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Complications of Exchange Transfusion in Hospitalized Neonates in Two Neonatal Centers in Hamadan, A Five-Year Experience

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Background: Exchange transfusion is commonly used in newborns for immediate treatment of severe hyperbilirubinemia to prevent bilirubin encephalopathy and kernicterus.
Objectives: This study aimed to determine etiology and complications in newborns who received exchange transfusion for severe hyperbilirubinemia over the last five years.
Patients and Methods: A retrospective study was performed on 28 days old infants who received exchange transfusion due to severe hyperbilirubinemia for a period of five years (from October 1st, 2006 through September 30th, 2011) in two neonatal units at Besat and Fatemieh hospitals in Hamadan, Iran. All data about patients' demographic characteristics, causes of hyperbilirubinemia, frequency, and complications of exchange transfusion were collected from medical records and analyzed using SPSS Version 12.0).
Results: Exchange transfusion was performed in 148 neonates. Eighteen patients (12.2%) received exchange transfusion twice and seventeen patients (11.4%) three times or more. Among 118 neonates 80 (54.9%) were female and the mean gestational age and birth weight were 37.2 ± 2.5 weeks and 2847 ± 699 grams, respectively. The mean maximum total serum bilirubin levels were 27. 7.6 ± 7.28 mg/dL. Hemolytic disease was found in 72 (48.6%) of newborns. The most common cause of hemolysis was ABO incompatibility in 54 (36.5%). The etiologic factors were unidentified in 61 (41.2%) neonates. Complications occurred in 57 (38.5%) neonates and the most common complications were thrombocytopenia in 26 (17.6%) and hypocalcaemia in 17 (11.5%) neonates. Mortality was found in one (0.7%) neonate.
Conclusions: The etiology of exchange transfusion was unidentified in most cases; however, ABO incompatibility was the most prevalent cause of hyperbilirubinemia. Complications were common after exchange transfusion and should be considered carefully.

Keywords: Hyperbilirubinemia; Exchange Transfusion; Whole Blood; Complications; Infant; Newborn

1. Background

About 60% of term and 80% of preterm infants have clinical jaundice in the first week after birth but only 0.02 to 0.16% of them develop severe hyperbilirubinemia (Total Serum Bilirubin (TSB) > 25 mg/dL), which is an emergency because it may cause neonatal bilirubin encephalopathy, which can result in death or irreversible brain damage in survivor (1-3). Intensive phototherapy and exchange transfusion (ET) play important roles in the treatment of severe hyperbilirubinemia of newborns to prevent bilirubin encephalopathy (4). Although the value of exchange transfusion in the treatment of neonatal hyperbilirubinemia is recognized, the bilirubin levels in which ET is necessary remained a matter of disagreement (5-7). ET is effective and considered to be a safe procedure; however, it is not without risks and complications have been reported and mortality rates vary from 0.5 to 3.3%. Therefore, the current recommendations for performing ET are based on balance between the risks of encephalopathy and adverse events related to the procedure (8, 9). Complications of ET may be increased by the amount of blood exchanged. Most of these complications are asymptomatic and transient, such as severe thrombocytopenia, apnea, hypocalcemia, bradycardia, and hyperkalemia, but life threatening infections and even death can occur within seven days after the exchange (10-13).

2. Objectives

The purpose of this study was to investigate the etiology and complications of exchange blood transfusion in a patient population visited in our center over the last five years.

3. Patients and Methods

The medical records of infants, 28 day old, who received exchange transfusion due to severe hyperbilirubinemia in neonatal units at Besat and Fatemieh university hospitals in Hamadan for a period of five years (from October

1st 2006 through September 30th, 2011) were reviewed retrospectively. Exchange transfusion was performed by pediatric residents under direct supervision of pediatric professor. The double volume exchange method (170 mg/kg) was completed for approximately 1 - 2 hours by repeatedly removing and replacing a small amount of blood (5 mL/kg) according to standard practice guidelines. Infants' heart rate and oxygen saturation were monitored during exchange transfusion.

Laboratory investigations were performed such as complete blood counts, direct and total bilirubin, erythrocyte glucose -6- phosphate dehydrogenase (G6PD) level, direct coombs test, maternal and baby blood groups, serum calcium, glucose, sodium, potassium, and blood cultures before and after the exchange.

Intravenous calcium gluconate was used during exchange transfusion to neutralize the effect of citrate in Citrate Phosphate Dextrose Adenine (CPDA) solution. All episodes of complication were recorded up to three days after exchange transfusion. The definition of complications used were as hypoglycemia when serum glucose was < 50 mg/dL, hypocalcemia if serum calcium was < 8 mg/dL (for preterm newborn, 7 mg/dL), hyperkalemia when serum potassium was > 6 meq/dL, thrombocytopenia when platelet count was < 100.000/mm^3, bradycardia if heart rate was < 80 beat/minute, apnea cessation of respiration for > 20 seconds, seizure any tonic or clonic movement, necrotizing enterocolitis defined as per bell's criteria. Complications of severe neonatal hyperbilirubinemia, consisting of kernicterus were not included in this study. Exclusion criteria were incomplete records of patients and those older than 28 days old. Statistical analysis was performed using SPSS Version 12.0 (SPSS, Inc, Chicago, USA).

4. Results

There were 6108 neonatal admissions due to neonatal jaundice that exchange transfusion was performed in 148 neonates (2.4%). Among them 68 (45.1%) were male and 80 (54.9%) female. Mean birth weight was 2847 ± 699 grams and mean gestational age of neonates was 37.2 ± 2.5 weeks. Overall, 102 (68.9%) infants were term and 46 (31.1%) preterm. The mean maximum total serum bilirubin was 27.76 ± 7.28 mg/dL and the mean age of exchange transfusion was 4.97 ± 2.65 days (Table 1).

Among 148 cases, no etiologic factors were identified in 61 (41.2%) neonates, ABO incompatibility was found in 54 (36.5%), RH incompatibility in 15 (10.1%) and G6PD deficiency in 14 (9.5%) neonates (Table 2). During and immediately after exchange transfusion, 57 (38.5%) neonates developed complications. Most complications were thrombocytopenia (17.6%), hypocalcemia (11.5%), hypoglycemia (9.5%), hyperkalemia (5.4%), hyponatremia (4.1%), apnea (4.7%), and septicemia (2%). One (0.7%) neonate died of complications probably attributable to exchange transfusion (Table 3). Comparing variables between term and preterm infants showed no significant difference in complications between the two groups (Tables 4 and 5).

Table 1. Baseline Demographic Characteristics [a]

Characteristic	Value
Gender	
Male	68 (45.1)
Female	80 (54.9)
Gestational Age Group	
Term	102 (68.9)
Preterm	46 (31.1)
Gestational age, wk	37.2 ± 2.5
Maximum total serum bilirubin, mg/dL	27.76 ± 7.28
Age at exchange transfusion, d	4. 97 ± 2.65
Frequency of Exchange Transfusion	
One	113 (76.4)
Two	18 (12.2)
Three	17 (11.4)
Complication rate	57 (38.5)
Duration of hospital stay, d	6.79 ± 6.64

[a] Data are presented as No. (%) or mean ± SD.

Table 2. Etiology of Neonatal Hyperbilirubinemia

Causes	NO (%)
ABO incompatibility	54 (36.5)
RH incompatibility	15 (10.1)
ABO and RH incompatibility	3 (2.0)
G6PD deficiency	14 (9.5)
Polycythemia	1 (0.7)
Unidentified	61 (41.2)
Total	148 (100)

Table 3. Complications of Exchange Transfusion

Complications	No (%)
Thrombocytopenia	26 (17.6)
Hypocalcemia	17 (11.5)
Hypoglycemia	14 (9.5)
Hyperkalemia	8 (5.4)
Hyponatremia	6 (4.1)
Bradycardia	12 (8.1)
Apnea	7 (4.7)
Necrotizing enterocolitis	3 (2)
Septicemia	3 (2)
DIC	2 (1.4)
Cardiorespiratory arrest	2 (1.4)
Death	1 (0.7)

Table 4. Comparing Variables Between Term and Preterm Infants [a]

Variables	Term 102 (68.9)	Preterm 46 (31.1)	P Value
Gender			0.374
Male	44 (43.1)	24 (52.2)	
Female	58 (56.9)	22 (47.8)	
Causes			0.171
ABO incompatibility	42 (41.2)	12 (26.1)	
RH incompatibility	11 (10.8)	4 (8.7)	
ABO&RH incompatibility	2 (2)	1 (2.2)	
G6PD deficiency	11 (10.8)	3 (6.5)	
Polycythemia	0 (0.0)	1 (2.2)	
Unidentified	36 (35.6)	25 (54.3)	
Complications			0.529
Yes	39 (38.2)	18 (39.1)	
No	63 (61.8)	28 (60.9)	
Thrombocytopenia			0.400
Yes	19 (18.6)	7 (15.2)	
No	83 (81.4)	39 (84.8)	
Hypocalcemia			0.160
Yes	14 (13.7)	3 (6.5)	
No	88 (86.3)	43 (93.5)	
Hypoglycemia			0.238
Yes	8 (7.8)	6 (13.0)	
No	94 (92.2)	40 (87.0)	
Hyperkalemia			0.523
Yes	6 (5.9)	2 (4.3)	
No	96 (94.1)	44 (95.7)	
Hyponatremia			0.273
Yes	3 (2.9)	3 (6.5)	
No	99 (97.1)	43 (93.5)	
Bradycardia			0.545
Yes	8 (7.8)	4 (8.7)	
No	94 (92.2)	42 (91.3)	
Apnea			0.131
Yes	3 (2.9)	4 (8.7)	
No	99 (97.1)	42 (91.3)	
Necrotizing enterocolitis			0.232
Yes	1 (1.0)	2 (4.3)	
No	101 (99.0)	44 (95.7)	
Septicemia			0.324
Yes	3 (2.9)	0 (0.0)	
No	99 (97.1)	46 (100.0)	
DIC			0.526
Yes	1 (1.0)	1 (2.2)	
No	101 (99.0)	45 (97.8)	
Cardiorespiratory arrest			0.526
Yes	1 (1.0)	1 (2.2)	
No	101 (99.0)	45 (97.8)	
Death			0.689
Yes	1 (1.0)	0 (0.0)	
No	101 (99.0)	46 (100.0)	

[a] Values are presented as No (%).

Table 5. Comparing Variables With and Without Complications

Variables	Complications		P Value
	Yes = 57 (38.5)	No = 89 (61.5)	
Gender [a]			0.341
Male	29 (42.6)	39 (57.4)	
Female	28 (35.0)	52 (65.0)	
Gestational age group [a]			0.918
Term	39 (38.2)	63 (61.8)	
Preterm	18 (39.1)	28 (60.9)	
Gestational age, wk [b]	36.8 ± 3.0	37.5 ± 2.0	0.120
Birth weight, g [b]	2771 ± 764	2894 ± 656	0.299
Admission age, d [b]	4.6 ± 3.9	4.4 ± 2.3	0.844
Maximum total Serum bilirubin, mg/dL [b]	28.8 ± 8.6	27.1 ± 6.3	0.167
Causes [a]			0.145
ABO incompatibility	15 (27.8)	39 (72.2)	
RH incompatibility	8 (53.3)	7 (46.7)	
ABO&RH incompatibility	2 (66.7)	1 (33.3)	
G6PD deficiency	4 (28.6)	10 (71.4)	
Polycythemia	0 (0.0)	1 (100.0)	
Unidentified	28(45.9)	33(54.1)	
Hospital stay, d [b]	9.0 ± 7.2	5.3 ± 5.8	0.001

[a] Values are presented as No (%).
[b] Values are presented as mean ± SD.

5. Discussion

Exchange blood transfusion has reminded the gold standard for rapid lowering higher level serum bilirubin concentration and prevention of bilirubin encephalopathy and kernicterus. Although reports show progressive decline over the years in number of neonates who need exchange transfusion because of anti-Rh globulin for mothers and widespread use of phototherapy for neonatal jaundice, it is still required in up to 7% of neonates admitted to nurseries (13).

Despite advances in neonatal care in the recent years, exchange transfusion still remains a high risk procedure with common adverse effects. We observed a high rate of complications associated with exchange transfusion in 57 (38.5%) neonates; however, most of these were asymptomatic and transient. Most common complications in our study were thrombocytopenia (17.6%), hypocalcemia (11.5%), hypoglycemia (9.5%), hyperkalemia (5.4%), and hyponatremia (4.1%), which are similar to the findings of most previous studies (14, 15). Similarly, the rate of serious complication such as necrotizing enterocolitis and septicemia from ET is very low, approximately 1% and prior reports indicated that necrotizing enterocolitis and septicemia are the most common severe complications (11, 12, 16, 17).

Other serious complications of our study were apnea and bradycardia observed in 4.7% and 8.4% of neonates, respectively. Mortality directly attributable to exchange transfusion is reported to be at least 1% and is due to unexplained cardiac arrest, cardiac arrhythmias or air embolism (18). We observed a mortality of 1.4%; while, other studies reported a mortality rate range from 0.66% to 3.2% and (10, 12, 16, 19) Chime and Davutoglu reported no death in their study (20, 21).

Because many complications of exchange transfusion are unavoidable even with careful monitoring, early diagnosis of severe hyperbilirubinemia and phototherapy is the best way to reduce these complications that reduce the need for exchange transfusion in turn.

Multiple exchange transfusion was required in 23.6% of our neonates, which is similar to the findings of Dikshit (22), but more than Abu-Ekteish et al. (23). In our study, no etiologic factors were identified in 61 (41.2%) neonates, a rate reported previously as 17 - 40% (16, 24-27) and ABO incompatibility was observed in 54 (36.5%) neonates, which is similar to other studies (28-30). Rh incompatibility alone or concomitant with ABO incompatibility was observed in 15 (10.1%) and 3 (2.0%) neonates, respectively. The reduction in Rh incompatibility may be due to the use of anti-Rh globulin for Rh negative mothers (31). G6PD deficiency accounted for 14 (9.5%) of all causes of ET in our

study. This figure is lesser than Badiee's study (12), which estimated 19% prevalence of G6PD deficiency and higher than Bhat et al. (32) who reported no patient with G6PD deficiency. This difference in prevalence could be due to racial differences in the prevalence of G6PD deficiency.

This report indicated that complications are common after exchange transfusion despite technological advances in neonatal care and careful monitoring. Therefore, early recognition of infants at risk of severe hyperbilirubinemia and the use of intensive phototherapy can significantly reduce the need of exchange transfusion.

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Authors' Contributions

Study concept and design: Mohammad Kazem Sabzehei. Acquisition of data: all authors. Analysis and interpretation of data: Saadat Torabian. Drafting of the manuscript: Behnaz Basiri and Maryam Shokouhi. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Saadat Torabian. Administrative, technical and material supports: all authors. Study supervision: Maryam Shokouhi and Behnaz Basiri.

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