DOI: https://doi.org/10.53350/pjmhs221610271

ORIGINAL ARTICLE

Frequency of Indirect Hyperbilirubinemia Requiring Exchange Transfusion, Etiology and its Immediate Outcome in Term Neonates in Neonatal ICU of National Institute of Child Health, Karachi

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ABSTRACT

Objectives: The present study assessed the frequency of causes of indirect hyperbilirubinemia (IH) requiring exchange transfusion and its immediate adverse events of exchange transfusion in term neonates.

Methods: A prospective, observational study was undertaken at the Neonatal ICU of National Institute of Child Health, Karachi between July 2021 and December 2021. Term neonates arriving at the newborn unit of NICH with indirect hyperbilirubinemia were included in this study. All enrolled neonates were monitored for clinical, biochemical, and hematological adverse events for 7 days following exchange transfusion, and a predesigned performa was used to document observations.

Results: Among 730 neonates with indirect hyperbilirubinemia, a total of 63 term neonates underwent exchange transfusion. The most common causes of hyperbilirubinemia were sepsis in 19 (30.2%) patients and ABO incompatibility in 13 (20.6%) patients. The most common adverse events noted were hypokalemia, which occurred in 10 (15.9%) and thrombocytopenia, which occurred in 10 (15.9%) cases. In six patients, sepsis developed. In total, five neonates died while four developed bilirubin encephalopathy. The total serum bilirubin and direct bilirubin among patients were significantly lowered after exchange transfusion ($p<0.0001$). There were no umbilical catheter-related complications. Bilirubin encephalopathy was present in 4 patients. There were five deaths, but not due to the procedure. Practical implication

Conclusion: We highlighted the main causes of indirect hyperbilirubinemia as sepsis and ABO incompatibility in our setting. Furthermore, we also identified the immediate and short-term outcomes of exchange transfusion with a mortality rate of 7.9%. The overall outcome was favorable after the exchange transfusion.

Keywords: Hyperbilirubinemia, kernicterus, exchange transfusion, indirect bilirubin, neonates , jaundice

INTRODUCTION

Hyperbilirubinemia occurs when serum or plasma bilirubin levels exceed the reference range of the laboratory and is caused by impairment of bilirubin metabolism.[1] In the first week of their lives, in about 80% preterm neonates had developed jaundice whereas 60% term neonates were found to have jaundice.[2]

Physiologic IHB is usual and benign in most neonates, but a subset will develop severe IHB that requires medical intervention. As a consequence of untreated and extreme indirect hyperbilirubinemia, and its ability to be fat soluble, it, therefore, passes through the BBB causing bilirubin encephalopathy. [3] Gilbert syndrome, glucose-6-phosphate dehydrogenase deficiency, and premature babies are especially prone to extreme IHB and Kernicterus spectrum disorder [4] Infants usually present with jaundice when their total serum bilirubin level goes up above 5 mg/dL (85.5 mmol/L). IHB indicates a pathology if one or more of the following conditions are observed: 1) the baby has jaundice within 24 hours of birth, 2)On the basis of hour-specific bilirubin nomogram, the newborn's bilirubin levels go beyond the 95th percentile on the age range, 3) there is a surge in total bilirubin level by more than 5 mg/dL (>85.5 mmol/L) each day, or greater than 0.2 mg/dL (>3.4 mmol/L) in each hour or 4) the condition lasts longer than 3 weeks in full-term infants.[5]

According to the American Academy of Pediatrics (AAP), a screening test for serum neonatal bilirubin levels should be performed in the first 72 hours of a newborn's life with either TSB or transcutaneous bilirubin testing [6] Identifying and treating unconjugated HB aims to limit neurotoxicity caused by bilirubin. In 2004, and in 2009, the AAP published guidelines to decrease the risks of severe IHB and bilirubin-induced encephalopathy in infants who were at 35 weeks of gestational age.[3]

Exchange transfusion may cause adverse events (AEs) owing to changes in blood volume, blood pressure and pH, as well as modification in platelets range as a result of the usage of packed red blood cells without thrombocytes and coagulating elements, electrolyte disruption, and contamination with contagious pathogens.[7] The incidence of these complications has not been adequately studied despite blood exchange transfusions being considered a major procedure similar to major surgery. Studies published in the literature are typically retrospective, use varying definitions of AEs, and have fluctuating follow-up timelines.[7-10]

The current study was thereby designed to establish the causes of indirect hyperbilirubinemia in term neonates as well as the repercussions of blood exchange transfusion in term neonates.

METHODS AND MATERIALS

A cross-sectional observational study was carried out in Neonatal ICU at the National Institute of Child Health (NICH), Karachi from July 2021 to December 2021. Data acquisition was initiated after getting the required ethical permission from the Institutional Review Board (IRB). A non-probability convenience sampling technique was employed to recruit neonates in the study.

Neonates born at term who were provided with exchange transfusion for significant indirect hyperbilirubinemia were made part of the study after written and informed consent was obtained from the parents of these neonates.

For the diagnosis and management of indirect hyperbilirubinemia, we followed the recommendations of the American academy of pediatrics 2004.[1]

Preterm neonates under 37 weeks of fetal age, neonates with conjugated hyperbilirubinemia, and neonates who underwent partial exchange transfusions for polycythemia rubra vera, anemia or had exchange transfusions on different grounds unrelated to unconjugated hyperbilirubinemia were eliminated from this study.

We imminently supervised all the enlisted neonates for haematological, clinical, radiological, haematological, and biochemical adverse events in the subsequent 7 days of exchange transfusion.

This procedure was performed using fresh (<5 days old) cross-matched blood from both mother and baby. Double-volume BETs were used each time.

A predesigned proforma included information about the patient demographics, the age at which symptoms of jaundice started to appear, the age at which neonates were admitted to the NICU, the reasons for hyperbilirubinemia, the signs for exchange transfusion of blood, co-existing conditions that can cause adverse effects, the characteristic of the donated blood (age, blood grouping, and biochemical criteria), the method (staffing, time span

and route), the haematological, biochemical and clinical surveillance (prior to starting the procedure, in the midst of and following the treatment), neurological condition, and any effects related to blood exchange transfusion. A thorough history of former and ongoing pregnancies was obtained from mothers of the enrolled neonates such as antenatal workup, known alloimmunization, blood transfusion, previous sibs exchange transfusion or deaths and history of taking immunoglobulin.

The term double-volume can be described as the interchanging of two times the quantity of blood flowing in the body of a neonate. The institutional blood bank was given prior notice of the required blood type, quantity and indication for DVE transfusion after a directive for exchange transfusion was given. For the most part, whenever it was feasible, relatives of the neonates were picked to be the donors for the transfusion, and if it was not possible then the arrangement of blood was made by an accredited blood bank.

A senior resident appointed at the NICU was selected to carry out the treatment. Following the confirmation that all connections are correct. The cord blood sample prior to the exchange was dispatched for total serum bilirubin, serum electrolytes, CBC, blood grouping, serum G6pd level, reticulocyte count, direct coombs test, and blood culture and sensitivity. A small amount of blood exchange was done by using the push-pull method, (every transfer beginning from the pull of the neonate's blood from the umbilical venous catheter, discarding it into the old blood chamber, trailed by extracting donor blood and infusing the drawn blood into neonate) it takes approximately 2-3 minutes for each cycle. the whole procedure takes an hour and half to two hours to accomplish. Continuous vital monitoring along with oxygen saturation was done during and after the procedure, in the time after the exchange transfusion, phototherapy was continued until the safe decline of total bilirubin .serum bilirubin, serum electrolyte, blood glucose level, and FBC were calculated right after DVET and serum bilirubin level was tracked every 6- 8 hours until bilirubin levels were safely reduced.

Exchange transfusion-associated adverse episodes were described as any developments that were not seen before the procedure and developed in the course of and within a weeks after exchange .adverse events observed were anaemia, thrombocytopenia, hypocalcemia, hyponatremia, hypokalemia, hyperkalemia, hypo or hyperglycemia, bacteremia, apnea, seizures or cardiopulmonary arrest. All the term neonates are clinically followed up until discharged.

This analysis was conducted using SPSS version 20, and P <0.05 was regarded as statistically notable. All the data were summed up as descriptive statistics, namely mean, median, frequency and percentages.

RESULTS

Among 730 admitted cases of indirect hyperbilirubinema , 70 term neonate requiring exchange transfusion and a total of 63 term neonates were included in our study Out of 63 babies 38 were males (60.3%) and 25 were females (39.7%) resulting in male: female ratio of 1.52. The mean age at admission was 4.8 ± 2.5 days. The mean birth weight was 2.46 ± 0.53 and the mean gestational was 37±0.56 weeks. The deliveries through caesarean section were carried out in 36 (57.1%) cases while 27 (42.9%) babies were born through spontaneous vaginal delivery. For patient's characteristics and baseline parameters, kindly refer to (table-1).

Most common causes of Hyperbilirubinemia were sepsis in 19 (30.2%) patients, and ABO incompatibility in 13 (20.6%) patients, While in 23(36 %) cases cause were unknown .Figure-1.

Out of 63 babies underwent exchange transfusion, 21 babies (33.3%) did not develop any studied complication while 42 (66.6%) were found to have one or more complications. Hypokalemia was found in 10 (15.9%), thrombocytopenia in 10 (15.9%), and sepsis was observed in 6 (9.5%) neonates. Complications after exchange transfusion are described in (table-II).

Table 1: Baseline demographic characteristics

Characteristics	No. (%) of neonates
Gender	
Male	38 (60.3%)
Female	25 (39.7%)
Mode of Delivery	
Cesarean	36 (57.1%)
Vaginal	27 (42.9%)
Feeding	
Breast Milk	32 (50.8%)
Formula Milk	13 (20.6%)
Mixed	18 (28.6%)
History of Jaundice in Sibling	
Yes	14 (22.2%)
No	49 (77.8%)
Mothers Blood Group	
O –VE	6 (9.5%)
A –VE	3 (4.8%)
B –VE	2 (3.2%)
O +VE	27 (42.9%)
A +VE	11 (17.5%)
B +VE	9 (14.3%)
AB +VE	5 (7.9%)
Baby Blood Group	
O –VE	2 (3.2%)
A –VE	4 (6.3%)
B –VE	3 (4.8%)
O +VE	16 (25.4%)
A +VE	12 (19%)
B +VE	20 (31.7%)
AB +VE	6 (9.5%)

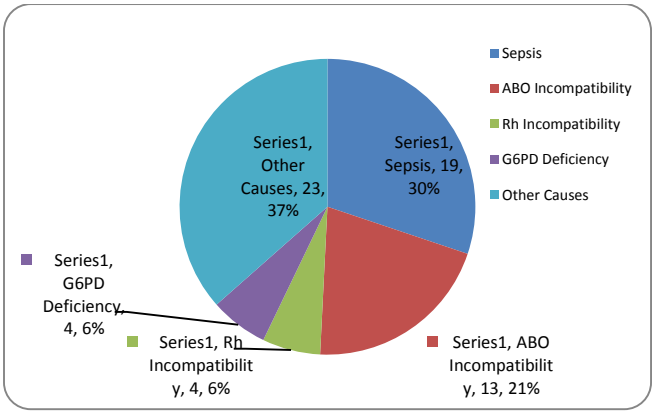

Figure-1: Causes of severe neonatal hyperbilirubinemia

Table 2: Complications of exchange transfusion.

Complications	
Hyperglycemia	1 (1.6%)
Hypernatremia	5 (8%)
Hyperkalemia	7 (11.1%)
Thrombocytopenia	10 (15.9%)
Hyponatremia	5 (7.9%)
Hypocalcemia	7 (11.1%)
Hypokalemia	10 (15.9%)
Anemia	2 (3.2%)
Hypothermia	1 (1.6%)
Sepsis	6 (9.5%)
Hypercalcemia	1 (1.6%)
None	21 (33.3%)

Table 3: Comparison of Pre-exchange transfusion rate and Post-transfusion Rate among Participants - Immediate Outcome of Exchange Transfusion

Parameters	Pre-exchange transfusion	Post-exchange transfusion	p-value
Total Bilirubin	34.63 ± 38.70	19.86 ± 4.86	<0.0001
Direct Bilirubin (Conjugated)	3.99 ± 3.26	2.99 ± 2.16	<0.0001
Serum Sodium	144.03 ± 6.41	141.60 ± 5.73	0.001
Serum Potassium	4.28 ± 0.69	4.47 ± 1.37	0.271
Serum Calcium	10.69 ± 12.97	11.65 ± 18.92	0.688
Hemoglobin	14.74 ± 19.19	18.65 ± 25.47	0.228
Platelet Counts	205226.25 ± 82082.28	80791.58 ± 35640.66	0.007
Total Leukocyte Count	1517.85 ± 8338.57	964.43 ± 6930.20	0.529

It was found that the total serum bilirubin among patients was significantly lowered after exchange transfusion (p<0.0001). Similarly, the mean value of direct bilirubin was 3.99 ± 3.26 which reduced to 2.99 ± 2.16 after transfusion (p<0.0001). Platelet count significantly decreased to 80791.16 ± 35640.66 after transfusion,

p=0.007. However, it was found that the total hemoglobin, serum calcium, potassium, and the leukocyte count did not differ significantly (Table III). Out of 63 term neonates, 58 (92.1%) patients discharged while 4 (6.34%) neonates were developed bilirubin encephalopathy and 5 (7.9%) patients were died.

DISCUSSION

Hyperbilirubinemia still stands as one of the leading causes of newborn hospitalization in low and middle income countries. Severe hyperbilirubinemia in newborns might result in acute bilirubin encephalopathy, also referred to as kernicterus, irreversible neurodevelopmental consequences,[11] or sometimes mortality if left untreated.

Neonatal hyperbilirubinemia encompasses various causative conditions that include physiological jaundice, pathological jaundice, breastfeeding, hemolytic disease of the newborn owing to Rh factor or ABO group incompatibility, or G6PD deficiency.[12] The physiological variant is most prevalent, the unconjugated form predominantly which has a serum concentration of less than 15 mg/dl, [13] and is not associated with any serious complications.

Up to 85% of neonates delivered at term (>37 gestational week) and 80% of preterm babies are reported with hyperbilirubinemia. [14] Hyperbilirubinemia can be potentially averted by certain treatment modalities including exchange transfusion (ET), phototherapy, and intravenous immunoglobulins (IVIg) to reduce serum bilirubin levels. [15]

In this study 63 (8.6 %) neonates out of 730 cases of indirect hyperbilirubinemia underwent into exchange transfusion in 6 months period . A similar prospective study done in Nepal which reported 6 % (29 out of 481) over a period of 14 months.[19] On the contrary ,quite decrease incidence (0.9 exchange transfusion per 1000 live birth s) was documented in south Africa by Ballot et al.[16]

In our study we also found that we didn't need of multiple or repeated exchange transfusion which is contrary to a study done in Bangladesh in which repeated exchange transfusion were done in 12.2 % of cases [18] Early detection of high risk cases and timely and proper management also a better quality of phototherapy may explain the zero percentage of repeated exchange transfusion in our setup.

In this study, mean pre exchange TSB was 34.63 ± 38.70 and post exchange TSB was 19.86 ± 4.86 and this decline is statistically significant (p value < 0.0001) which is similar to the study by Kakker. [20] We also found in our study that ABO incompatibility and sepsis were the most common causes of indirect hyperbilirubinemia which required blood transfusion ,this data is consistent with the published data in Nepal. [19]

Our study identified hypokalemia and thrombocytopenia as the most frequently associated outcomes of ET which is comparable to the results of literature by Wolf et al. in 2020 that also reports these two biochemical derangements as the commonly observed adverse effects. [15] Thrombocytopenia was observed in 17.6% of the subjects in the previous study which is consistent with the current findings i.e; 15.9%.

Despite its shown benefits, exchange transfusions can precipitate cardiovascular, biochemical, or hematological problems, with a mortality rate ranging from 0.5 to 3.3% as per the study by Sabzehei et al., in 2015 [17], as opposed to a relatively higher mortality rate of 7.9% in our study. As a result, the current exchange transfusion advice is premised on maintaining an equilibrium of risks and benefits associated. Some researchers suggest the declining use of exchange transfusions in recent years due to its adverse effects.[18]

Severe hyperbilirubinemia necessitating exchange transfusions to prevent the acute bilirubin encephalopathy which is difficult complications in the newborn. To limit the need for exchange transfusions and deter potential damaging sequelae, policies and protocols should be devised that include blood group analysis of pregnant women, programs educating parents about breastfeeding and jaundice, and monitoring bilirubin levels of high-risk neonates.

CONCLUSION

The present study highlighted the main cause of indirect Hyperbilirubinemia as sepsis and ABO incompatibility in term neonates in our setting. Early detection of high risk cases and timely and proper management by double volume exchange transfusion (DVET), also a better quality of phototherapy may explain the zero percentage of repeated exchange transfusion in our setup Furthermore we also identified the immediate and short term outcomes of exchange transfusion. Exchange transfusion in neonates with indirect hyperbilirubinemia is a high-risk procedure and should be performed under supervision of an experienced pediatrician and only when the benefit of the procedure outweighs the risks.

Conflicts of Interest: None declared
Acknowledgements: Nil
Funding: No funding was secured for this study

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