of calcium[7]. The catheters were left in place when the neonate was expected to receive another ECT for severe hyperbilirubinemia. The complete blood count, blood culture, serum bilirubin level, sodium, potassium, glucose, and calcium were measured after ECT. ECT-related adverse events were defined as any complication not present before ECT, which occurred within three days after the exchange. Complications included: thrombocytopenia (platelet count $<100000/mm^3$), hypocalcemia (total serum calcium <8 mg/dl or plasma ionized calcium <1 mmol/L), hypoglycemia (serum glucose <45 mg/dl), and sepsis (identified as a positive blood culture and/or signs and symptoms consistent with sepsis). ECT–related mortality was defined as infant death within three days after exchange that was directly related to the ECT procedure. All data were analyzed using the Statistical Package for Social Sciences 13 software for Windows (SPSS Inc, Chicago, IL). Data were summarized using descriptive statistics. The Pearson χ^2 test and Student *t*-test were used to compare categorical variables. A p value less than 0.05 was considered to be statistically significant.

Results

During the three-year study period, 1,737 newborn infants were admitted with hyperbilirubinemia. Of these newborns, 155 patients met the inclusion criteria. Five of them were excluded from the study because of incomplete data or invalid medical records. A total of 176 ECT procedures were performed in 150 infants. Twenty- three neonates required more than one ECT. Demographic data of the studied patients are shown in Table I.

Sixty-six (44%) of the newborns were female. The mean gestational age was 37.94±1.79 weeks (range: 32-40 weeks).

Among 150 cases, the most common causes of hyperbilirubinemia were ABO incompatibility (49.3%), Rh disease (7.3%) and idiopathic (28%). Causes of ECT are shown in Table II.

Of 20 infants who had two ECT procedures,

Table I. Baseline Demographic Characteristics of Patients

Characteristics	
Gestational age mean±SD, weeks	37.94±1.79
Body weight mean ± SD, g	2972.51±578.89
Age of ECT	
mean± SD, day	5.72±3.95
range	1-12
ECT duration mean± SD, min	54±11.12
range	30-90
Male gender, n (%)	84 (56%)
Breast-feeding, n (%)	150 (100%)
History of jaundice in sibling, n (%)	15 (10%)
Method of delivery Cesarean section, n (%)	53 (35.6%)
Birth order First born, n (%)	82 (55.8%)

SD: Standard deviation.

Table II. Causes of Hyperbilirubinemia

Causes	N	%
Rh disease	11	7.3
ABO incompatibility	74	49.3
G6PD deficiency	3	2
Sepsis	7	4.7
Idiopathic	42	28
Concomitant ABO & Rh	6	4
*Weight loss >10%	7	4.7

* Calculated as birth weight-readmission weight ×100 Birth weight

45% had ABO incompatibility, 25% unknown etiology, and 20% Rh disease. Three patients had 3 ECT and all of them had ABO incompatibility. We had administered IVIG to 17 neonates with isoimmune hemolytic disease after the first ECT and 9 cases needed a second exchange. In 75% of blood-group incompatible patients, a blood group O mother had delivered babies of blood group A. The mean TSB levels before ECT were 29.59±6.88 mg/dl and immediately after ECT were 11.51±3.72 mg/dl.

ECT procedure-related adverse events occurred in 55 (36.7%) infants (Table III).

The most common complications were thrombocytopenia (36.4%) and hypocalcemia (25.5%). Only five cases of hypocalcemic infants were treated with intravenous calcium. The average duration of the ECT procedure was 54±11.12 minutes. No cases of ECT-related mortality were observed. The mean TSB levels in patients who required more than one ECT was higher than in patients with single ECT but the difference was not statistically significant (35.66±12.21 vs. 29.12±6.30, p=0.09). The mean TSB immediately after ECT was significantly lower in patients with single ECT (11.03±3.47 vs 17.66±4.99, p=0.000). There was no significant difference between neonates with ECT–related complication and those without complication in duration or number of ECT procedures.

Table III. Adverse Events of Exchange Transfusion

	n	%
Thrombocytopenia Platelet < 100000	20	36.5
Hypocalcemia Calcium <8 mg/dl	14	25.5
Hypoglycemia Blood glucose <45 mg/dl	4	7
Apnea	11	20
Sepsis	6	11
Total events	55	100

Discussion

There are a few systematic studies about the causes of hyperbilirubinemia and complications of ECT[4,9]. Our study shows an association of hyperbilirubinemia with identified risk factors such as gender, gestational age and incompatibility of blood groups of neonates-mothers.

In our study, the most common cause of ECT was ABO incompatibility. It was also common in neonates who required more than one ECT. In comparison with other studies[10-12], there was higher ABO incompatibility (49.3%). Although the higher rate may be due to increased maternal anti-A or anti-B IgG antibodies against A or B substances occurring in food, vaccines or on bacteria[6], presence of another icterogenic factor in addition to ABO incompatibility may cause severe hyperbilirubinemia[13,14]. It has been shown that administration of O type whole blood increases risk of re-ECT in ABO incompatibility[15]. This may be a reason for the

repeated ECT in ABO- incompatible patients in our study.

Kaplan and associates[13] found that 43% of direct agglutination test (DAT)-negative, ABO-incompatible infants who were homozygous for the variant uridyl glucuronosyl transferase (UGT) promoter associated with Gilbert syndrome had a TSB level ≥15 mg/dl versus none of the ABO-incompatible DAT-negative infants that were normal homozygous for the variant promoter[13]. We do not know the frequency of this variant in our patients, and other studies are needed for its determination in our population.

Rh disease alone or concomitant with ABO incompatibility was observed in 7.3% and 4% of neonates, respectively. The reduction of Rh disease may be due to the routine use of anti-Rh-globulin for Rh-negative mothers. IVIG is an adjunctive treatment for hyperbilirubinemia due to isoimmune hemolytic disease and reduces the need for ECT[7,16]. In our study, 53% of patients receiving IVIG underwent a second ECT.

No cases of ECT-related mortality were observed, but 59 patients (39.3%) experienced an adverse event related to ECT. Most of these adverse events were transient and asymptomatic such as thrombocytopenia and hypocalcemia[1,2,17,18]. Five cases of hypocalcemic infants were treated with intravenous calcium, but none of the thrombocytopenic neonates required platelet transfusion. Infection with positive blood culture occurred in 8.5% of patients treated with antibiotic. The most common pathogen was *Staphylococcus aureus*. There were no cases of necrotizing enterocolitis or cardiac arrest.

We speculate that a combination of factors, including the use of standard ECT practice, the high experience level of the residents and the increasing supervision of the attending, may be important for decreasing the number of severe procedure-related adverse events and mortality.

Although reports show a dramatic decline in the frequency of ECT over the last two decades, it remains the most rapid method for lowering serum bilirubin concentration, especially with higher levels of hyperbilirubinemia[2,3].

All of the studied neonates were readmitted to our referral hospital with high TSB. Pre-discharge risk assessment is necessary because most infants are discharged before 48 hours and the bilirubin level has not yet peaked. The problem appears to be related to lack of appropriate follow-up and intervention. It is important to point out that early detection and treatment of infants with significant jaundice during the critical risk period of the few first days and thereafter could cause a decline in the number of necessary ECTs.

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 neonates born from mothers with blood group O, especially when the infant's blood group is A.

REFERENCES

1. Steiner LA, Bizzarro MJ, Ehrankranz RA, Gallagher PG. A decline in the frequency of neonatal exchange transfusions and its effect on exchange-related morbidity and mortality. Pediatrics 2007; 120: 27-32.
2. Chen HN, Lee ML Tsao LY. Exchange transfusion using peripheral vessels is safe and effective in newborn infants. Pediatrics 2008; 122: e905-e910.
3. Chou SC, Ezhurhachan S, Newman C, Pradell-Boyd B, Maisels J, Testa MA. Management of hyperbilirubinemia in newborns: measuring performance by using a benchmarking model. Pediatrics 2003; 112: 1246-1273.
4. Bhutani VK, Johnson LH, Keren R. Diagnosis and management of hyperbilirubinemia in the term neonate: for a safer first week. Pediatr Clin North Am 2004; 51: 843-861.
5. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004; 114: 297-316.
6. Wong RJ, Desandre GH, Sibley E, Stevenson DK. Neonatal jaundice and liver disease. In: Martin RJ, Fanaroff AA, Walsh MC (eds). Neonatal Perinatal Medicine: Disease of the Fetus and Infant (8th ed). Philadelphia: Elsevier Mosby; 2006: 1446-1449.
7. Alcock GS, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Cochrane Database Syst Rev 2002; 3: CD003313.
8. Sakha SH, Gharehbaghi MM, Rahbani ME. The effect of clofibrate with phototherapy in late pre-term newborns with non hemolytic jaundice. Indian J Med Sci 2009; 63: 174-179.
9. Johnson L, Brown AK, Bhutani VK. System-based approach of management of neonatal jaundice and prevention of kernicterus. J Pediatr 2002; 93: 488-494.
10. Badiee Z. Exchange transfusion in neonatal hyperbilirubinemia: experience in Isfahan, Iran. Singapore Med J 2007; 48: 421-423.

11. Drabik-Clary K, Reddy VV, Benjamin WH, Boctor FN. Severe hemolytic disease of the newborn in a group B African-American infant delivered by a group O mother. Ann Clin Lab Sci 2006; 36: 205-207.

12. Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ 2006; 175: 587-590.

13. Kaplan M, Hammerman C, Renbaum P, Klein G, Levy-Lahad E. Gilbert syndrome and hyperbilirubinemia in ABO-incompatible neonates. Lancet 2000; 356: 652-653.

14. Kaplan M, Vreman HJ, Hammerman C, et al. Combination of ABO blood group incompatibility and glucose-6-phosphate dehydrogenase deficiency: effect on hemolysis and neonatal hyperbilirubinemia. Acta Pediatr 1998; 87: 455-457.

15. Yigit S, Gursoy T, Kanra T, et al. Whole blood versus red cells and plasma for exchange transfusion in ABO haemolytic disease. Transfusion Med 2005; 15: 313-318.

16. Huizing KM, Roislien J, Hansen TW. Intravenous immune globulin reduces the need for exchange transfusions in Rhesus and ABO incompatibility. Acta Pediatr 2008; 97: 1362-1365.

17. Patra K, Storfer-Isser A, Siner B, Moore J. Adverse events associated with neonatal exchange transfusion in the 1990s. J Pediatr 2004; 144: 626-631.

18. Abu-Ekteish F, Daaud A, Rimavi H, Kakish K, Abu-Heija A. Neonatal exchange transfusion: a Jordanian experience. Ann Trop Paediatr 2000; 20: 57-60.