Frequency, Etiology, and Complications of Neonatal Exchange Transfusion: A Prospective Cross-Sectional Study

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Abstract

Background: Neonatal hyperbilirubinemia is one of the most prevalent neonatal risk factors for neurological development disorders in pre-term and full-term babies. Despite being an invasive procedure, blood exchange transfusion (ET) is still the most effective procedure in reducing total serum bilirubin levels after the failure of phototherapy.

Objective: This study aims to detect the various complications of ET and its frequencies among neonates admitted to the neonatal Intensive Care Unit (ICU) in a tertiary hospital.

Methods: A prospective cross-sectional study included neonates of gestational age ≥ 35 weeks and had ET. ET was done using a single catheter pull-push technique via insertion of an umbilical venous catheter with documentation of etiology, routine laboratory tests, and associated complications of ET.

Results: 118 neonates had ET and were recruited in our study. The most common causes for ET were due to hyperbilirubinemia of ABO incompatibility (61.9%), and 22.9% were due to Rh disease. The glucose-6-phosphate dehydrogenase deficiency (G6PD) participated in 8.5% of ET among our cases, and 6.8% were due to other causes. The incidence of complications due to ET occurred in 20 (16.9%) of cases. The most prevalent complication of ET was thrombocytopenia, which was presented in 7 (5.9%) of cases, and two cases died.

Conclusion: Complications of ET were less frequent; thrombocytopenia was the most prevalent, followed by electrolyte disturbances. Neonatal mortality due to ET was very rare.

Keywords: Neonatal hyperbilirubinemia, Exchange transfusion, Kernicterus.

Background:

Neonatal hyperbilirubinemia usually occurs due to the disturbance between bilirubin production and excretion in the early neonatal life. Severe hyperbilirubinemia can lead to serious complications, including neurological dysfunction and death [1-3].

Neonatal exchange transfusion (ET) is a common procedure done routinely to reconstitute the normal elements of the blood and to remove any circulating harms with preservation of the same circulating capacity of the blood volume [4]. Recently, the advances in neonatal care, especially the administration of anti-D for all Rh-negative mothers, improved in prophylaxis and early antenatal detection of Rhesus hemolytic disease of the newborns, the earlier and safer delivery of babies with anticipated hemolytic disease of the newborn, and phototherapy, have led to a decrease in the number of ETs being performed [5-9]. Despite improvements in neonatal care, ET is considered a primary treatment modality if phototherapy does not correct jaundice as initial non-invasive therapy [10, 11]. We sought to estimate the frequency, indications, and associated adverse effects of

ET in a tertiary university hospital in our neonatal population.

Aim of the Study:

This study aims to evaluate neonatal hyperbilirubinemia requiring ET and to detect the various complications of ET and its frequencies among neonates admitted to the Neonatal Intensive Care Unit (NICU) of Assiut University Children's Hospital (AUCH).

Patients and Methods:

Study Type and Participants:

A prospective cross-sectional study included the neonates who underwent ET of blood in the NICU at AUCH, Assiut – Egypt, from March 2018 till the end of February 2019.

Inclusion Criteria:

Neonates of a gestational age ≥ 35 weeks and suffering from hyperbilirubinemia when phototherapy fails are indicated for ET.

Neonates suffering from hemolytic disease of the newborn (ABO and Rh incompatibility), especially if the bilirubin level is > 4.5 mg/dl, the cord hemoglobin level is < 11gm/dl, and if the bilirubin level increases > 1 mg/dl/hr despite phototherapy.

Exclusion Criteria:

Pre-term infants born < 35 weeks gestation, neonates whose parents refused participation in the study, and sick neonates with other comorbidities were excluded from our study. We excluded the neonates below 35 weeks gestation because of their greater liability to hyperbilirubinemia, which subsequently increases the incidence of ET, which may subsequently enhance the incidence of associated complications of ET. Also, pre-term infants – less than 35 weeks gelation – are more liable to death and other complications of prematurity, which may interfere with the complications of ET [12].

Laboratory Investigations:

All recruited neonates were subjected to complete blood count (CBC), reticulocyte count, hematocrit level, blood grouping, total bilirubin level, direct and indirect bilirubin pre-ET, at 6 hours, at 24 hours, and 72 hours post-ET.

Also, measurements of serum calcium, sodium, potassium, and glucose levels pre-ET, at 6 hours, at 24 hours, and 72 hours post-ET were documented.

Our neonates and their mothers were tested for ABO and Rh (D) blood types. A direct Coombs test, blood type, and an Rh (D) type on the infant's (cord) blood was done if a mother was Rh-negative.

Study Procedure:

Our neonatology department routinely uses the 2004 American Academy of Pediatrics hyperbilirubinemia guidelines to manage admitted newborn infants [13]. A cross-matched fresh (< 72 hrs old) citrated blood was used in ET. The volume of exchanged blood was calculated using the pochedly formula:

"Required blood volume (ml) = 80 ml × Infant's weight [kg] × 2" [14].

ET is always done after written parental consent. ET was done using a single catheter pull-push technique by inserting an umbilical-inferior vena cava venous catheter. We connected the umbilical venous catheter to a two or 3-way stopcock or one 4-channels stopcock. The four ways of connection to the umbilical catheter should be connected to the umbilical catheter, catheter draining the blood withdrawn, donor's blood, plus a prefilled saline syringe, respectively, in the same order. Usually, 15 – 20 mL aliquots may be infused or withdrawn at 5 ml/kg/min. The procedure is usually completed within an average of one hour, and 28 – 32 cycles of infusions and withdrawals are completed with the preservation of the same blood volume. During the procedure, continuous monitoring and documentation of the vital data of each infant was observed. During the procedure, all infants were on a radiant warmer/flat incubator mattress [4, 15, 16].

During the ET procedure, calcium gluconate was administered intravenously after every 100 ml of blood was removed.

ET-associated complications were defined as any adverse events during or within three days of the exchange.

Sample Size Calculation:

As reported in many previous studies, the incidence of adverse events following blood ET varies from 12% to 28%. To detect 12% of complications, with an error of 5% (α error of 5% and a study power of 80%), a total of 68 blood ETs needed to be recruited.

Data Analysis:

Statistical analysis was done using IBM SPSS version 22 (SPSS Inc.; Chicago, IL, USA). Data were tested for normality by Shapiro-Wilk, and then data were shown as mean ± standard deviation (SD) for continuous data with a normal distribution or median with range for the not normally distributed data.

Categories were described as percentages with frequency. Comparing continuous data variables was done using independent samples t-tests for normally distributed data and Wilcoxon signed rank test for skewed data. A p value of less than 0.05 was considered statistically significant.

Ethical Consideration:

All parents of our neonates signed an informed consent form for participation in the study. An agreement was obtained before initiating the ET procedure after simply describing the study's nature and the rights to participate or refuse participation.

The Faculty of Medicine, Assiut University's local ethical committee approved all the study protocols under the IRB local approval number 17100045.

Results:

A total of 118 neonates – fulfilling the inclusion criteria – underwent ET and were enrolled in a prospective cross-sectional study during one year in AUCH. Demographics of our studied neonates are shown in Table (1).

A total of 88 (74.6%) of our participants had ET once, 26 (22%) had ET twice, and just 4 (3.4%) cases were exposed to ET 3 times. Indications for ET were variant among our patients, the vast majority were due to hyperbilirubinemia of ABO incompatibility (61.9%), and 22.9% were due to Rh disease. The G6PD deficiency participated in 8.5% of ET among our cases, and 6.8% were due to other causes, Table (2). The biochemical and hematological characteristics of the studied cases before and after ET are shown in Table (3). The mean hemoglobin level was 12.4 ± 2.1 gm/dl compared to 11.2 ± 3.2 gm/dl post-exchange, with no significant difference (p = 0.12). The mean total serum bilirubin pre-exchange was 340.8 ± 82.2 µmol/L in comparison to 183.1 ± 24.5 µmol/L post-exchange with a strong significant difference between them (P < 0.001), Table (3).

The adverse events or complications most probably due to ET are presented in Table 4. The incidence of complications due to ET occurred in 20 (16.9%) of cases. The most prevalent complication of ET was thrombocytopenia, which was presented in 7 (5.9%) of cases, and two cases died.

A total of 108 (91.5%) cases were discharged well, 8 (6.8%) developed Kernicterus due to high serum bilirubin before the blood exchange, and 2 cases (1.7%) died.

Table 1: Demographic characteristics of the study populations (N=118):

Variables	Mean ± SD or N (%)
Maternal age (Years)	32.1 ± 6.8
Age at admission (Days)	3.1 ± 1.2
Age at exchange (Days)	4.5 ± 2.1
Gestational age (Weeks)	36.5 ± 2.1
Birth weight (Kg)	2.8 ± 0.78
Gender - Males - Females	 - 74 (62.7%) - 44 (37.3%)
Feeding - Breastfeeding - Artificial feeding	 82 (69.5%) 36 (30.5%)

Mode of delivery	
- Normal vaginal delivery	68 (57.6%)
- Cesarean section	50 (42.4%)

Variables	Mean ± SD or N (%)
Frequency of blood exchange	
- Once	88 (74.6%)
- Twice	26 (22%)
- Triple	4 (3.4%)
History of sibling requiring ET	
- Yes	22 (18.6%)
- No	56 (81.4%)

Table 2: Etiology of neonatal hyperbilirubinemia requiring ET among the studied cases:

Causes	Number (%)
ABO incompatibility	73 (61.9%)
Rh disease	27 (22.9%)
G6PD deficiency	10 (8.5%)
Others as sepsis, DIC, Severe fluid or electrolyte imbalance, polycythemia, breastfed jaundice, and unknown causes	8 (6.8%)

Table 3: Biochemical and hematological characteristics of the studied cases before and after ET:

Lab parameters (Mean ± SD)	Pre-exchange (Mean ± SD)	post-exchange (Mean ± SD)	P- Value
HB (gm/dl)	12.4 ± 2.1	11.2 ± 3.2	0.12
Platelets count (x10^3/µl)	112.1 ± 21.3	85.2 ± 29.4	0.027*
Hematocrit (%)	41.2 ± 6.9	39.7 ± 5.6	0.17
Total serum bilirubin (µmol/L)	340.8 ± 82.2	183.1 ± 24.5	<0.001*
Serum Calcium (mg/dl)	8.2 ± 1.1	8.4 ± 1.0	0.81
Serum potassium (mEq/L)	4.1 ± 1.2	4.5 ± 1.3	0.58
Serum sodium (mEq/L)	141.2 ± 12.5	136.5 ± 15.5	0.47
Glucose (mg/dl)	88.5 ± 18.8	90.2 ± 12.5	0.98

*Independent samples t-test

Table 4: Adverse events of ET among the studied cases:

Complications	Number (%)
Thrombocytopenia	7 (5.9%)
Hypocalcemia	3 (2.5%)
Hypoglycemia	2 (1.7%)
Hyponatremia	1 (0.8%)
Hypercalcemia	1 (0.8%)
Apnea and/or bradycardia	2 (1.7%)
Sepsis	1 (0.8%)
Disseminated Intravascular Coagulation (DIC)	1 (0.8%)
Death	2 (1.7%)
Total	20 (16.9%)

Discussion:

ET is still the best method for rapidly declining elevated serum bilirubin levels with prophylaxis against Kernicterus and brain encephalopathy. Despite the progressive decrease in the number of neonates who need ET over the past years due to anti-D use for all Rh-negative women in addition to accessibility and usage of phototherapy for neonatal jaundice, it is still mandatory in nearly 7% of neonates admitted to NICU [17]. Despite the recent advances in neonatal care in Egypt, ET is still a high-risk procedure with possible severe adverse effects. In our study, we noticed a lowering rate of adverse effects associated with ET in 20 cases (16.9%) of neonates; however, most of the associated adverse effects were transient and asymptomatic.

As in many other studies, a variant of adverse effects occurred during ET; the most prevalent was thrombocytopenia (5.9%), then hypocalcemia (2.5%), hypoglycemia (1.7%), and hyperkalemia and hyponatremia (0.8%) [18, 19].

Similarly, the incidence of serious adverse effects such as septicemia and necrotizing enterocolitis from ET is minimal; it accounts for less than 1%, and previous studies showed similar results besides that septicemia and necrotizing enterocolitis are the most serious complications [20].

These results are inconsistent with Jackson [19], who reported that because of the high rate of complications in severely diseased infants, ET has to be postponed till the risk of bilirubin encephalopathy is as high as – or even higher – the risk of severe complications from the ET itself. These findings are against the guidelines of using lower exchange levels in severely diseased neonates compared to healthy neonates.

Our results contradict Badiee, 2007 [21], who reported that ET is associated with many complications, even in full-term and near-term infants. So, ET can be done when the benefit of preventing Kernicterus outweighs the complications associated with the ET itself, as the advances in neonatal care in recent years and the use of phototherapy before and even after ET, besides the increasing use of intravenous immunoglobins, declined the associated complications of ET. Also, our results contradict Bulbul et al., 2011 [22], who reported that no definite cause was determined in nearly 50% of all infants recruited in their study who received ET. Despite the recent advances in neonatal intensive care units in the last years, the ET-associated adverse event rates remained unchanged.

Furthermore, the most severe complications of ET among our neonates were bradycardia and apnea, which were observed in 3.4% of infants. Deaths directly due to ET among our neonates are reported in 1.7% and can be attributed to sudden heart arrhythmias, cardiac arrest, and/or air embolism. These results are against other studies that reported a death rate ranging from 0.66% to 3.2% [20, 21].

Our data are inconsistent with those of Chime and Davutoglu, who reported no deaths in their studies [23, 24]. Multiple ET was done in 25.4% of our neonates, consistent with the findings of Min-Sun Kim et al., 2020 [25], but more than Abu-Ekteish et al., 2000 [11].

In our study, the other uncommon etiologic factors like sepsis, disseminated intravascular coagulation, polycythemia, severe fluid or electrolyte imbalance, and severe anemia were identified in 6 (5.1%) neonates, a similar incidence reported previously in other studies as 17 – 40% as Bulbul et al., 2011 [21], Sanpavat, 2005 [26], Saxena et al., 2014 [27].

The ABO incompatibility was observed in 73 (61.9%) neonates, while Rh incompatibility alone was observed in 27 (22.9%) neonates; these results are inconsistent with other studies [28-30]. The recent reduction in Rh incompatibility may be due to the use of anti-D globulin for all Rh-negative mothers [5].

G6PD deficiency was estimated to be 10 (8.5%) of all causes of ET in our study. This prevalence is lower than the study done by Badiee, 2007 [20], which estimated a 19% rate of G6PD deficiency, and higher than Bhat et al., 2011 [31], who reported that no one of their recruited patients with G6PD deficiency had ET. This difference in prevalence can be attributed to racial differences in the G6PD deficiency prevalence.

Our results are inconsistent with Sabzehei, who reported that ET-associated complications are still common despite the updates in management options of neonatal hyperbilirubinemia and early recognition of risky neonates of severe hyperbilirubinemia and the use of phototherapy can markedly decline the need for ET [32].

In our study – like others – most of our neonates were born vaginally (57.6%), and more likely, early hospital discharge and oxytocin use during vaginal delivery can provocate the developing extreme neonatal jaundice [33, 34].

According to our results, most of our neonates, 82 (69.5%) fed, were exclusively breastfed. It was similar to other published studies by Salas and Mazzi, 2008 [35] and Ling Duan et al., 2021[36].

Breastfed infants may show an early onset jaundice in which lack of sufficient breastfeeding can lead to a lack of adequacy of taking calories and, as a result, increase serum bilirubin levels (breastfeeding jaundice). So, it may be due to insufficient lactation in the early days after delivery, resulting in malnutrition and/or dehydration. In other circumstances, using water or glucose in water can exacerbate jaundice [37, 38]. But neonatal hyperbilirubinemia can also be seen in well-fed infants as well. In breast milk jaundice, it is estimated that glucuronidase-containing breast milk increases infant serum bilirubin levels. Also, like previous reports, most of our neonates had bilirubin serum levels between (26 – 30 mg/dl) [39].

Conclusion:

Complications of ET were scarce; thrombocytopenia was the most prevalent, followed by electrolyte disturbances. Neonatal mortality due to ET was very rare.

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Disclosures and conflict of interests: The authors declare they have no competing interests.

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