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## RESEARCH ARTICLE

# A PROSPECTIVE STUDY ON EXCHANGE TRANSFUSION IN NEONATAL UNCONJUGATED HYPERBILIRUBINEMIA IN A TERTIARY CARE HOSPITAL, AHMEDABAD, INDIA

**[1,*]Dr. Subhas Das, [1]Dr. Kiran Chaudhari and [2]Dr. Chirag D Shah**

[1]Resident Doctor BJMC, Civil Hospital, Ahmedabd
[2]Associate Prof, BJMC, Civil Hospital, Ahmedabd

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**ABSTRACT**

**Background:** An exchange transfusion involves replacing patient's blood with donor blood in order to remove abnormal blood components and circulating toxins while maintaining adequate circulating blood volume.
**Objective:** To observe the incidence, causes of jaundice requiring Exchange and any adverse event of exchange transfusion in newborns with unconjugated hyperbilirubinemia.
**Method:** Prospective study undertaken at Neonatal Intensive Care Unit (NICU) of BJMC, Civil hospital ahmedabad from July 2015 to june 2017.Both mothers and neonates blood group and Rh typing and for all newborns pre and post exchange complete blood count with peripheral smear, serum bilirubin, haemoglobin, calcium, potassium, random blood sugar, C-reactive protein and blood culture and where ever required Direct Coombs test, reticulocyte count, G6PD activity were done. The incidence, indications, positive outcome, complications and mortality were noted.
**Result:** Out of 1970 cases of unconjugated hyperbilirubinemia 18(0.913%) required exchange transfusion. Over all male preponderance was noted around55.55%.majority of babies who required ET was full term at birth 77.77%,while only 27.78% babies had low birth weight for their age. The mean age of neonates at presentation was 131 hours (arithmetic mean) Median age of presentation was 144 hours. Maximum no of babies presented to us after 72 hrs of birth is around 66.67%. In 11.11% of cases previous siblings were affected with unconjugated hyperbilirubinemia required ET. Rh incompatibility was the major cause 38.89% cases closely followed by ABO incompatibility 33.33% . Prior ET mean bilirubin was 31 mg/dl, who presented with in 24 hrs of birth. For those who admitted between 24 -72 hours mean bilirubin was 36.4 and 38.75 mg/dl for those who presented after 72 hrs. The complications noted were anemia (61.11%), hypocalcaemia (27.5%), sepsis 38.89%, hypoglycaemia (11.11%), seizure (22.22%), hyperkalemia (11.11%),
**Conclusion:** Exchange transfusion is an effective procedure to decrease bilirubin levels but is associated with many complications. Rh incompatibility was one of the commonest cause of jaundice requiring Exchange transfusion.



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## INTRODUCTION

Kernicterus (Bilirubin encephalopathy) is an acquired metabolic encephalopathy of the neonatal period. It is caused by unconjugated hyperbilirubinemia that develops either as a result of haemolytic disease (Rh incompatibility, hereditary spherocytosis, other haemolytic disorders) or because of inability of the liver to conjugate bilirubin due to either defect of glucuronyltransferase enzyme or when this enzyme is not fully functional (Shapiro, 2003). For preventing the Kernicterus and other complications of hyperbilirubinemia, jaundice should be managed by phototherapy or Exchange transfusion (ET).

***Corresponding author:*** **Dr. Subhas Das,**
Resident Doctor BJMC, Civil Hospital, Ahmedabd.

Although ET is considered to be a safe procedure, it is not risk free, and mortality rates vary from 0.5 to 3.3% (Bowman, 1997; Philip, 2003; Ip, 2004; Boggs, 1960). Over recent years, the introduction of anti- Rh(D) specific immunoglobulin, intrauterine transfusions, prenatal monitoring, high-intensity phototherapies and, more recently, the use of nonspecific human immunoglobulin have made considerable contributions to reducing the indications for ET (American Academy of Pediatrics, 2004; Alcock, 2002; Pishva *et al.,* 2000; Aggarwal *et al.,* 2002; Gottstein, 2003). Unfortunately these technologies are not available or affordable in developing country like ours so we still rely on ET for the management of severe unconjugated hyperbilirubinemia.

Thus this study highlights the incidence, causes requiring ET and adverse events of this procedure.

## MATERIALS AND METHODS

### Study setting

Prospective, hospital based observational study conducted in NICU of BJMC, Civil hospital, Ahmedabd. The study period was 24 months, from July 2015 to June 2017.

### Enrolment of cases

Enrolled. ET was decided based on the followings:

- Guidelines for ET bilirubin levels based on the American Academy of Paediatric Guidelines (American Academy of Pediatrics, 2003).

### Inclusion criteria

- All babies with indirect hyperbilirubinemia.
- Both Term and preterm babies with or without underlying pathology.

### Exclusion criteria

- Direct hyperbilirubinemia – neonatal cholestasis.
- Babies with congenital malformations, TORCH infection, neonatal hepatitis
- Consent refused.

### Dependent variable/exposure variable

Double volume ET
*Blood Volumes*

The volume of blood for exchange is calculated using an estimate of the neonate's circulating blood volume (Cloherty *et al.,* 2008):

- Term infants 80ml/kg
- Preterm infants 100ml/kg

### Double volume ET: 13

Most commonly used for removal of bilirubin and antibodies 2 x circulating blood volume (for example, for a term infant 2 x 80ml/kg = 160ml/kg). This replaces approximately 85% of the blood volume. This will cause an approximate reduction of 50% of the pre-exchange bilirubin level (but can be expected to rebound 4 hours post transfusion to approximately two thirds of pre-exchange level).

### Independent variables/outcome variables

### Definitions of outcome measures

**Improvement:** Those babies who improved and survived.
**Adverse events:** During and after the procedure all babies were monitored and the adverse events monitored in this study were:

- Catheter related complications - haemorrhage, infection
- Haemodynamic (related to excess removal or injection of blood): hypo or hypertension, intraventricular haemorrhage (preterm)
- Hypoglycemia [blood sugar <45 mg/dl], 14hyperglycaemia [whole blood >125 mg/dl, plasma >145 mg/dl] (Greeley, 1993)
- Hypocalcaemia [S. calcium <7 mg/dl], (Greeley, 1993) hyperkalaemia [S.potassium>6 mg/dl], (Greeley, 1993)
- Anemia [<15 gm/dl] (Lockitch, 1988)
- Arrhythmias, Bradycardia
- Feed intolerance, necrotizing enterocolitis
- Septicaemia
- Hypothermia [core temp < 360C or hyperthermia] (Cloherty *et al.,* 2008)

### Preparation of the baby

The doctor discussed the procedure with the parents/ guardian and obtained consent. The baby was kept under the radiant warmer throughout the procedure. The baseline observations (temperature, respiratory and heart rate, blood pressure and oxygenation) were ensured. Baby was kept nil orally as soon as decision was made to perform ET. An oro/nasogastric tube was passed to aspirate stomach contents and it was kept in-situ on free drainage for duration of procedure. Then a vascular access was established via single vein that was through umbilical vein.

### Preparation of the Equipment

The equipments required for the procedure were - Gowns, Sterile gloves, Sterile drape Blood administration set, Exchange transfusion recording sheet, 3-way taps, Syringes assorted sizes as required, drawing up needles, urine drainage bag, Sodium chloride 0.9% and Water for Injection ampoules, Emergency resuscitation equipment including medications and fluids, Calcium gluconate 10%, Sodium bicarbonate 7.5%, Glucose 10%, Frusemide (20 mg/2ml), Lab collection tubes as required, Sterile gauze and donor whole blood of less than seven days old.

### Set-Up and procedure

All babies in this study underwent an umbilical vein double volume exchange transfusion using venous 1 line technique. At least one doctor and one experienced registered nurse were allocated for the care of the baby throughout the procedure. Resuscitation equipments, medications and cardio-respiratory monitors was kept ready. Without contaminating the ends of the lines - two 3-way taps were attached - one end attached to the umbilical venous line. The 3-way tap nearest to the baby was kept free for donor blood inlet and medication administration. In the next outlet, the urine collecting bag was attached and fastened below the cot for draining out of exchanged blood. A 10ml or 20 ml syringe was connected to the uppermost port of the 3-way tap furthest from the baby to push in donor blood and to withdraw babies exchanged blood out. ET involved sequential withdrawal and injection of aliquots of blood, through umbilical vein. ET was performed slowly over approximately 2 hours to avoid major fluctuations in blood pressure. Strict aseptic technique was maintained throughout procedure. The baseline observations (infant temperature, heart rate, respiratory rate, blood pressure,

oxygen requirement, oxygen saturations, neurological status) were recorded prior to commencement and throughout the procedure. A pre- and post exchange blood samples was sent for– Complete blood count with Peripheral smear, haemoglobin, C-reactive protein (CRP), blood cultures, serum direct and indirect bilirubin, blood glucose, serum calcium and electrolytes. For all babies Demographic parameters like Gestational ages, sex, birth weight, maternal age, Parity, mode and place of delivery, history of sibling with jaundice were also collected. For each cases serum was collected for maternal and baby blood group and Rh typing and where required Direct Coombs test, reticulocyte count, G6PD activity, thyroid function test were done. Causes for jaundice was identified from the medical history, physical examination or laboratory evaluation.

### Post Procedure Care of the Infant

Vital signs were monitored and recorded 30 minutely for first 4 hours post procedure. If stable after this time routine observations was continued. Blood glucose level was performed immediately post procedure and then hourly until stable. Serum bilirubin was measured one hour Post ET and repeat 6 hourly. Phototherapy was continued until bilirubin levels were within acceptable range. Catheter sites were observed for signs of bleeding. The baby was kept nil by mouth for at least 4 hours post ET, or longer when indicated as ET carries a potential risk of necrotizing enterocolitis especially in the preterms. The appearance of abdomen was monitored and presence of bowel sounds checked. Signs of feeding intolerance was observe ones the feed was started.

## RESULTS

During 24 months of study period there were total 15700 newborns. Out of which 1970 (12.54%) newborns presented with jaundice out of which 18 (0.913%) cases underwent ET.

**Table 1. Incidence**

| Total admission | Unconjugated hyperbilirubinmea (%) | Exchange transfusion |
|---|---|---|
| 15700 | 1970 (12.54%) | 18(0.913%) |

**Table 2. Jex Ratio**

| Male (%) | Female (%) |
|---|---|
| 10 (55.55%) | 8 (45.45%) |

Among total cases of ET 55.55 % were males and 45.45 % were females.

**Table 3. Matwity**

| Full term (%) | Preterm (%) |
|---|---|
| 14 (77.77) | 4(22.23) |

In our study there were 77.77% term, 22.23% preterm babies.

**Table 4. Birth weight**

| Normal birth weight (%) | Low birth weight (%) |
|---|---|
| 13(72.22%) | 5(27.78%) |

72.22 % babies had normal weight, 27.28 % were LBW babies.

**Table 5. Place of delivery**

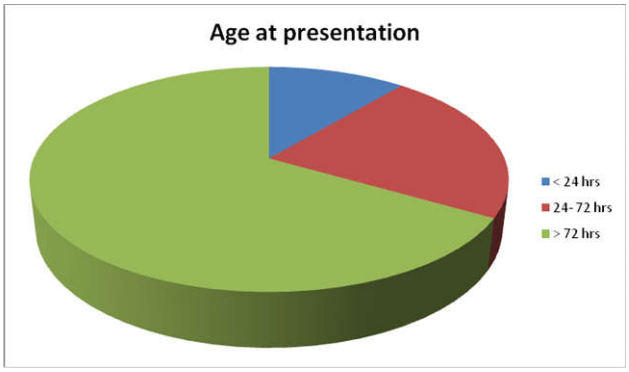
| Institutional delivery | Home delivery |
|---|---|
| 17 | 1 |

94.44% were hospital delivered and 5.56% were home delivered babies.

**Table 6. Age of presentation**

| Age at the time of presentation | Number (%) |
|---|---|
| <24 hrs | 2(11.11%) |
| 24 -72 hrs | 4(22.22%) |
| >72 hrs | 12(66.67%) |

Maximum no of babies presented to us after 72 hrs of admission, is around 66.67%. 11.11% babies were presented within 24 hrs with jaundice.




*The mean age at presentation was 131 hours (arithmetic mean), median was 144 hrs.

**Table 7. Family History**

| Previous sibling affected (%) | Unaffected (%) |
|---|---|
| 2 (11.11%) | 16 (88.89%) |

In 11.11% of cases previous siblings were affected with unconjugated hyperbilirubinemia.

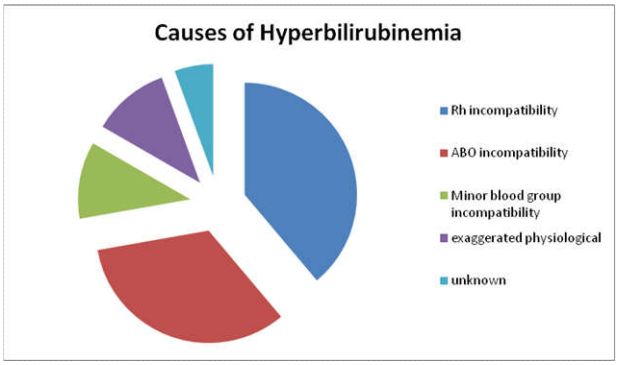
**Table 8. Etiology**

| Primary Pathology | No of patients | Percentage (%) |
|---|---|---|
| Rh incompatibility | 7 | 38.89% |
| ABO incompatibility | 6 | 33.33% |
| Minor blood grouping incompatibility | 2 | 11.11% |
| Exaggerated physiological | 2 | 11.11% |
| Unknown | 1 | 5.56% |

Of all babies requiring ET 33.33% had ABO incompatibility, 38,89% Rh incompatibility. Minor blood grouping was positive 11.11% and 11.11% had exaggerated physiological jaundice, 5.56 % of cases cause was undetermined.

**Table 9. Mean bilirubin. pre exchange:**

| Time of presentation (hrs) | Mean bilirubuin(gm/dl) |
|---|---|
| <24 hrs | 31 |
| 24 -72 hrs | 36.4 |
| >72 hrs | 38.75 |




Prior ET mean bilirubin was 31 mg/dl, who presented with in 24 hrs of birth. for those who admitted between 24 -72 hours mean bilirubin was 36.4 and 38.75 mg/dl for those who presented after 72 hrs.

**Table 10. Mean bilirubin: post exchange: at 6, 12 and 24 hrs**

| Time of presentation (hrs) | At 6 hrs | 12 hrs | 24 hrs | 48 hrs |
|---|---|---|---|---|
| <24 hrs | 18.15 | 12.1 | 10.2 | 7 |
| 24 -72 hrs | 23.5 | 17.9 | 12.3 | 7.8 |
| >72 hrs | 23.06 | 16.73 | 11.77 | 7.9 |

Mean post exchange bilirubin at the end of 48 hours were 7,7.8,7.9 in babies who admitted with jaundice <24 hrs,24-72 hrs,>72 hrs respectively.

**Table 11. Mean Haemoglobin :: pre exchange**

| Time of presentation (hrs) | Mean haemoglobin (gm/dl) |
|---|---|
| <24 hrs | 17.7 |
| 24 -72 hrs | 16.5 |
| >72 hrs | 15.9 |

Prior to ET mean haemoglobin was 17.7 mg/dl, who presented with in 24 hrs of birth. for those who admitted between 24 -72 hours mean haemoglobin was 16.5 and 15.9 mg/dl for those who presented after 72 hrs.

**Table 12. Mean Haemoglobin :: post exchange 6,12 and 24hrs**

| Time of presentation (hrs) | At 6 hrs | 12 hrs | 24 hrs | 48 hrs |
|---|---|---|---|---|
| <24 hrs | 16.2 | 13.8 | 14.2 | 14.5 |
| 24 -72 hrs | 14.6 | 13.45 | 14.9 | 14.4 |
| >72 hrs | 14.5 | 15.2 | 15.7 | 15.9 |

Mean post exchange haemoglobin at the end of 48 hours were 14.5,14.7.15.9 in babies who admitted with jaundice <24 hrs,24-72 hrs,>72 hrs respectively.

**Table 13. DCT & ICT grading**

| Grade | Direct coomb test | Indirect coomb test |
|---|---|---|
| 1 | 0 | 1(5.56%) |
| 2 | 7(38.89%) | 7(38.89%) |
| 3 | 6(33.33%) | 1(5.56%) |
| 4 | 0 | 1(5.56%) |

Maximum no of patients showing DCT grade 2 positivity and ICT grade 2 positivity is around 38.89%.

**Table 14. Complications**

| Complication | Number | Percentage (%) |
|---|---|---|
| Hypoglycaemia | 2 | 11.11% |
| Hypocalcemia | 5 | 27.5% |
| Hyperkalemia | 2 | 11.11% |
| Seizure | 4 | 22.2% |
| Metabolic alkalosis | 1 | 5.55% |
| Anemia | 11 | 61.11% |
| Sepsis | 7 | 38.89% |

The complications noted were anemia (61.11%), hypocalcaemia (27.5%), sepsis 38.89%, hypoglycaemia (11.11%), seizure (22.22%), hyperkalemia (11.11%),. Bradycardia, apnea and feed intolerance procedure related complications, hemodynamic instability, arrhythmia, necrotizingenterocolitis, kernicterus, temperature instability were not noted. There were no mortalities during the procedure or as a direct consequences of such.

**Table 15. Outcome**

| Outcome | Number | Percentage (%) |
|---|---|---|
| Survived | 16 | 88.89% |
| Bilirubin encephalopathy grade 1 | 4 | 22.2% |
| Grade 2 | 3 | 16.65% |
| Grade 3 | Nil | 0% |
| Expired | 2 | 11.11% |

Among all 18 babies underwent exchange transfusion 16 (88.89%) survived and Discharged. where as 11.11% babies expired during hospital stay. Bilirubin encephalopathy grade 1 noted in 4 babies (22.22%) grade was observed in 3 babies (16.65%)

## DISCUSSION

ET was the first successful treatment which was introduced for severe neonatal jaundice.4,5 Current recommendations for performing ET are based on seeking a balance between the risks of encephalopathy and the adverse events related to the procedure.**16** In this context, the objective of this study was to determine the incidence, causes requiring ET and complications related to ET.

### Incidence of ET

In our study 18/1970(0.913%) babies required ET in 24 months. This was 106 babies over 15 years and 203 over 10 years period in other studies.16,17 Much higher incidence than our study 14.45% & 22.1% has been reported by other authors.18,19 The difference may be due to the different levels of bilirubin used for ET in various studies, better antenatal and postnatal services in our hospital . In our study we had followed the American Academy of Paediatric Guidelines.6 Like other study ET was more common in boys.18 The mean age of neonates at presentation was was 131 hours (arithmetic mean) Median age of presentation was 144 hour; range 7 – 192 hours in this study. This is the time when exaggerated physiological jaundice is noticed more. In our study that was the scenario, exaggerated physiological jaundice with no pathology accounted for 11.11% of cases. In our view the reason for this jaundice maybe breast milk jaundice. When jaundice lasts past the first week of life in a breastfed baby who is otherwise healthy is called “breast milk jaundice.”20

### Causes of jaundice requiring ET

According to our study Rh incompatibility was the major cause 38.89% cases closely followed by ABO incompatibility 33.33%. Minor blood grouping was positive 11.11% and 11.11% had exaggerated physiological jaundice,5.56 % of cases cause was undetermined ABO incompatibility was found to be the most common cause for ET in other studies (Behjati, 2009; Sgro, 2006; Chen *et al.,* 2006). G6PD deficiency a commonly occurring enzymatic defect is an important risk factor for the neonatal hyperbilirubinemia and

ET. Many of reported cases of Kernicterus have been found to be enzyme deficient (Kaplan *et al.,* 2004), We recommend that all neonates with severe hyperbilirubinemia be screened for congenital hypothyroidism. Rh incompatibility, exaggerated physiological jaundice with risk factor as preterms, cephalhematoma and with no underlying pathology were other causes that required ET in this study. Rh incompatibility, prematurity, maternal age ≥ 25, maternal diabetes, previous sibling with jaundice were some causes mentioned in different studies (Sgro, 2006; Chen *et al.,* 2006; Gourley, 2005). In our study 11.11% of cases previous siblings were affected with unconjugated hyperbilirubinemia.

**Improvement**

Prior ET mean bilirubin was 31 mg/dl, who presented with in 24 hrs of birth. for those who admitted between 24 -72 hours mean bilirubin was 36.4 and 38.75 mg/dl for those who presented after 72 hrs. Mean post exchange bilirubin at the end of 48 hours were 7,7.8,7.9 in babies who admitted with jaundice <24 hrs,24-72 hrs,>72 hrs respectively.

**Adverse Event Associated with Exchange Transfusion**

The frequency of ET-related adverse events varies in different studies from 15 to 74%, depending on the definition of adverse event taken into consideration and on the severity of the newborn infants studied (Jackson, 1997; Patra *et al.,* 2004). In the present study 93.1% had complications which were much higher than other studies. The complications noted were anemia, sepsis, hypocalcemia, hypoglycemia, hyperkalaemia, seizure metabolic alkalosis. Among the complications anemia and septicemia was found to be highest. In this study CPD (citrate phosphate dextrose) blood was used, The citrate of CPD blood binds with ionic calcium leading to hypocalcemia. During the procedure in this study a negative balance [pulling out 10 ml blood in the end] was maintained which maybe the cause for higher rate of anemia. Similar complications were also noted by Tan KL but unlike our study they reported two deaths (Tan *et al.,* 1976). Mortality rate of our study was 11.11%. The reported mortality associated with the ET is around 2% in the literature (Bowman, 1997; Philip, 2003). In another study most common adverse events noted were thrombocytopenia (44%), and metabolic acidosis (24%) (Patra *et al.,* 2004). However they have not mentioned what was the percentage of sepsis in their study as thrombocytopenia can be part of sepsis. In our study 5.55% cases developed metabolic alkalosis. Though sepsis was one of the most common complications we did not observe thrombocytopenia in any case. The majority of adverse events associated with ET are laboratory abnormalities where most babies may remain asymptomatic. Therefore, ET should be performed carefully with close monitoring of the laboratory and clinical status of the baby during and after the procedure.

**Conclusion**

We conclude that although ET is an effective procedure in the management of severe hyperbilirubinemia, the frequency of associated complications are high. Therefore a high degree of parents and physicians awareness is essential in the identification and timely management of neonatal hyperbilirubinemia so that the procedure is not required for all. In addition, ET should only be carried out in institutions that have teams prepared to identify and treat possible adverse events. The commonest cause of jaundice requiring ET was Rh incompatibility but in this study along with Rh incompatibility ABO incompatibility was found to be commonest cause for ET. Complications noted were much higher than other studies. ET is effective way to decrease bilirubin level.

**Limitation**

A larger sample size and a control study would have given a better result.

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