

Exchange Transfusion for Hyperbilirubinemia among Term and Near Term in NICU of a Tertiary Care Hospital of Bangladesh: Findings from a Prospective Study

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ABSTRACT

Background: Exchange transfusion in newborns is recommended as emergency management of hyperbilirubinemia to prevent bilirubin encephalopathy and kernicterus.

Aim: This study aimed to determine the frequency and document common side effects of exchange transfusion and outcomes of newborns requiring exchange transfusion.

Materials and methods: This prospective study was done in the Neonatal Intensive Care Unit (NICU) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh, from January 2016 to December 2019. Information was obtained regarding maternal details, newborn demographics, and clinical status. Blood grouping and Rh typing were done for both mothers and newborns. In all newborns, pre-exchange complete blood count, peripheral blood film, Coombs test, reticulocyte count, serum bilirubin and post-exchange serum bilirubin, hemoglobin, random blood sugar, serum electrolyte, and calcium were done. G6PD level was done wherever suspected. Frequency, maternal and neonatal factors, indications, and outcomes were analyzed.

Results: Among 839 admitted cases of unconjugated hyperbilirubinemia, 41 patients (4.9%) required exchange transfusion. Most of the babies were inborn (90.2%). Ninety-five percent of mothers received regular antenatal care; among them, 76.3% had bad obstetric history. Only 36.6% of mothers received anti-D in previous pregnancy. None had sonographic findings of hydrops. The commonest indication was Rh incompatibility (80.5%). Coombs test was positive in 58.5% of cases. Mean pre-exchange TSB was 9.44 ± 6.4 , and post-exchange TSB was 4.41 ± 2.59 . The commonest adverse events noted were hyperglycemia (51.2%), sepsis (19.5%), anemia requiring top-up transfusion (17.1%), and hypocalcemia (14.6%). There were no catheter-related complications. Bilirubin encephalopathy was present in 4.9% of cases. There was one mortality but not due to the procedure.

Conclusion: Exchange transfusion was required among 4.9% of the admitted newborns with unconjugated hyperbilirubinemia. The common adverse effects were hyperglycemia and sepsis. The commonest indication was Rh incompatibility (80.5%). Overall outcome after exchange transfusion was favorable.

Keywords: Exchange transfusion, Neonatal hyperbilirubinemia, Prospective observational study, Term and near-term neonate.

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INTRODUCTION

Hyperbilirubinemia remains a common reason for hospital admission during the neonatal period. Severe hyperbilirubinemia in neonates can lead to acute bilirubin encephalopathy or permanent neurological sequelae in survivor.¹ Kernicterus or bilirubin encephalopathy is caused by unconjugated hyperbilirubinemia that develops either as a result of hemolytic process or because of the inability of the liver to conjugate bilirubin.² The risk of mortality and severe long-term neurodevelopmental sequelae due to severe hyperbilirubinemia is high in low- and middle-income country like Bangladesh. The burden is likely to be exacerbated by lack of poor or timely access to proven therapies.³

Treatment modalities for significant hyperbilirubinemia requiring hospital admission are phototherapy and exchange transfusion.⁴ Exchange transfusion (ET) is considered as an effective and quick method to achieve safe bilirubin level in infants at high risk of kernicterus.⁴ Despite proven benefit, exchange transfusion might give rise to cardiovascular, biochemical, or hematological complications and mortality rates vary from 0.5 to 3.3%.² Thus, current recommendation for exchange transfusion is based on seeking a balance between risk and benefit.⁵ Moreover, the

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introduction of anti-Rh (D)-specific immunoglobulin, intrauterine transfusions, prenatal monitoring, high-intensity phototherapies, and the use of nonspecific human immunoglobulin have made considerable contributions to reducing the indications for ET.⁶⁻¹⁰ Many of these technologies are not available or cost-effective in developing country, so reliance on exchange transfusion for the management of severe unconjugated hyperbilirubinemia is acceptable.

Most of the relevant published studies are retrospective; few reported trends of exchange transfusion in their study place,^{1,11,12} while some authors focused on incidence, indication of the exchange transfusion, and adverse events related to exchange transfusion.^{2,4,5,13,14} Some recent prospective studies in the South Asia region mainly focused on adverse events following exchange transfusion.^{15,16} According to a retrospective hospital-based study in Bangladesh, ABO incompatibility was the commonest identified cause of exchange transfusion and adverse events remain common after exchange transfusion.¹⁷ In this context, this study was intended to share the experience of exchange transfusion in the NICU of a tertiary care center of Bangladesh. In a developing country like Bangladesh and also in developed countries, it will ultimately help to reduce the need for doing exchange transfusion and the complications of exchange transfusion.

MATERIALS AND METHODS

This prospective observational study was conducted in the NICU of Bangabandhu Sheikh Mujib Medical University, Bangladesh, from January 2016 to December 2019. Term and near term neonates who underwent exchange transfusion for significant unconjugated hyperbilirubinemia were enrolled in the study after taking informed written consent from the parents. Before doing the study, clearance was taken from Institutional Review Board (IRB). American Academy of Pediatrics recommendation 2004 was followed for identification, monitoring, and management of hyperbilirubinemic neonates of gestational age 35 weeks or more. Consideration of double volume exchange transfusion was also supplemented by the experience and knowledge of the clinician of the Department of Neonatology, Bangabandhu Sheikh Mujib Medical University. Preterm babies less than 35 weeks of gestational age, newborns presenting with direct hyperbilirubinemia, newborns with congenital malformation, and newborns requiring partial exchange transfusion were excluded from the study.

Baseline neonatal data and clinical information were obtained and recorded in a predesigned form. The age of onset of jaundice, postnatal age of NICU admission, postnatal age of performing double volume exchange transfusion, cause of hyperbilirubinemia, indication of exchange transfusion, and duration of hospitalization were recorded. A detailed history of the previous and current pregnancies was taken from the mother such as antenatal care, bad obstetric history including miscarriages, ectopic pregnancy, known alloimmunizations, blood transfusion, previous sib death, and H/O taking immunoglobulin. Women who received antenatal care at least four times were considered to have regular ANC. Antibody titer equal or more than 1:32 was considered as critical level. Intrauterine transfusion facility is not available in the study setting. Fetal condition was assessed by serial antenatal ultrasonogram in booked cases.

Cord blood investigations in the setting of Rh incompatibility were sent for complete blood count, peripheral blood film, reticulocyte count, ABO blood grouping, and Rh typing, and direct Coombs test. In the probable ABO setting, ABO blood grouping, Rh typing, serum bilirubin, complete blood count, reticulocyte count, and Coombs' tests were sent from peripheral blood. In suspected case of sepsis, septic workup was done as per unit protocol. Glucose-6-phosphate dehydrogenase deficiency (G6PDH) and minor blood grouping were done whenever suspected.

Rh incompatibility was defined as jaundice in Rh-positive newborns born to Rh-negative mothers with elevated antibody titers to the Rh antigen and evidence of hemolysis. ABO disease was attributed to the presence of jaundice in newborns of A or B type born to O-type mother with suggestive laboratory features of hemolysis. Significant hyperbilirubinemia was defined as hyperbilirubinemia in a newborn requiring hospital admission for either phototherapy or exchange transfusion or both. Double volume exchange transfusion (DVET) is defined as exchange of twice the circulating blood volume of the newborn.

Blood transfusion department was notified regarding the indication, blood type, desired hematocrit, and volume of blood required for double volume exchange transfusion once the decision of exchange transfusion was taken. Parents and/or the family members were explained about the reason for doing exchange transfusion, procedure of exchange, possible immediate and late complications, and the precautions taken to prevent or manage them. Blood was collected mostly from donors/relatives of patients whenever possible; otherwise, it was managed from authorized blood bank. All fresh blood drawn for the purpose of exchange transfusion was screened for HBsAg, HIV, syphilis, malaria, and HCV. Anti-HBc screening of blood donor is not being practiced yet in the transfusion medicine department. Informed written consent was taken from the parents or legal guardian.

Throughout the procedure, the baby was kept under radiant warmer. The baseline observations (temperature, heart rate, respiratory rate, blood pressure, oxygen saturations, and neurological status) were recorded prior to commencement, and vital signs were monitored by cardiac monitor continuously throughout the procedure. In all babies' umbilical vein, catheterization was done under sterile conditions, using an umbilical venous catheter (UVC-5 fr for <3.5 kg infant and 8 fr for >3.5 kg infant for performing the procedure).

All patients were given phototherapy before and after the procedure. The baby was kept nil per os as soon as the decision was made to perform exchange transfusion. In case of Rh incompatibility, ABO-compatible to baby, RhD-negative RBCs were used when available; otherwise, O negative blood was used. In case of ABO incompatibility, group O, Rh-specific RBCs were used. In other conditions, ABO- and Rh-compatible blood was used. The blood was cross-matched with both baby and mother before exchange.

The procedure was performed by attending skilled senior residents of the NICU. After making sure that all connections are tight, pre-exchange sample was sent for TSB. Small amount of blood (5 mL/kg) was exchanged in each pass using the pull and push technique. Each pass (starting from the drawing of the baby's blood per UVC, disposing of that old blood, followed by drawing donor blood and transfusing that blood into the infant) takes approximately 1.5 to 2 minutes for completion. No intermittent calcium was given during the procedure as per unit protocol. The procedure took 1 to 2 hours to complete.

Vital signs including SpO₂ were monitored continuously during the procedure, 4 hourly for 24 hours and 8 hourly thereafter. Phototherapy was continued in post-exchange transfusion period until safe reduction of the bilirubin. Serum bilirubin, hematocrit, platelets, blood glucose, serum electrolytes, and ionized calcium were measured immediately after the DVET and serum bilirubin was monitored every 6-8 hourly until safe decline. DVET-related

adverse events were defined as any complications that were not present before DVET and occurred during and within 3 days after the exchange. Complications observed were thrombocytopenia (platelet count $<100,000/\text{mm}^3$), hypocalcemia (serum calcium level $<7 \text{ mg/dL}$ in preterm and $<8 \text{ mg/dL}$ in term babies), hyponatremia (serum sodium $<135 \text{ mEq/L}$), hyperkalemia (serum potassium $>5.5 \text{ mEq/L}$), hypoglycemia (random blood sugar $<2.6 \text{ mmol/L}$), hyperglycemia (random blood sugar $>7.8 \text{ mmol/L}$), bacteremia (detected colonization in the culture taken after ET), apnea, and cardiorespiratory arrest. UVC was kept *in situ* for 24 to 48 hours till further need of exchange transfusion was excluded. All the newborns were clinically followed up until discharge. Hearing screening was done at discharge or during the first follow-up. The newborns who developed sepsis were treated accordingly based on institutional protocol. Intravenous fluid was administered if the newborn had weight loss of 10% or more in comparison with birth weight. All the newborns were exclusively breast-fed. Outcomes were determined in terms of development of bilirubin encephalopathy, rebound hyperbilirubinemia requiring phototherapy, hearing impairment, and death.

The Statistical Package for the Social Sciences version 20 (IBM Inc., Armonk, New York, USA) was used for the data analysis, and $p < 0.05$ was taken as statistically significant. Data were summarized as descriptive statistics, namely mean, median, frequency, and percentages.

RESULTS

The total number of admissions during the study period of 4 years from January 2016 until December 2019 in the Department of Neonatology was 4,919. Among total admissions, 17% (839/4,919) were diagnosed with significant hyperbilirubinemia. Among them, 41 patients (41/839, 4.9%) underwent exchange transfusion. Five newborns required exchange transfusion twice; thus, the total number of exchange transfusions was 46.

Baseline characteristics of the enrolled newborns are shown in Table 1. Nearly 60% of enrollments were female and the rest (43.9%) were male. There were 43.9% term and 56.1% preterm babies. Normal (48.8%) and low birth weight (51.2%) distributions are almost similar. Majority (90.2%) of the enrolled newborns were inborn, while only 10% of babies were outborn. Majority of babies (85.4%) presented within 24 hours. Median age at jaundice presentation was 0.5 hours (minimum 0.5 hours and maximum 63 hours), and median postnatal age of exchange transfusion was 8.25 hours (range 3–131 hours). Newborns' blood group distribution shows that B+ve, A+ve, O+ve, and AB+ve were as 43.9, 26.8, 19.5, and 9.8%, respectively.

Clinical diagnoses of enrolled hyperbilirubinemic newborns are presented in Table 2. More than three-fourth of babies (33/41, 80.5%) requiring exchange transfusion had Rh incompatibility, and four babies (9.8%) had ABO incompatibility. The remaining four patients were diagnosed with minor blood group incompatibility, hyperbilirubinemia in an infant of diabetic mother where no other cause could be identified, G6PD deficiency, and exaggerated physiological jaundice.

Laboratory investigations of newborn underwent exchange transfusion are shown in Table 3. Direct Coombs test was positive in 58.5% of cases. Mean cord TSB was 4.18 ± 2.15 . Mean pre-exchange TSB was 9.44 ± 6.45 and post-exchange TSB was 4.41 ± 2.59 (Fig. 1) and the reduction is statistically significant (p value < 0.001). Mean cord Hb was 11.82 ± 3.07 , and mean post-exchange Hb was

Table 1: Baseline characteristics of patients, $n = 41$

Variable	No (%)
Gender	
Male	18 (43.9)
Female	23 (56.1)
Gestational age	
Term	18 (43.9)
Late preterm	23 (56.1)
Birth weight	
LBW	21 (51.2)
Normal	20 (48.8)
Mode of delivery	
NVD	5 (12.2)
LUCS	36 (87.8)
Place of delivery	
Inborn	37 (90.2)
Outborn	4 (9.8)
Age of onset of jaundice	
<24 hours	35 (85.4)
24–72 hours	6 (14.6)
Age of onset of jaundice in hours median (range)	0.5 hours (0.5–63 hours)
Mother's blood group	
B negative	13 (31.7)
O negative	8 (19.5)
A negative	7 (17.1)
O positive	6 (14.6)
AB negative	5 (12.2)
A positive	1 (2.4)
Baby's blood group	
B positive	18 (43.9)
A positive	11 (26.8)
O positive	8 (19.5)
AB positive	4 (9.8)
Postnatal age of exchange transfusion in hours median (range)	8.25 (3–131 hours)

NVD, normal vaginal delivery; LUCS, lower uterine cesarean section

Table 2: Etiology of newborns requiring exchange transfusion, $n = 41$

Clinical diagnosis	No (%)
Rh incompatibility	33 (80.5)
ABO incompatibility	4 (9.8)
Minor blood group incompatibility	1 (2.4)
Hyperbilirubinemia in IDM (no other cause specified)	1 (2.4)
G6PDH deficiency	1 (2.4)
Exaggerated physiological jaundice	1 (2.4)

IDM, infant of diabetic mother; G6PDH, glucose-6-phosphate dehydrogenase deficiency

12.97 ± 2.57 . Mean post-exchange RBS (mmol/L) and serum calcium (mg/dL) were 8.82 ± 2.58 and 8.48 ± 1.08 , respectively. Reticulocyte count was $>10\%$ in 9.7% of patients.

Among studied newborns, 68.3% of babies had at least one related adverse event. The list of complications noted is presented in Table 4. The most common complication related to the exchange transfusion was hyperglycemia (51.2%). Next to hyperglycemia, sepsis following exchange transfusion was the second most common complication found in 19.5% of newborns. Anemia requiring top-up transfusion and hypocalcemia were found

Table 3: Laboratory parameters of newborn underwent exchange transfusion, *n* = 41

Variable	No (%)	Minimum	Maximum	Mean ± SD
Cord TSB (mg/dL)		1.20	11.65	4.04 ± 2.29
Cord Hb (gm/dL)		5.10	18.50	11.82 ± 3.07
Venous Hb* (gm/dL)	9	10.80	18.90	15.46 ± 2.69
Reticulocyte count (%)				
<10%	37 (90.2%)			
>10%	4 (9.7%)			
Coombs test				
Positive	24 (58.5)			
Negative	17 (41.5)			
Pre-exchange TSB ^a (mg/dL)		2.60	27.60	9.44 ± 6.45
Post-exchange TSB ^a (mg/dL)		1.30	11.90	4.41 ± 2.59
Post-exchange Hb (gm/dL)		7.20	17.90	12.97 ± 2.57
Post-exchange RBS (mmol/L)		3.00	14.50	8.82 ± 2.58
Post-exchange Ca (mg/dL)		5.76	11.73	8.48 ± 1.08

*Venous Hb done in patients for whom cord Hb was not done;

^aDifference between pre-exchange TSB and post-exchange TSB is statistically significant, *p* value <0.001

Table 4: Adverse events related to exchange transfusion, *n* = 41

Variable	No (%)
Hyperglycemia	21 (51.2)
Sepsis following exchange transfusion	8 (19.5)
Anemia requiring top-up transfusion	7 (17.1)
Hypocalcemia	6 (14.6)
Thrombocytopenia	4 (9.7%)
Catheter-related complications	0

Table 5: Outcome of newborn underwent exchange transfusion, *n* = 41

Variable	No (%)
Bilirubin encephalopathy	2 (4.9)
Rebound hyperbilirubinemia requiring phototherapy	4 (9.7)
Death	1
Hearing impairment	0

in 17.1 and 14.6%, respectively. There were no catheter-related complications. There were multiple adverse events in 12 patients (29.3%). The events were hyperglycemia and hypocalcemia in three patients (7.3%), hyperglycemia and sepsis in three patients (7.3%), and hyperglycemia and anemia requiring top-up transfusion in three patients (7.3%). The remaining events were sepsis and anemia (2.4%); hyperglycemia, hypocalcemia, and sepsis (2.4%); and hypocalcemia, sepsis, and anemia requiring top-up transfusion (2.4%).

The overall outcome of the newborn underwent exchange transfusion is depicted in Table 5. Two babies (4.9%) had features

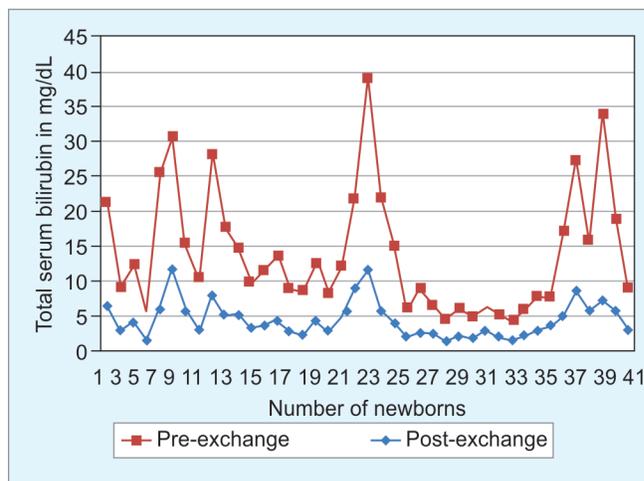


Fig. 1: Pre-exchange and post-exchange total serum bilirubin of newborn required exchange transfusion, *n* = 41

of bilirubin encephalopathy. The requirement of phototherapy for rebound hyperbilirubinemia was found in four (13.7%) patients, and all of them were cases of Rh incompatibility. The duration of the hospital stay of enrolled newborns was 7.64 ± 4.69 days. Mortality was observed in one patient but not from exchange transfusion. There were no readmission and no hearing impairment.

DISCUSSION

Despite worldwide steady decline in the neonatal exchange transfusion rate, the risk of acute bilirubin encephalopathy and permanent neurological damage from severe hyperbilirubinemia due to delay in identification and lack of access to appropriate care in the context of low- and middle-income country is still remaining. Considering this background, this study was intended to share exchange transfusion experience in the NICU of a tertiary care center of Bangladesh.

In this study, 41/839 (4.9%) babies required exchange transfusion in 4 years. A prospective study done in Nepal reported 6% (29/481) over 14 months' period.¹⁶ Much higher incidences 14.45% (50/346) and 22.1% (57/258) than this study have been reported by the other authors in a study done in Iran and Canada, respectively.^{18,19} On the contrary, much lower incidence (0.9 exchange transfusions per 1,000 live births) was documented in South Africa by Ballot et al.⁴ The dissimilarity may be due to the different enrollment criteria, diversity in the study population and settings, variation in the etiology of hyperbilirubinemia and different levels of bilirubin used for exchange transfusion, standard of antenatal care, and also availability and wide use of anti-D.

In spite of appropriate management, some would require multiple exchange transfusions, especially in the setting of ongoing hemolytic process. In this study, 12.2% of babies required multiple exchange transfusions. The finding is in line with an earlier retrospective study done in Bangladesh.¹⁷ Bujandric et al.¹² reported slightly higher frequency (17.6%) of repeated exchange transfusion in their 17 years' observation, whereas an Iranian retrospective study reported much higher frequencies (23.6%) of multiple exchange transfusions.² Early detection of high-risk cases, timely intervention, and better quality of phototherapy may explain the low frequency of repeated exchange transfusion in this study.

Median age at jaundice presentation according to the present study was 0.5 hours (minimum 0.5 hours and maximum 63 hours), and median postnatal age of exchange transfusion was 8.25 hours (range 3–131 hours). In a recent prospective study done in Nepal,¹⁶ the mean age of neonates at jaundice presentation was 55.00 ± 36.854 hours (range 7–192 hours), which is also late presentation in comparison with the present study. The late presentation reflects exaggerated physiological jaundice causing significant hyperbilirubinemia requiring exchange transfusion where no other pathology could be detected, and this group shared 27.6% total enrollment.¹⁶ In a hospital-based cross-sectional study done in Nepal, the mean age of exchange transfusion was done at 5.5 days, which is late than the present study; the reason was late referral from the peripheral health centers.²⁰

In this study, mean pre-exchange TSB was 9.44 ± 6.45 and post-exchange TSB was 4.41 ± 2.59 and the reduction is statistically significant (p value <0.001). Mean cord Hb was 11.82 ± 3.07, and mean post-exchange Hb was 12.97 ± 2.57. According to the study by Kakkar,¹³ a statistically significant reduction in serum bilirubin levels was noted post-procedure (p <0.001) with an overall reduction in bilirubin levels/procedure being 46%. Similar expectant efficacy was published by other authors.^{4,16,20}

In this study, Rh incompatibility (80.5%) was the most common cause of hyperbilirubinemia, followed by ABO incompatibility (9.8%). The data of this study are consistent with published data because it was found that maternal alloimmunization on fetal antigens inherited from the father was a major cause of neonatal hyperbilirubinemia that required ET. According to Bujandric,¹² 76% of exchange transfusion procedures were performed because of acute hemolysis due to ABO and RhD incompatibilities. Similar findings were observed in a study conducted in Turkey from 2002 to 2008.²¹ In other studies, ABO incompatibility was found to be the most common cause for ET.^{16,18,19} In the current study, the other causes were minor blood group incompatibility, hyperbilirubinemia in an infant of diabetic mother, and G6PDH deficiency. In a study done by Chacham et al.,¹⁵ G6PD deficiency (27%) was the commonest cause, followed by Rh isoimmunization (23.4%) and ABO incompatibility (12.1%). A deficit of G6PD is often associated with severe hyperbilirubinemia requiring ET in newborns with lower concentrations of bilirubin. Reporting of a single patient among newborns requiring exchange transfusion reminds the need for G6PD screening in neonates.

The frequency of exchange transfusion-related adverse events varies in different studies (15–74%).^{12,14} In our study, 57.5% of babies had ET-related adverse events. Jackson et al.⁵ reported slightly increased frequency (62%) of adverse events after the procedure, although the definition of adverse events was different from the present study. In 2002, Patra et al.²² also observed a higher incidence (74%) of adverse events as their enrolled newborns had a clinical condition of more severe profile. Much lower frequency (23%) of adverse events was observed in 207 procedures in a study done by Sa CAM.¹⁴ The most common complication related to the exchange transfusion was hyperglycemia (51.2%). Next to hyperglycemia, sepsis following exchange transfusion was the second most common complication found in 19.5% of newborns. In a previous study done in 1990, the most common adverse events noted were thrombocytopenia (44%) and metabolic acidosis (24%).²² In another study by Chacham et al.,¹⁵ thrombocytopenia was observed in 57.4% of neonates. In this study, thrombocytopenia was present in 9.7% of cases. As ABG was not routinely done in an apparently healthy

baby, metabolic acidosis could not be explored in the present study. Catheter block during the exchange transfusion procedure in a study by Chacham et al.¹⁵ was documented as 15.8%. There was no such event in the present study. The reasons behind the wide variation in the frequencies of adverse events are due to difference in the definition of the adverse events, difference in the enrollment criteria, and maximum time limit after exchange transfusion.

Feature of bilirubin encephalopathy was present in 6.1% of cases in the current study. In a previous study by Chacham et al.,¹⁵ 28.4% of neonates had acute bilirubin encephalopathy at presentation.¹¹ In our study, we did not have any mortality that is similar to previous study.¹⁶ In our study, seven babies (21.2%) required top-up transfusion. It was 10% in previous study.¹⁷ There were no readmission and no hearing impairment.

The study was conducted in a tertiary hospital, so it is not necessarily representative of all babies with hyperbilirubinemia in Bangladesh. Preterm babies <35 weeks were not included in this study.

CONCLUSION

Exchange transfusion was required among 4.9% of the admitted newborns with unconjugated hyperbilirubinemia. Hemolytic disease of the newborn due to Rh incompatibility is the most common indication of exchange transfusion (80.5%). The common adverse effects were hyperglycemia and sepsis. The overall outcome was favorable.

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