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Short-term complications associated with exchange transfusion in neonates with severe hyperbilirubinemia

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ABSTRACT

Background and Objective: Neonatal jaundice is a common condition among neonates in the first few days of life and is a leading cause of admission among neonates. The aim of this study was to investigate the most common risk factors associated with severe neonatal hyperbilirubinemia (NNH) and short-term complications of the exchange transfusion (ET).

Methods: In this retrospective study, the medical records of newborns <28 days with severe hyperbilirubinemia who underwent ET during 2015-2018 were analyzed. Medical records and files were searched using the keyword "exchange transfusion". The clinical and demographic characteristics of the study population as well as the short-term complications of ET were descriptively analyzed.

Findings: Totally, 74 newborns with the mean age of 5.6±3.4 days were included in the current study. The baseline mean peak total serum bilirubin (TSB) was 25.8±5.7 mg/dl. In neonates, the ABO incompatibility was the most frequent cause of severe hyperbilirubinemia requiring ET (54.1%), followed by sepsis (39.2%). Moreover, 57.7% of neonates developed complications secondary to ET. The most common complication was hyperglycemia (71.6%), followed by thrombocytopenia (48.6%).

Conclusion: Hemolysis and sepsis are common causes of NNH; therefore, the extensive screening and identification of the at-risk population can help decrease the incidence of severe NNH. Frequent monitoring of blood sugar and screening of thrombocytopenia before and after ET procedures are necessary to reduce adverse events.

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Introduction

Neonatal jaundice is a common medical problem among neonates in the first few days of life, occurring in >60% of all newborns, particularly in developing countries. In severe cases, hyperbilirubinemia can progress to acute bilirubin encephalopathy (ABE) and chronic bilirubin encephalopathy (CBE) or kernicterus [1, 2].

Even though the neonatal hyperbilirubinemia (NNH) is a common condition among newborns, the use of appropriate guidelines and management strategies leads to a drastic decrease in the condition and its neurological sequelae in developed countries. On the contrary, due to the wide variations in protocols, unavailability of diagnostic tests and treatment modalities, the condition remains problematic in low- and middle-income countries [1].

Pathological hyperbilirubinemia usually occurs in the first few days of life and is often caused by hemolysis, internal bleeding and infection or sepsis [3]. Globally, resource-limited countries account for 80% of severe NNH, and the estimated rates of mortality and neurological sequelae are 25% and 13%, respectively. Choreoathetoid cerebral palsy, hearing disorders, gaze disturbances and dental enamel hypoplasia are common neurological sequelae of severe NNH [4, 5]. Though the severe NNH can lead to irreversible neurological sequelae, it is highly preventable with timely diagnosis and treatment [6].

The treatment modalities for NNH include phototherapy, intravenous immunoglobulins (IVIG), pharmacological treatment and exchange transfusion (ET). Although the ET is associated with many complications, it is still commonly used in pathologic hyperbilirubinemia to rapidly reduce the serum levels of indirect bilirubinemia to tolerable levels. It is also indicated when phototherapy is not sufficient to reduce bilirubin concentrations to acceptable levels or when there are clinical manifestations of the ABE [3]. The advancements in neonatal care, screening of Rh incompatibilities, increased frequency of phototherapy as well as the use of IVIG as adjuvant therapy have decreased the use of ET, especially in developed countries; however, the frequency of this procedure has been reported as 21 and 61% in Latin America and the Middle East, respectively [7, 8].

The main objective of this retrospective study was to investigate the most common etiologies associated with severe NNH and short-term complications of ET.

Methods

The medical records of newborns <28 days with severe hyperbilirubinemia who were admitted to the neonatal ward neonatal and intensive care unit (NICU) of Bahrami Children's Hospital and who underwent ET from 2015 to 2018 were analyzed in this retrospective study. Newborns who underwent ET for reasons other than hyperbilirubinemia were excluded from the study.

Clinical characteristics of the study population

Data were retrieved from medical files and records using the keyword “exchange transfusion”. The demographic data of the newborns included age at the time of presentation, gender, gestational age at birth and birth weight. The clinical data were date of admission to the hospital, cause of the severe hyperbilirubinemia, neonatal and maternal blood group, history of gestational diabetes mellitus (GDM), short-term complications secondary to ET and number of times. The ET was performed for each newborn. Laboratory investigations performed to aid the diagnosis of hyperbilirubinemia were also recorded. These included glucose-6-phosphate dehydrogenase (G6PD) status, total and direct serum bilirubin levels, complete blood count, Coombs and indirect Coombs tests, random blood sugar, blood culture, urine analysis, serum electrolytes and reticulocyte count.

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Definition of variables

Exchange-range or severe hyperbilirubinemia:

Our medical center uses the 2004 American Academy of Pediatrics guidelines for the management of NNH. The indication for starting ET is based on bilirubin thresholds varying by TSB, age of neonate, gestational age at birth and presence or absence of risk factors such as isoimmune hemolytic disease, G6PD deficiency, asphyxia, lethargy, sepsis and acidosis [9]. This guideline provides recommendations for neonates born at ≥35 weeks. Local guidelines are used in our medical center for the management of NNH in neonates born <35 weeks. Diagnoses of the etiology of the severe hyperbilirubinemia were made by attending neonatologists.

Exchange transfusion:

The presence of bilirubin-induced neurologic dysfunction in the neonates was not documented; hence, it was not presented in the current study. The ET was indicated for patients diagnosed with severe hyperbilirubinemia. All patients underwent phototherapy at least once before ET. Exchange transfusion was either performed by attending neonatologist or neonatology fellow under the direct supervision of an attending. The date of the procedure, number of times the neonate is undergoing the procedure, indications for the procedure and any complications during and after the procedure were recorded in the procedure forms in our medical center. The age of red blood cells (RBCs) used for ET was recorded in this center; thus, it could not be presented in the present study.

Short-term complications:

All complications associated with ET, which occurred during the procedure or within 6 days after the procedure were documented. The short-term complications of ET were defined as follows: Hyperglycemia (blood glucose concentration >150 mg/dl); hypoglycemia (blood glucose concentration <50 mg/dl); thrombocytopenia (platelet count <100 000/mm3); bradycardia (heart rate <80 beats/minute); hypocalcemia (total serum calcium level of <8 mg/dl); hyperkalemia (total serum potassium level of >6 mEq/L); necrotizing enterocolitis (NEC) (diagnosed based on clinical and radiographic features) as well as metabolic acidosis (arterial blood pH <7.35 and HCO3< 18 mmol/L).

Statistical consideration

The data presented in the ongoing study were expressed as mean± standard deviation. Moreover, the collected data were descriptively analyzed using SPSS 26.0.

Results

Clinical Characteristics of the newborns

In the current study, the clinical and demographic data of 74 neonates with severe hyperbilirubinemia who underwent exchange transfusion were examined for the etiology of hyperbilirubinemia and complication of exchange transfusion. Among them, 41 (55.4%) were male and 33 (44.6%) were female and 45 (60.8%) and 29 (39.2%) of them were term and preterm infants, respectively. In terms of birth weight, 57 (77%) infants had normal weight and 17 (23%) cases had LBW. No cases of VLBW were observed. N= number of neonates. N (%) = number of neonates expressed in percentage.

The mean age of the newborns at the time of admission was 5.5 ± 3.4 days, and the mean gestational age at birth was 36.9±1.7 weeks. Moreover, the average birth weight of the newborns was 2985±535 grams and the smallest weight was 1850 grams. The clinical characteristics of the newborns are presented in table 1.

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Etiologies of severe hyperbilirubinemia in the newborns

In this study, the ABO incompatibility was the most frequent cause of severe hyperbilirubinemia requiring ET (40 (54.1%) neonates), followed by sepsis (22 (39.2%)). In addition, 16 (21.6%) and 12 (16.2%) neonates had G6PD deficiency and severe dehydration, respectively. Other etiologies of severe hyperbilirubinemia identified in the current study are illustrated in table 2.

Short term complications attributed to ET

In the present study, 52 (57.7%) infants developed complications secondary to ET. The most common complication of ET was hyperglycemia (53 (71.6%)), followed by thrombocytopenia (36 (48.6%)). Among 36 neonates who had thrombocytopenia, 1 infant died 5 days after ET. Moreover, 1 (1.4%) newborn died 6 days after ET because of underlying problems such as sepsis and disseminated intravascular coagulation (DIC) but not due to the ET-related complication. Besides, 12 (16.2%) neonates developed metabolic acidosis which resolved in 11 newborns after 4 hours. Moreover, 5 (6.8%) infants developed seizures so that 1 and 4 of them suffered from seizure during procedure and 6 days after procedure, respectively. Hyperkalemia occurred in 5 (6.8%) neonates of whom 4 (5.4%) ones needed a second ET during hospitalization. Other complications were bradycardia (2 (2.7%)), febrile non-hemolytic transfusion reaction (FNHTR) (1 (1.4%)), hypoglycemia (1 (1.4%)), hypocalcemia (1 (1.4%)) and NEC (1 (1.4%)). Table 3 shows the frequency of various complications associated with ET. No cases of hypokalemia were observed in the present study.

Furthermore, the baseline mean peak TSB on admission and mean peak TSB immediately before ET were 25.8 ± 5.7 and 20.4 ± 5.0 mg/dl, respectively. The mean peak TSB was 10.1 ± 3.3 mg/dl immediately after ET, but it increased to13.0 ± 3.5 mg/dl 4 hours after transfusion. Thus, the mean peak TSB level decreased by 50.4% immediately after ET, and its level reached to 63.8% four hours after ET.

Table 1. Clinical characteristics of the neonates

Characteristics	N (%)	
Males	41(44.6)	
Females	33(55.4)	
Term infants	45(60.8)	
Preterm infants	29(39.2)	
Normal birth weight	57(77)	
Low birth weight (LBW)	17(23)	
Characteristics	**Range**	**mean± SD**
Gestational week (W) at birth	32-41	37.0 ±1.7
Age on admission (days)	1-26	5.6 ±3.4
Birth weight (g)	1850-4700	2985.8 ±535.9

Table 2. Frequency of causes of severe hyperbilirubinemia identified in this study

Causes of hyperbilirubinemia		N (%)
ABO incompatibility		40(54.1)
Rh incompatibility		2(2.7)
Dehydration		12(16.2)
G6PD disease		16(21.6)
Polycythemia		2(2.7)
Cephalohematoma		3(4.1)
Sepsis		29(39.2)
GDM		7(9.5)
Idiopathic		2(2.7)
Other causes	TORCH	1(1.4)
	Intraabdominal bleeding	1(1.4)
	GI obstruction	2(2.7)
	Total	4(5.4)

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Table 3. Short-term complications of the exchange transfusion

Complications	N(%)
Thrombocytopenia	36(48.6)
Hypoglycemia	1(1.4)
Hyperglycemia	53(71.6)
Hypocalcemia	1(1.4)
Hyperkalemia	5(6.8)
Metabolic acidosis	12(16.2)
NEC	1(1.4)
Seizure	5(6.8)
Bradycardia	2(2.7)
Death secondary to thrombocytopenia	1(2.8)
FNHTR	1(1.4)
Death	1(1.4)

Discussion

Based on the results of the ongoing study, the mean age of the newborns was 5.6±3.4 days, and the mean gestational age at birth was 37.0±1.7 weeks. In addition, the baseline mean peak TSB was 25.8 ± 5.7 mg/ dl, which are consistent with the parameters for pathological hyperbilirubinemia in a study [3]. A retrospective cohort study has evaluated the contribution of clinical risk factors to the development of significant hyperbilirubinemia in term and near-term infants and suggested that the gestational age and predischarge TSB are the most important predictors of severe hyperbilirubinemia in neonates. The authors indicated that gestational age <38 weeks is an important predictor of severe hyperbilirubinemia (OR: 9.2; 95% CI: 4.4–19); therefore, it is recommended that neonates should be assessed for predischarge TSB based on their gestational age to identify the at-risk population as early as possible [10].

In this study, the ABO incompatibility was the most frequent cause of severe hyperbilirubinemia requiring ET among the neonates (54.1%). Similar to the ongoing study, in a large study conducted in Southwestern China involving 644 neonates who underwent ET due to the severe hyperbilirubinemia over 11 years [11] and in another study performed in Turkey with clinical characteristics [12], the ABO incompatibility was the most common cause of severe hyperbilirubinemia with a prevalence of 59.9 and 27.8%, respectively. The overall prevalence of ABO incompatibility among Iranian neonates with neonatal jaundice was 16.9% (95% confidence interval (CI) 10.9–22.8) [13]. Several other studies identified ABO incompatibility as the most common cause of severe hyperbilirubinemia requiring ET [14- 17]. The second most common cause of severe hyperbilirubinemia in the present study was sepsis. In a recent study carried out in a resource-limited setting in Nigeria, which evaluated the risk factors for severe hyperbilirubinemia among neonates, the sepsis accounted for 35.3% of the cases, which is close to the prevalence of sepsis among our study population (39.2%) [6]. Additionally, the sepsis was identified as a major cause of pathological unconjugated hyperbilirubinemia in a Tertiary care hospital in Nepal [18].

Overall, the G6PD was 21.6% of severe hyperbilirubinemia in neonates of the current study. In 2004, Abolghasemi et al. reported the prevalence of G6PD deficiency in neonatal jaundice in Tehran. They divided their study population into G6PD-deficient and G6PD-normal groups, and they found that hyperbilirubinemia and jaundice were 3-fold higher in G6PD-deficient neonates than in G6PD-normal neonates [19]. The other study evaluated the burden of the NNH in countries with significant G6PD deficiency and suggested that there was a substantial burden in resource-limited countries, mainly due to the lack of clearly defined practice guidelines for screening and management of the disease [20].

Moreover, severe dehydration was one of the important causes of severe hyperbilirubinemia in the population of the present study (16.2% of the cases). In a recent root-cause analysis on the NNH conducted in Turkey, the dehydration (27.6% (1,551/5,620)) was the second most common cause of neonatal jaundice after hemolytic disease. Educational programs for mothers on proper feeding and adequate hydration of newborns can help

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decrease the incidence of neonatal jaundice [21]. The prevalence of Rh incompatibility among our study population was 2.7%. This was relatively low compared with other studies, reporting a prevalence of 28% in the Hilly Terrain of India [14] and 38% in Serbia [22]. The low prevalence of Rh incompatibility in the infants of the ongoing study could be attributed to the intensive screening programs and management of Rh incompatibility in our medical center.

In all neonates underwent ET (100%) in the present study, the rate of ET-related complications was 57.7%. In the ongoing study, the duration of RBCs used for ET was not documented; however, it seems that the duration of RBCs storage could have a major impact on the clinical outcomes of the procedure. In a recent study in China, the effect of storage duration of RBCs on the clinical outcomes of ET was evaluated. In the mentioned study, the population was divided into two groups based on storage duration of RBCs including <7 days old and >7 days old and it was found that there was a significant reduction in the incidence of post-ET complications in <7-day-old group compared with the other group (P <0.05) [23]. In another recent study in India conducted on 14 neonates who underwent 23 ETs, only 5 (21.7%) cases developed mild complications. Moreover, in that study, the duration of RBCs storage was <5 days old [24]. In a national root-cause analysis on neonatal jaundice in Turkey, out of 132 neonates underwent ET, 39 received IVIG and phototherapy prior to ET. In this study, the incidence rate of post-ET complications was 8.5%, but the duration of RBCs storage was not mentioned in the study [21]. In the ongoing study, the mean peak TSB decreased by 50.4% immediately after the ET, but it reached 63.7% of the level immediately before ET when measured 4 hours later. In the study carried out in China, in addition to significant reduction in the incidence of post-ET complications, there was a significant decrease in TSB levels measured 12 hrs after the procedure (P<0.01), even though the difference was not significant at the end of ET(P> 0.05) [23]. Thus, it seems that using RBCs <7 days old could decrease the need for another ET.

In the present study, the most common complication of ET was hyperglycemia (71.6%). In a prospective study on ET in neonatal unconjugated hyperbilirubinemia fulfilled (2015) in a tertiary care hospital in Nepal, the hyperglycemia (51.7%/p<0.001) was the second most common complication of ET after anemia (89.7%/p<0.018). In another single-center study which assessed the complications of ET in 306 neonates from 2005 to 2012, the hyperglycemia (56.5%) was reported as the most common complication, followed by hypocalcemia (22.5%) and thrombocytopenia (16%). Nevertheless, a recent large cohort study was performed on more than 1200 neonates of whom about 1162 underwent ET, and the hyperglycemia was not reported as a common adverse event [8] while some other studies were identified hyperglycemia as a common complication associated with the procedure [11].

The second most common complication associated with ET was thrombocytopenia. In a recent large multicenter cohort study, more than 1200 infants born at ≥23 weeks of gestation with hyperbilirubinemia and underwent ET during 1997-2016, and the thrombocytopenia (64% (646/1013)) was the most common complication related to the procedure [8]. In another study done in Southwestern China from 2001 to 2011, 614 neonates were evaluated for adverse events of ET and it was observed that the thrombocytopenia (54.6% (335/614)) was the most common adverse event, followed by hyperglycemia (42.8% [263/614])[11]. Thrombocytopenia is a frequent adverse event associated with ET [12, 16, 17]; thus, it is recommended that appropriate measures should be taken to prevent thrombocytopenia complications. In the present study, out of the 36 neonates who developed thrombocytopenia secondary to ET, 2.8% died because of a complicated thrombocytopenia. Boskabadi et al. in Iran, the severity and duration of thrombocytopenia following ET in NNH were evaluated. They suggested that 80% of the infants developed thrombocytopenia after ET, but it was mild to moderate in more than 86% of the cases. Only 3.7% of the cases developed severe thrombocytopenia (<50000) but no mortality was reported [25]. Death secondary to thrombocytopenia in infants undergoing ET has not been frequently reported.

Metabolic acidosis and hyperkalemia were less common findings in the current study. In addition, metabolic acidosis (31.1% (191/614)) was a common complication in the Southwestern China study [11], and hyperkalemia

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(5% (46/886)) was a common finding in the recent large cohort study [8]. Although many previous studies have reported high rate of hypoglycemia [16- 18] secondary to ET, the incidence of hypoglycemia was low in the ongoing study (1.4% (1/74)) and recent large cohort study (2% (19/818)). The overall rate of NEC secondary to ET is estimated to be between 0.9%-1.3%, which is similar to that in the present study [8]. The incidence of FNHTR to RBCs is estimated to be between 0.1-0.3% [26]. To our best knowledge, this is the first study reporting the occurrence of FNHTR in neonates with severe hyperbilirubinemia undergoing ET.

Data for the present study were retrieved from medical records of the newborns. Inaccuracy of the information recorded in the files might affect the results of the present study.

Hemolysis and sepsis are common causes of NNH; thus, the extensive screening and identification of the at-risk population can help decrease the incidence of severe NNH. Besides, most of the short-term complications of ET are reversible as well as metabolic and laboratory abnormalities. Frequent monitoring of blood sugar and management of electrolyte abnormalities as well as screening for thrombocytopenia before and after ET procedures are necessary to reduce adverse events. Furthermore, it seems that the use of RBCs for newborns <5 days old may lead to reduce the incidence of post-ET complications and the need for another ET during hospitalization.

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Ethical considerations

The study was approved by the Ethics Committee of Tehran University of Medical Sciences (Ethical code: IR.TUMS.REC.1394.626). The authors avoided from data fabrication and falsification.

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Conflict of interest

The authors report no conflict of interest.

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