The etiology of severe neonatal hyperbilirubinemia and complications of exchange transfusion

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Exchange transfusion (ECT) has an important role in preventing kernicterus in the treatment of indirect hyperbilirubinemia of the newborn. In present study, the etiology of hyperbilirubinemia and complications of ECT were studied over a five-year period in the Eastern Mediterranean region of Turkey. We describe our experience of 89 ECTs performed from 2003-2008 in 79 newborns with hyperbilirubinemia. The mean gestational age was 37±2.1 weeks and the mean of peak total bilirubin levels was 28.1±6.4 mg/dl. The most common cause of hyperbilirubinemia was ABO isoimmunization (38%). Complications of ECT developed in 17 neonates (21.5%), the most common being thrombocytopenia and seizure. None of newborns died secondary to ECT.

Our data showed higher morbidity rates associated with ECT in the treatment of hyperbilirubinemia in our region. In order to prevent adverse effects of ECT, serum bilirubin levels should be closely monitored in newborns with ABO immunization.

Key words: hyperbilirubinemia, etiology, exchange transfusion, complications, ABO isoimmunization.

Exchange transfusion (ECT) has an important role in preventing kernicterus in the treatment of indirect hyperbilirubinemia of the newborn. However, considerable rates of complications have also been reported due to ECT[1,2].

The bilirubin level indicating ECT remains controversial. Previous reports attracted attention regarding the benefits of ECT in prevention of bilirubin toxicity together with the risks of ECT[3,4].

According to the American Academy of Pediatrics Practice Guidelines (AAPP), new epidemiological studies are needed to document the incidence of adverse effects attributable to hyperbilirubinemia and the number of term infants whose total serum bilirubin levels exceed 25-30 mg/dl[5].

Kernicterus is the most easily preventable form of brain injury in both term and near-term infants[6]. In the past decade, little information has been reported concerning the risks of adverse events related to ECT[1,7].

Early diagnosis and appropriate management of hyperbilirubinemia in the neonatal period are critical for decreasing the morbidity and mortality. Unfortunately, there is insufficient data in Turkey on the complications of ECT. Therefore, the aim of this study was to investigate the etiology of hyperbilirubinemia and the incidence of adverse events attributable to ECT in a patient population seen in our institution over the past five years.

Material and Methods

All neonates aged below 30 days who were admitted to the Department of Neonatology in Kahramanmaraş Sütçü İmam University Faculty of Medicine over the past five-year period were reviewed. Patients who underwent ECT according to their medical records were selected. After excluding the records of patients who underwent only partial ECT due to polycythemia, septicemia and/or direct hyperbilirubinemia, the medical records of

the 79 remaining newborns were included in this study.

Maternal age, gestational age, birth weight, age at the time of admission, treatment methods, and outcomes of all neonates were recorded.

Laboratory investigations, including complete blood count and reticulocyte count, blood group typing, Rhesus and direct Coombs tests, blood smear, blood culture, thyroid-stimulating hormone, T4, glucose-6-phosphate dehydrogenase (G6PD) activity, and pre- and post-ECT levels of direct and indirect bilirubin, calcium, potassium, hemoglobin, and glucose in blood, were performed.

The causes of indirect hyperbilirubinemia were classified as follows: Rh disease was defined as hyperbilirubinemia in a Rh-positive newborn from a Rh-negative mother with elevated titers of the Rh antigen and evidence of hemolysis (e.g. increased indirect bilirubin, reticulocytes and normoblasts). ABO disease was defined as jaundice in a newborn with positive direct Coombs test against the A or B antigens from type O mothers[1].

Either whole blood ABO compatible with both the infant and mother, or group O red cells resuspended in compatible (usually AB) plasma were used. The double volume exchange procedures were generally completed in about two hours by repeatedly removing and replacing small aliquots of blood (5 ml/kg) according to standard published guidelines[1]. All patients received phototherapy before ECT.

Adverse effects were reviewed using previous definitions, and any complication that occurred within seven days of an ECT was recorded[3]. The following definitions were used: hypoglycemia: serum glucose level <40 mg/dl; hypocalcemia: total serum calcium level <8 mg/dl (for preterm newborn <7.5 mg/dl); hyperpotassemia: total serum potassium level >6.5 mEq/dl (for preterm newborn >8 mEq/dl) associated with electrocardiographic alterations; thrombocytopenia: platelet count <100,000/mm^3; apnea: cessation of respirations for >20 seconds; and seizure: any tonic and/or clonic movement[8].

Kernicterus was diagnosed when neurological predictors of severe kernicteric sequelae were observed (cessation of feeding, bicycling movements, inconsolable irritability and crying, fever, possible seizures and coma)[6,9,10].

Results

During the study period, 79 patients underwent ECT. The male/female ratio was 1.08, and mean gestational age was 37±2 weeks. Of these, 12 patients were below gestational age of 38 weeks. The mean age at presentation was 4.9±2.2 days, and the mean maximum total bilirubin level was 28.1±6.4 mg/dl. A total of 89 ECT procedures were performed. Ten infants underwent ECT twice and kernicterus developed in 5 of these neonates. Two of these kernicteric infants were premature. Characteristics of the study population are shown in Table I.

Table I. Characteristics of the Study Population (n=79)

	Mean	Standard deviation	Minimum	Maximum
Birth Weight, g	2815	679	1200	4350
Gestational age, week	37.0	2.1	29	38
Maternal age, year	26.6	6.3	16	40
Presenting age, day	4.9	2.2	1	12
Peak total bilirubin level, mg/dl	28.1	6.4	14.5	48.4
Direct bilirubin level, mg/dl	0.8	0.9	0.1	3,4
Hemoglobin, g/dl	15.9	3.2	7.1	24.1
T_4, μg/dl	11.7	3.8	2.4	24
TSH, mIU/L	7.2	7.4	0.1	40.7

The most common cause of hyperbilirubinemia was hemolysis secondary to sensitization against ABO antigens (n=30, 38%). Other etiologies for indirect hyperbilirubinemia were Rh isoimmunization in 10 infants (12.6%), ABO plus Rh isoimmunization in 2 (2.5%), G6PD deficiency in 9 (11.4%), prematurity in 5 (6.3%), and unknown causes in 11 (13.9%). The causes of neonatal hyperbilirubinemia are shown in Table II.

Seventeen infants (21.5%) developed adverse events attributable to ECT. The most common adverse event was thrombocytopenia (n=5, 6.3%). The other observed adverse events were as follows: seizure (n=4, 5.1%), hypoglycemia (n=3, 3.8%), hypocalcemia (n=2, 2.5%), hyperpotassemia (n=1, 1.3%), apnea (n=1, 1.3%), and catheter malfunction (n=1, 1.3%). There were no occurrences of necrotizing enterocolitis, sepsis, or cardiopulmonary arrest in any patient.

None of the patients died, but 13 (16.5%) patients developed a clinical picture compatible with kernicterus. Mean total bilirubin level of kernicteric patients was 37±5.7 mg/dl. ABO and Rh incompatibility was present in 8 of the kernicteric patients.

Discussion

Neonatal hyperbilirubinemia has been present probably since the dawn of human existence[11]. Long-term results of severe hyperbilirubinemia, including bilirubin encephalopathy and kernicterus, were thought to be rare since the advent of ECT, maternal Rhesus immunoglobulin prophylaxis and phototherapy[5,12,13].

In our study, the most common cause of ECT was found to be ABO immunization (38%). In the literature, ABO hemolytic disease of newborns was also reported as the most common cause of ECT in term neonates. ABO hemolytic disease has been reported as the cause of ECT by Badiee[8], Dikshit[14] and Sanpavat et al.[15] at rates of 22.5%, 35.9% and 21.3%, respectively. Our ratio of ABO incompatibility, as an etiologic cause for ECT, was higher than those of previous reports. This diversity may be attributed to the different ethnic and geographic characteristics of our study population.

In our study, G6PD deficiency accounted for 12.5% of all causes of ECT. This rate is parallel to the mean value estimated for Mediterranean countries[16].

The mean age at presentation was 4.9±2.2 days in the present study. In the literature search, the mean age at presentation was 4.4 days in Badiee et al.'s[8] study and 111.6 hours (approximately 4.6 days) in the study of Sgro et al.[13]

In the current study, 10 infants (12.6%) required more than one ECT. The requirement for more than one ECT was similar to the rates reported in the literature by Badiee et al.[8] (13.2%), Patra et al.[3] (20%), Sanpavat et al.[15] (10.9%), and Abu-Ekteish et al.[17] (11.9%).

The rates of ECT applications have declined in the recent years due to the complications encountered. Nonetheless, ECT still maintains its importance in the treatment of severe hyperbilirubinemia[18,19].

Table II. Causes of Neonatal Hyperbilirubinemia

Cause of hyperbilirubinemia	n (%)
ABO incompatibility	30 (38)
Rh disease	10 (12.6)
ABO plus Rh incompatibility	2 (2.5)
Glucose-6-phosphate dehydrogenase deficiency	9 (11.4)
Polycythemia	3 (3.8)
Hypothyroidism	2 (2.5)
Prematurity	5 (6.3)
Prematurity and ABO incompatibility	4 (5.1)
Prematurity and Rh incompatibility	1 (1.3)
Prematurity and polycythemia	1 (1.3)
Prematurity and hypothyroidism	1 (1.3)
Unknown	11 (13.9)

TSH: Thyroid stimulating hormone.

Steiner et al.[20], in their detailed study covering 21 years, determined higher administration of calcium and thrombocytes in the last 10 years even though they observed similar rates of hypocalcemia and thrombocytopenia. In addition, they reported no cases of ECT-related mortality. Keenan et al.[2] reported a serious adverse event rate of 5.2% and a mortality rate of 0.5%. Jackson et al.[1] reported a high serious adverse event rate of 12% and a mortality rate of 2% related to ECT. Patra et al.[3] reported a high rate of ECT-related adverse events, at 74%, and a mortality rate of 2%.

In our study, the majority of complications were transient and the rate of ECT-related adverse events was 21.5%. The most common morbidities were seizure in 5.1%, hypoglycemia in 3.8% and apnea in 1.3%. Furthermore, no case of ECT-related mortality was observed.

Fortunately, even though the rate of adverse events related to ECT is high, they are transient and treatable[3]. Since many adverse events of ECT are probably inevitable, the best way to reduce complications is to prevent the need for ECT.

In conclusion, our results indicated higher morbidity rates related to application of ECT in the treatment of hyperbilirubinemia in our region. In order to decrease the necessity of the ECT procedure and avoid ECT-related morbidity, bilirubin levels should be monitored closely in newborns in whom ABO immunization was determined at birth.

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