A Prospective Study on Exchange Transfusion in Neonatal Unconjugated Hyperbilirubinemia – in a Tertiary Care Hospital, Nepal

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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 Manipal Teaching Hospital, Pokhara, Nepal from March 2014 to April 2015. For 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, hemoglobin, calcium, potassium, random blood sugar, C-reactive protein and blood culture and where ever required Direct Coombs test, reticulocyte count, G6PD activity and thyroid function test were done. The incidence, indications, positive outcome, complications and mortality were noted.

Result

Out of 481 cases of unconjugated hyperbilirubinemia 29(6%) required exchange transfusion. 55.2% Pathological Jaundice [13.8% ABO incompatibility, sepsis and hypothyroidism was commonest causes] and 44.8% exaggerated physiological jaundice [27.6% with no underlying pathology, 10.3% preterms 3.4% cephalhematoma] required exchange transfusion. Post transfusion, bilirubin level decreased significantly ($p<0.001$). The commonest adverse events noted were anemia (89.7% / $p<0.018$), hyperglycemia(51.7% / $p<0.001$), hypocalcaemia (48.3% /$p<0.001$)), sepsis(10.3%), hypernatremia (13.8%), hyperkalaemia, bradycardia, apnea and feed intolerance (6.9%). None of them had kernicterus and there was no mortalities.

Conclusion

Exchange transfusion is an effective procedure to decrease bilirubin levels but is associated with many complications. Hypothyroidism was one of the commonest cause of jaundice requiring Exchange transfusion.

KEY WORDS

Exchange transfusion, hyperbilirubinemia, kernicterus, neonate.

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 hemolytic disease (Rh incompatibility, hereditary spherocytosis, other hemolytic disorders) or because of inability of the liver to conjugate bilirubin due to either defect of glucuronyl transferase enzyme or when this enzyme is not fully functional.[1] For preventing the Kernicterus and other complications of hyperbilirubinemia, jaundice should be managed by phototherapy or Exchange transfusion (ET). Although ET is considered to be a safe procedure, it is not risk free, and mortality rates vary from 0.5 to 3.3%.[2-5] 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.[6-10] 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.

METHODS

Study setting:

Prospective, hospital based observational study conducted in NICU of Manipal Teaching Hospital. The study period was 14 months, from March 2014 to April 2015.

Sample size calculation:

In hypothesis testing for two means (equal variances) for power 99% and α error1% with 95% level of confidence standard deviation for pre-echange indirect bilirubin was 4.740 and for post-exchange indirect bilirubin was 4.307 with mean difference of 15.02 and effect size 3.32043771415939. We estimated total required sample size per group to be 4 and we had enrolled 29 cases.

Approval of Ethical committee:

Ethical approval was obtained from the Ethics committee of the hospital and written consent from parents of the neonates was also obtained before the commencement of the study. Study was done according to the latest declaration of Helsinki.[11]

Enrollment of cases:

All babies both term and preterm admitted for hyperbilirubinemia requiring ET were enrolled. ET was decided based on the followings:

1. Guidelines for ET bilirubin levels based on the American Academy of Pediatric Guidelines.[6]

Table I. Guidelines for exchange transfusion in infants 35 or more weeks of gestation.

Age (hrs)	Infants at higher risk 35-37+6 weeks + risk factors	Infants at medium risk ≥38 weeks + risk factors or 35-37+6 weeks and well	Infants at lower risk 38 weeks and well
	SBR (micromol/L)	SBR (micromol/L)	SBR (micromol/L)
Birth	200	235	270
12 hours	230	255	295
24 hours	255	280	320
48 hours	290	320	375
72 hours	315	360	405
96 hours	320	380	425
5 days	320	380	425
6 days	320	380	425
7 days	320	380	425

Table II. Guidelines for exchange transfusion in low birth weight infants based on age.

Age in hours	Wt <1500g	Wt 1550-2000g	Wt >2000g
	SBR (micromol/L)	SBR (micromol/L)	SBR (micromol/L)
<24	>170-255	>255	>270-310
24-48	>170-255	>255	>270-310
49-72	>170-255	>270	>290-320
>72	>255	>290	>310-340

Rate of rise >0. 5mg/dl/hour or >5mg/24hours .[12]

Inclusion criteria:

1. All babies with indirect hyperbilirubinemia.

2. Both Term and preterm babies with or without underlying pathology.

Exclusion criteria:

1. Direct hyperbilirubinemia – neonatal cholestasis.

2. Babies with congenital malformations, TORCH infection, neonatal hepatitis

3. 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:[12]

- 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],[14] hyperglycaemia [whole blood >125 mg/dl, plasma >145 mg/dl][14]

- Hypocalcaemia [S. calcium <7 mg/dl],[14] hyperkalaemia [S.potassium >6 mg/dl],[14]

- Anemia [<15 gm/dl][15]

- Arrhythmias, Bradycardia

- Feed intolerance, necrotizing enterocolitis

- Septicaemia

- Hypothermia [core temp < 36^0C or hyperthermia][12]

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 donar 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 donar 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 donar 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, hemoglobin, 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.

Statistical analysis:

Data processing and analysis was conducted by using statistical package SPSS 19.0 version. Data were summarized as descriptive statistics namely means frequency and percentages. We used paired t-test for comparing pre and

Post Exchange values. A P<0.05 was considered significant.

RESULTS

During 14 months of study period there were total 1114 newborns. 481 (43.17%) newborns presented with jaundice out of which 29 (6%) cases underwent ET.(fig 1)

Figure 1 shows that out of 1114 newborns, 481(43.17%) presented with jaundice and 29(6%) cases required ET.

There were 69 % term, 27.6% preterms and 3.4% postterm babies, out of which (51.7 %) were males and (48.3%) females. The mean age of neonates at presentation was 55.00 ± 36.854 hours, range 7 – 192 hours (Table 1).75.9% babies had normal weight, 13.8% were LBW and in 10.3%

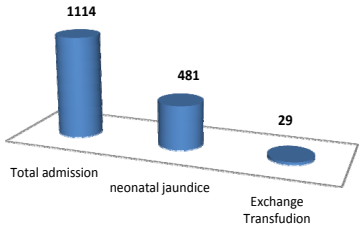

Figure 1. Number of Cases Requiring ET.

cases birth weight was unknown. Among the ethnic groups maximum mongol babies 34.5%, followed by newar, dalit 17.2% and Brahmin 13.8% required ET. 82.8% were hospital delivered and 17.2% were home delivered babies. 79.3% were normal, 17.2% were LSCS delivered babies. 21.1% had jaundice at <24hrs of life, 65.5% at 24-72hrs and 10.3% at >72 hrs of life. 10.3% mothers had blood group A+ve, 13.8% had B+ve, 65.5% O+ve and 10.3% had B-ve blood goup. Similarly 37.9% babies had A+ve,37.9%had B+ve, 3.4% had AB+ve and 20.7% O +ve blood group. 44.8% babies had ABO setting .

All 29 babies were exclusively breast fed. Of all babies requiring ET 55.2% had Pathological jaundice [13.8% ABO incompatibility, 13.8% Sepsis, 13.8% hypothyroidism, 10.3% Rh incompatibility, 3.4% G6PD deficiency and Polycythemia] and 44.8% had exaggerated physiological jaundice(13.8% preterm 3.4% cephalhematoma, 27.6% with no underlying pathology) (Table 2).

Statistical difference was noted in pre and post exchange Total bilirubin (p<0.001), Direct bilirubin (p<0.032), Indirect bilirubin (p<0.001), Hemoglobin (p<0.018), Random blood sugar(p<0.001) and Serum calcium (p<0.001) values (Table 3). On admission 31% of babies had low hemoglobin and 31 %had elevated reticulocyte, Direct coombs test was done in 58.6% cases which was negative in all (Table 3).

The complications noted were anemia (89.7%), sepsis (10.3%), hypocalcaemia (48.3%), hyperglycemia (51.7%), hypoglycemia(3.4%), hypernatremia (13.8%), hyperkalemia (6.9%), bradycardia, apnea and feed intolerance (6.9%).

Table 1. Sample Characteristics

Variables	N	Total = 29 %
Sex:		
Male	15	51.7
Female	14	48.3
Gestation age:		
Term	20	69
Preterm	8	27.6
Post term	1	3.4
Birth Weight:		
Normal	22	75.9
Low birth weight	4	13.8
Unknown	3	10.3
Ethnic group:		
Brahmin	4	13.8
Newar	5	17.2
Dalit	5	17.2
Mongol	10	34.5
Chettri	3	10.3
Muslim	2	6.9
Place of delivery:		
Hospital	24	82.8
Home	5	17.2
Mode of delivery:		
Normal vaginal	23	79.3
LSCS	5	17.2
Normal with Vacuum	1	3.4
Age at onset of jaundice:		
<24 hrs	7	21.1
24-72 hrs	19	65.5
>72 hrs	3	10.3
Mother's blood group:		
A+ve	3	10.3
B+ve	4	13.8
O+ve	19	65.5
B-ve	3	10.3
Baby's blood groups:		
A+ve	11	37.9
B+ve	11	37.9
AB +ve	1	3.4
O+ve	6	20.7
ABO setting:		
Yes	13	44.8
No	16	55.2

** Age at presentation = 55.00 ±36.854 hours (range 7–192 hours)
** All 29 babies exclusively breast fed.

Catheter related complications, hemodynamic instability (hypo or hypertension), arrhythmia, necrotizingenterocolitis hypothermia/hyperthermia, kernicterus were noted. There were no mortalities from ET. (Table 4)

Table 2. **Causes of Jaundice requiring Exchange Transfusion.**

Cause of jaundice [N=29]		Number	Percentage
Pathological (n=16/55.2%)	ABO incompatibility	4	13.8
	Rh incompatibility	3	10.3
	Sepsis	4	13.8
	G6PD deficiency	1	3.4
	Polycythemia	1	3.4
	Hypothyroidism	4	13.8
Physiological (n=13/44.8%)	No identifying pathology	8	27.6
	Preterm	4	13.8
	Cephalhematoma	1	3.4

Table 3. **Pre and Post exchange Lab parameters with mean ± SD:**

Lab parameters	Pre exchange Mean ± SD	Post exchange Mean ± SD	t-test	P value
Total bilirubun	31.79±4.832	16.50±4.278	15.192	<0.001
Direct bilirubin	0.97±0.0.613	0.72±0.513	2.256	<0.032
Indirect bilirubin	30.85±4.740	15.83±4.307	15.200	<0.001
Hemoglobin	12.83±3.089	11.44±1.702	2.515	<0.018
Random blood sugar	89.59±33.393	139.31±68.439	4.059	<0.001
Serum sodium	140.28±6.430	141.72±5.725	0.973	<0.339
Serum potassium	4.11±0.565	4.08±0.541	0.184	<0.856
Serum calcium	11.02±1.260	8.85±1.073	8.842	<0.001

**Pre-exchange high reticulocyte count 9/29(31%); Low hemoglobin 9/29(31%); DCT done 17/29(58.6% = All negative

Table 4. **Adverse events during and after ET:**

Adverse events	Number	Percentage
Catheter related complications	0	0%
Haemodynamic (hypo or hypertension)	0	0%
Hypoglycemia	1	3.4%
Hyperglycaemia	15	51.7%
Hypocalcaemia	14	48.3%
Hyperkalaemia	2	6.9%
Hypernatremia	4	13.8%
Anemia	26	89.7%
Arrhythmia	0	0%
Bradycardia	2	6.9%
Apnea	2	6.9%
Sepsis	3	10.3%
Feed imtolerence	2	6.9%
Necotizingenterocolitis	0	0%
Hypothermia/hyperthermia	0	0%

** Adverse events noted in - 27/29[93.1%]

DISCUSSION

ET was the first successful treat¬ment 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 29/481(6%) babies required ET in 14 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. In our study we had followed the American Academy of Pediatric Guidelines.[6] Like other study ET was more common in boys.[18] The mean age of neonates at presentation was 55.00 ± 36.854 hours; 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 27.6% 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] In Nepal there is good practice of breast feeding and all our 29 neonates were exclusively breast fed.

Causes of jaundice requiring ET

According to our study 55.2% of Pathological and 44.8% of exaggerated physiological jaundice required ET. Among the Pathological causes the most common cause was ABO incompatibility hypothyroidism and sepsis followed by Rh ncompatibility, G6PD deficiency and Polycythemia. ABO incompatibility was also found to be the most common cause for ET in other studies.[18,19,21] 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,[22] and its reported incidence was 14% in one study,[18] but this was only 3.4% in our study and it could be because of its low rate in our race and also the facilities to do the enzyme level is not available in our set up. Interestingly hypothyroidism (13.8%) was found to be one of the commonest causes for ET in this study. The relevant literature for this was not available. We suggest 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.[19,21,23]

Improvement:

Statistical difference was noted in pre and Post Exchange Total bilirubin ($p<0.001$), Direct bilirubin ($p<0.032$), Indirect bilirubin ($p<0.001$). The mean total bilirubin decreased

from 31.79 ± 4.832 to 16.50 ± 4.278 indicating ET to be effective treatment for neonatal hyperbilirubinemia.

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.[16,24] In the present study 93.1% had complications which were much higher than other studies. The complications noted were anemia, sepsis, hypocalcemia, hyperglycemia, hypoglycemia, hypernatremia, hyperkalaemia, bradycardia, apnea and feed intolerance. Among the complications hyperglycemia, hypocalcemia and anemia was found to be highest. In this study CPD (citrate phosphate dextrose) blood was used and the high glucose content of CPD blood maybe the reason for hyperglycemia soon after exchange. 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.[25] We did not have any mortality. The reported mortality associated with the ET is around 2% in the literature.[2,3] In another study most common adverse events noted were thrombocytopenia (44%), and metabolic acidosis (24%).[24] However they have not mentioned what was the percentage of sepsis in their study as thrombocytopenia can be part of sepsis In this study Arterial blood gas analysis was not done. 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. Our clinical experience shows that many affected babies arrived late in hospital with high levels of bilirubin [Mean±SD total bilirubin 31.79±4.832 and highest 43 mg/dl] compared to other studies where it was 29.39±6.13 mg/dL and 20 ±5.50 mg/dl respectively.[18,26] This delay in seeking medical consultation can be due to lack of awareness, inadequate knowledge of parents, early discharge with no early follow up, failure to recognize the presence of risk factors for hyperbilirubinemia, delay in measuring the serum bilirubin level or delay in initiating phototherapy.

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 is ABO incompatibility but in this study along with ABO incompatibility hypothyroidism was found to be commonest cause for ET. Complications noted were much higher than other studies. ET is effective way to decrease bilirubin level. Finally, a further evaluation of hyperbilirubinemia requiring ET with thyroid function test should be carried out in a larger population to decide whether routine thyroid screening is mandatory.

Limitation

A larger sample size and a control study would have given a better result. Due to lack of facility or affordability certain investigation like TORCH screening, G6PD enzyme estimation, Thyroid function test could not be done in all cases so there might be overlapping of cases.

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