ORIGINAL ARTICLE

Exchange Transfusion in Neonatal Hyperbilirubinemia: Experience of A Tertiary Care Hospital in Dhaka

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Abstract

Background: Hyperbilirubinaemia is a benign condition in newborn babies in some infants may become severe, progressing to kernicterus with substantial risk of neonatal mortality and long-term neurodevelopmental impairments. Among many treatment options exchange transfusion (ET) is the standard method for treatment of severe hyperbilirubinemia.

Objectives: To investigate the frequency of primary risk factors for neonatal hyperbilirubinemia leading to ET, to evaluate the complications and immediate outcome of ET.

Methods: This was an observational cross sectional study conducted in Dr. MR Khan Shishu Hospital and ICH, Dhaka. Frequency of primary risk factors for severe neonatal hyperbilirubinemia leading to ET, characteristics of babies undergoing ET, complications and immediate outcome of ET were analyzed among the neonates admitted between January 2017 to February 2021.

Results: Among 61 neonates 49.18% were male and 50.82% were female, 65.57% of neonates were term and 34.43% pre term. The mean gestational age was 37.00 ± 1.50 weeks and mean birth weight was 2619±50gm. The leading causes of jaundice requiring ET were sepsis 31.17%, ABO incompatibility 24.59%, Rh incompatibility 14.75%, PT LBW with sepsis 14.75%, Infant of diabetic mother (IDM) 6.55%, PT LBW 6.55%, and neonatal sepsis with Down syndrome with congenital hypothyroidism 1.63%. Twenty (32.79%) neonates presented with signs of Kernicterus. Seven neonates (35%) presented with lethargy/poor feeding or hypotonic posture, 4(20%) patients had opisthotonus posture/hypertonia, and 9(45%) had convulsion. Nineteen (31.14%) neonates had complications related to ET. The most frequent complication was bradycardia (16.34%), then Catheter block (9.83%), apnaea (6.55%), cardiac arrest (6.55%), hypothermia (4.92%), NEC after ET (1.64%). Immediate outcome was good in 72.13% patients with smooth recovery, 14.75% had neurological deficit and 1.64% died. Among 20 neonates who presented with signs of Kernicterus 35% patients discharged with good recovery, 45% had neurological deficit.

Conclusion: The common causes of exchange transfusion in neonatal jaundice were sepsis, ABO incompatibility, PT LBW, and infants of diabetic mothers. Overall outcome was good few developed neurological deficit.

Keywords: Neonatal hyperbilirubinaemia, exchange transfusion, kernicterus.

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Introduction

Hyperbilirubinemia is common in all newborn infants during 1st week of life as a postnatal transitional fact which is mostly benign physiological jaundice, due to hepatic immaturity, short fetal RBC life span, relatively low activity of the enzyme glucuronosyl transferase which helps unconjugated bilirubin to be converted to conjugated and thereby excreted through GIT.[1,2]

A small percentage of babies can develop severe hyperbilirubinemia, known as pathological Jaundice.[3] Appearance of jaundice within 24 hours of birth, serum bilirubin of more than 5 mg/dl/day, peak levels greater than the predicted normal range, jaundice lasting >14 days and conjugated hyperbilirubinemia are known as pathological jaundice.[4]

Unbound unconjugated bilirubin can cross the blood-brain barrier and accumulate in the basal ganglia leading to "Bilirubin Induced Neurological Dysfunction" (BIND) or kernicterus.[5-7] Lethargy, tone abnormalities, poor feeding, convulsion and opisthotonus posturing characterize the acute phase. If the babies survive, they may develop chronic bilirubin encephalopathy which causes cerebral palsy, sensory neural hearing loss, dental dysplasia, upward gaze paralysis, and mental retardation, among other symptoms.[8]

Acute bilirubin encephalopathy (ABE) can lead to chronic devastating form called chronic bilirubin encephalopathy (CBE), permanently disabling neurologic condition similar to kernicterus.[9,10] As a result, preventing kernicterus is a major clinical concern for neonatal caregivers all over the world.[11,12] Despite the American Academy of Pediatrics (AAP) guidelines[13,14], efforts by the CDC, WHO and other organizations to minimize the occurrence of serious hyperbilirubinemia and bilirubin encephalopathy, cases of kernicterus continue to occur around the world.[15] Kernicterus in term babies is estimated to occur in 1 in 30,000 to 1 in 200,000 live births in developed countries, according to population-based estimates.[16]

Kernicterus can be prevented using both noninvasive and invasive methods such as phototherapy or ET. By transforming unconjugated bilirubin into lumirubin, phototherapy is the most effective method. Lumirubins are water soluble, they can be passed through the urinary tract.[17,18] ET reduces circulating bilirubin more rapidly, making it an effective treatment option.[19,20] Treatment entails taking the baby's blood and replacing it with donor blood.[21] It eliminates partially hemolyzed RBC, RBCs coated antibodies, and circulating immunoglobulins in addition to lowering bilirubin levels.[22,23] When bilirubin levels remain high despite intense phototherapy ET is recommended, especially if there is severe haemolysis.[24]

The actual level of bilirubin at which phototherapy or ET is needed is still a point of contention.[7] According to the AAP, ET is preferred in neonates with a weight of less than 2500 grams who are full term and whose indirect bilirubin level is between 25 and 20 mg/dl, as well as in cases with risk factors or a GA of 35-37 weeks who are doing well despite 6 hours of proper phototherapy. When the indirect bilirubin level reaches 18 mg/dl despite 6 hours of phototherapy in newborns aged 35-37 weeks with risk factors, ET is recommended.[8]

Although ET is most effective in treating and preventing kernicterus, it is associated with a long list of complications. Hypersensitivity responses, infection, catheter-induced vascular damage, hypotension, NEC, apnoea, cardio-respiratory arrest during the process of ET are the reported primary risks.[25] As well as there is 5% chance of death following ET.[26]

Kernicterus can be prevented by means of early recognition of neonatal jaundice and prompt treatment without any delay. To address this issue, we aimed to investigate the rate of primary risk factors for neonatal hyperbilirubinemia leading to ET, characteristics of babies undergoing ET, complications and immediate outcome of ET and thereby dropping the incidence of kernicterus.

Materials and Methods

This was a cross sectional study conducted in Dr. M R Khan Shishu Hospital and Institute of Child Health, Dhaka from January 2017 to February 2021 in neonatal hyperbilirubinemia requiring exchange transfusion (ET). After ethical approval, informed written consent was taken from the parents. A total of 61 neonates who underwent 65 times ET for hyperbilirubinemia were included in the study. Neonates with gross congenital anomalies and surgical abnormalities were excluded. A pre-designed questionnaire was used to collect all data. Baseline characteristics of the neonates were documented

such as gestational age, birth weight, mode of delivery and gender etc. Different causes of significant hyperbilirubinemia and exchange transfusion were noted. Clinical presentation of the studied neonates was observed in terms of neurological signs or kernicterus like lethargy/ poor feeding, opisthotonos posture, hypo or hypertonia, convulsion etc. Exchange transfusion was done following all aseptic precaution and unit protocol was maintained throughout. Any type of complication during the procedure was documented (catheter block, hypothermia, bradycardia, cardiac arrest etc.). Immediate outcome was observed in terms of discharge and death among all the neonates who underwent exchange transfusion. Babies who developed neurological signs, their outcome was also evaluated. All data were collected and analyzed by SPSS version 21.

Results

During the study period 61 patients underwent 65 times ET (4 patients needed second time double volume ET), of whom 30 (49.18%) were male and 31(50.82%) were female. 40 (65.57%) were term neonates and 21 (34.43%) were pre term. Term and pre term ratio was 1:1.9. The mean gestational age was 37.00 ± 1.50 weeks and mean birth weight was 2619±50gm (Table I)

Table I

Characteristics of all babies undergoing exchange transfusion

Variable	Frequency (%)
Male gender	30 (49.18)
Female gender	31(50.82)
Caesarean section	37(60.65)
Age at exchange transfusion (days)	5.5
Mean Gestational age (weeks) ± SD	37.00 ± 1.50
Mean Birth weight (grams) ± SD	2619±50
Number of exchange transfusions	
Single time	57 (93.44)
Two times	4 (6.56)

The most common causes of Jaundice who underwent ET was sepsis (31.17%), pre term LBW with sepsis (14.75%), only pre term LBW (6.55%), ABO incompatibility (24.59%), Rh incompatibility (14.75%),

infant of diabetic mother (6.55%), neonatal sepsis with down syndrome with congenital hypothyroidism (1.63%) which is shown in table II.

Table II

Causes of neonatal hyperbilirubinemia who underwent ET (N=61)

Causes of Hyperbilirubinarmia	Frequency	Percent
Neonatal sepsis	19	31.17
Pre term LBW with sepsis	9	14.75
Pre term LBW	4	6.55
ABO incompatibility	15	24.59
Rh incompatibility	9	14.75
Infant of diabetic mother	4	6.55
Neonatal sepsis with down syndrome with congenital hypothyroidism.	1	1.63

Among 61 neonate 20(32.79%) neonates presented with neurological signs compatible with Kernicterus. Seven neonates (35%) had lethargy/poor feeding or hypotonic posture, 4(20%) patients had opisthotonus posture/ hypertonia, and 9(45%) patients had convulsion (Table III).

Table III

Signs of kernicterus in patients with hyperbilirubinaemia (n=20)

Sign	Frequency	Percent
Lethargy / Poor feeding/ Hypotonic posture	7	35
Opisthotonus Posture/ hypertonia	4	20
Convulsion	9	45

Among 19 patient of neonatal sepsis 8 patients developed Kernicterus which accounts 40% of all kernicterus patient. Similarly 5 out of 9 Rh incompatibilities, 4 out of 9 pre-term LBW with sepsis, 2 out of 4 IDM, 1 neonate out of 15 ABO incompatibility patients developed kernicterus (Table IV).

Table IV
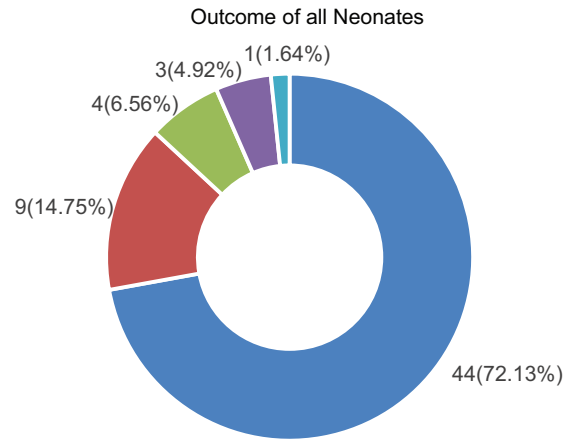*Diagnosis of neonates who developed kernicterus*

Causes of hyperbilirubinarmia	n(%) n=61	Neonates who developed Kernicterus n(%) n=20
Neonatal sepsis	19(31.15)	8 (40)
Pre term LBW with Sepsis	9(14.75)	4(20)
Pre term LBW	4(6.56)	0
ABO incompatibility	15(24.59)	1(5)
Rh incompatibility	9(14.75)	5(25)
IDM	4(6.56)	2(10)
Neonatal sepsis with down's syndrome wtih congenital hypothyrodism	1(1.64)	0

We observed the complications during and following ET, the average of 19(31.14%) out of 61 neonates had complications both during the procedure and after ET. Some neonates developed more than one complication at a time. We noted 9.83% patient had catheter block, 4.92% patients had hypotherm 16.34% had bradycardia, 6.55% patients had apna 6.55% had Cardiac arrest and (1.64%) patie developed NEC after procedure (Fig.-1).
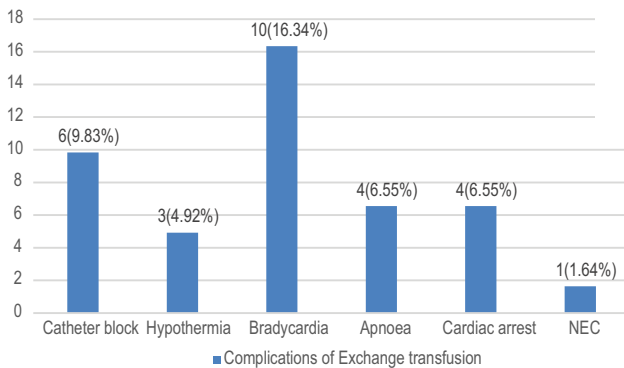

Fig.-1 *Complications of exchange transfusion*

Among 61 neonates who underwent ET for neonatal hyperbiliribinaemia 72.13% patients discharged with good recovery, 14.75% patients discharged with some sort of neurological deficit, 6.56% patients gave discharge on risk bond (DORB), 4.92% patients referred and 1.64% patient died. The neonate who died after ET was diagnosed as a case of Pre term, VLBW with neonatal sepsis (Fig.-2).

Fig.-2 *Outcome of all neonates who underwent ET*

Among 20 neonates who developed signs of Kernicterus 35% patients discharged with good recovery, 45% patients discharge with neurological deficit, 10% patients gave DORB, 10% patients referred (Fig.-3).
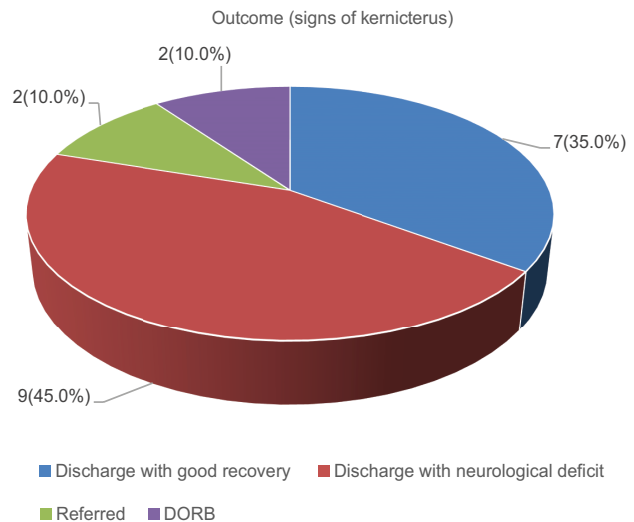
Fig.-3 *Outcome of neonates who developed signs of kernicterus*

Discussion
Neonatal hyperbilirubinaemiais a most frequent benign condition in newborn. 60% of full-term and 80% of preterm neonates are affected by neonatal jaundice and about one tenth newborn develop clinically significant jaundice requiring hospital admission for treatment.[27,28] Global incidence of severe jaundice was reported as 99 cases per 100000 live births and the incidence of kernicterus ranges

from 0.2 to 2.7 cases per 100000 live births.[29] Neonatal jaundice accounted for 1309.3 deaths per 100000 live births and ranked globally 7th among all causes of neonatal deaths in the early-neonatal period that is 1st week of neonatal life and 16th main cause of death in children less than 5 years among over 100 causes of child mortality globally.[30,31]

Published data on neonatal jaundice in Bangladesh is limited. A prospective cohort of neonatal admissions in Khulna Medical College Hospital over 36 months reported that severe jaundice represented 15.7% of all neonatal admissions leading to bilirubin encephalopathy or kernicterus in 2.8% neonates and 0.6% deaths related to jaundice.[32]

Among many treatment options ET is the standard method for treatment of severe hyperbilirubinemia. In our study we found almost equal male female study participants. Ballot et al[6] performed 64 ET in Johannesburg, South Africa and found more male neonate who underwent ET (37/64 , 57.8%).

We found 65.57% of neonates were term and 34.43% were pre term and the mean GA was 37.00 ± 1.50 weeks and mean birth weight was 2619±50gm. Alizadeh Taheri et al[7] did 94 ET, in their study they found 63% of neonates were preterm, mean birth weight was 1950±40 g and a mean GA was 35.2±1.4 weeks. Ballot et al[6] also reported more preterm neonates than term (38/64; 59.5%).

We found neonatal sepsis was the leading cause jaundice requiring ET which accounts 31.17%, then ABO incompatibility (24.59%), Rh incompatibility (14.75%), PT LBW with sepsis (14.75%), IDM (6.55%), PT LBW (6.55%), neonatal sepsis with Down syndrome with congenital hypothyroidism (1.63%). Ballot DE et al[6] observed that isoimmunehaemolysis that is Rh and ABO incompatibility were the primary cause of hyperbilirubinaemia requiring ET in 9/64 (14%) in their study. Burke et al[20] found the similar frequencies of risk factors for developing hyperbilirubinemia that was 38% RhD incompatibility, 38 % ABO incompatibility. On the other hand, similar to our study sepsis was the primary underlying cause for ET in the study performed by Koosha et al[33].

Kernicterus is a preventable disorder with tragic consequences; the actual incidences of kernicterus are not available because it is not a reportable condition. In our study, 20(32.79%) neonates presented with neurological signs compatible with of Kernicterus. Ballot et al[6] had similar observations; they found 23.0% neonate with neurological signs compatible with kernicterus. Among 19 patient of neonatal sepsis 8 patients developed Kernicterus which accounts 40% of all kernicterus patient. So we observed septic neonates had more chance to develop kernicterus.

Despite a lot of advances in neonatal management in the recent years, ET still remains a high risk procedure with common complications. We observed a high rate of clinical complications associated with ET in 19(31.14) neonates; The most serious clinical complications of our study were bradycardia (16.34%), then catheter block (9.83%), apnaea (6.55%), cardiac arrest (6.55%), hypothermia (4.92%), NEC after ET (1.64%). Sabzehei et al[34] found higher rate of complications in 57 (38.5%) neonates. Apnea, bradycardia, NEC, cardiac arrest observed in 4.7%, 8.4%, 2%, 1.4% of neonates, respectively in their study. Arpit et al[35] also reported immediate complications in 7 neonates out of 35 cases (20%).

To ensure good outcome of neonatal hyperbilirubinaemia it's very important to identify jaundice in early neonatal period, prompt initiation of available treatment. Outcome depends on gestational age, clinical presentations, time of initiation of treatment. In our study we can discharge 72.13% patients with good recovery, 14.75% with some sort of neurological deficit and 1.64% died. The neonate who died after ET was diagnosed as a case of PT, VLBW with neonatal sepsis. Sabzehei et al[34] observed a mortality of 1.4% in their study. Chime et al[36] and Davutoglu et al[37] reported no mortality in their study. Wolf et al[38] conducted a retrospective cohort study and found 4% (42/1161) of infants receiving ET died within 7 days following ET.

In our study among 20 neonates who presented with signs of Kernicterus 35.00% patients discharged with good recovery, 45.00% had neurological deficit. In a Prospective cohort study Arpit et al[35] reported that 11.76% patients showed gross motor and fine motor delay, 5.88% developed language delay and 8.82% social personal delay at 6 months follow up. At 12 months follow up 12.5% showed delay in developmental milestones.

Kernicterus is a condition that can be prevented by many treatment options; however still worldwide neonates are suffering from the disease. Proper

protocols for screening, early diagnosis of neonatal jaundice and prompt treatment of severe jaundice need to be enforced to prevent devastating neurological outcome of hyperbilirubinaemia.

Conclusion

The results of this study concluded that hyperbilirubinemia requiring exchange transfusion still challenging. The common risk factors are neonatal sepsis, ABO incompatibility, Rh incompatibility, preterm LBW, infant of diabetic mother. Among them in spite of ET some neonate developed kernicterus. Overall outcome was good few developed neurological impairment. Early diagnosis and treatment can prevent long term sequels.

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