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CLINICAL FEATURES, LABORATORY FINDINGS AND OUTCOMES OF IN FANTS WITH HYPERBILIRUBINAEMIA REQUIRING EXCHANGE BLOOD TRANSFUSION AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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A research report submitted to the faculty of health Sciences, University of Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of paediatrics and child health

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DECLARATION

I Karabo Pertunia Seake declare that this research report is my own work. It has been submitted for the degree of Master of Medicine in the branch of Paediatrics and Child Health in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature_____

Signed on this…….. day of …….. 2016

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I would like to take this this opportunity to thank my supervisor Prof S Velaphi, for guiding me through this journey, for his patience and selflessness. My entire family for believing in my abilities.

ABSTRACT:

Background: Severe hyperbilirubinaemia (SHB) requiring exchange blood transfusion (EBT) continues to be a problem despite use of anti-D immunoglobulin and kinder-gentle approach in its management. Knowing features of infants with SHB might assist in its prevention.

Objectives: To determine features, presentation and outcome of infants with SHB.

Methods: We conducted review of records of infants admitted at Chris Hani Baragwanath Academic Hospital with SHB requiring EBT in 2009-2013. Descriptive analysis of characteristics, clinical presentation, laboratory findings, and outcome at discharge was performed.

Results: Out of 150 patients who received EBT, 101 (67.3%) had records available for review. The majority were born by normal vaginal delivery (86.1%), weighed ≥2500g (65.4%), exclusively breastfed (82%) and were outpatients (66.3%). A higher proportion of outpatients were born at clinic (68.7% vs 5.9%, p<0.001), vaginally (92.5% vs 73.5%, p=0.009), male (62.6% vs 38.3%, p=0.020), weighing ≥2500g (76.1% vs 44.1%, p=0.001) than inpatients. Median postnatal age at EBT was 5days. Clinical presentation was suggestive of acute bilirubin encephalopathy (ABE) in 25%. Among mother-infant pairs with known blood groups 70% and 9% had ABO- and Rh-incompatibility respectively. Common abnormal laboratory findings post-EBT were thrombocytopaenia (77%), hypercalcaemia (55%) and anaemia (36%). A total of six patients (6%) died, all within 7days of EBT, but none during EBT. Infants who died had a higher serum bilirubin than survivors (623±100 vs 498±136 mmols/l, p<0.001). Common causes of deaths were ABE (n=3) and sepsis (n=2).

Conclusion

The majority of patients with SHB were vaginal term births, exclusively breastfed from home or clinic-referrals, and had ABO incompatibility. SHB is associated with significant morbidity and mortality.

INTRODUCTION

Neonatal jaundice due to unconjugated hyperbilirubinaemia remains one of the common clinical conditions that clinicians working with neonates encounter on a daily basis [1] . It is the leading cause of hospital readmissions during the neonatal period [2]. It occurs because of imbalance between bilirubin production and its elimination. The underlying mechanisms are often due to increased breakdown of red blood cells, or decreased uptake and conjugation by the liver or increased enterohepatic circulation. Severe hyperbilirubinaemia (SHB) at levels requiring exchange blood transfusion (EBT) is associated with serious morbidity and mortality if left untreated or if treatment is delayed [3]. Unconjugated hyperbilirubinaemia is known to be a neurotoxin that can lead to significant neuronal damage [4]. SHB presents acutely with signs of acute bilirubin encephalopathy (ABE) characterized by lethargy, abnormal tone, poor feeding, high pitched cry, seizures, opisthotonus and apnoeas, a risk of mortality is between 7%-10% [4]. Long term complications of SHB include athetoid cerebral palsy, sensorineural hearing loss, impaired upward gaze[4]. The other term that is commonly used to describe neurological injury associated with hyperbilirubinaemia is kernicterus, even though it was meant to describe the yellow staining of the basal ganglia and brain stem nuclei, therefore a post-mortem diagnosis. Therefore it is important to characterize neonates who develop SHB so that it can be prevented, in order to avoid neuronal injury that results in acute bilirubin encephalopathy or kernicterus.

There are a number of factors that have been associated with development of unconjugated hyperbilirubinaemia and these include early discharge, blood group incompatibilities, infections and cephalohaematoma[5]. Early postnatal discharge has become a common phenomenon in the world, with the escalation seen in the 1990's [2]. In the developing

countries, where the health care facilities are overwhelmed, early postnatal discharge has also become a common practice, for example in our local setting the mothers and newborns are discharged as early as 6 hours post normal vaginal delivery if they are both well. Though there are many benefits for early discharge like early family bonding or attachment, reducing exposure to hospital-acquired infections and less financial cost associated with hospitalisation, early discharge is however associated with an increase in neonatal readmissions with jaundice accounting for up to 50 % of readmissions [2].

Haemolytic disease secondary to ABO and Rh incompatibility is another major risk factor for development of SHB. In a study from South Africa in the early 1980's, it was found that ABO incompatibility lead to severe jaundice in 41.7% of cases and lead to EBT in 44.4% of infants [6]. Phototherapy is the treatment modality of choice for NNJ, it is thought to reduce the serum bilirubin by 25%-50% during its initial phase and EBT reserved for those who fail to respond to the phototherapy, at risk of bilirubin neurotoxity or those presenting with ABE [7]. The need for EBT has decreased significantly globally due to development of anti-D immunoglobulins, intensive phototherapy and use of guidelines for monitoring and managing infants at risk for jaundice [5]. The EBT can be associated with serious complications, such as apnoea, necrotizing enterocolitis, hypotension, seizures, arrhythmias, cardiac arrest and death [8]. In this study we sought to describe features and short-term outcomes of neonates with severe hyperbilirubinaemia requiring EBT during an era of early discharge.

METHODS

Study Design: It was a retrospective descriptive study.

Study Population: All neonates (postnatal age <29 days) admitted at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2009 to December 2013 with hyperbilirubinaemia and received EBT were included in this study.

Study Procedures: Names of infants who were issued with blood for EBT were requested from the local blood bank. In addition, patient registers in paediatric and neonatal wards were reviewed for names of patients who received EBT. The names and hospital numbers of patients who had EBT were used to retrieve the clinical and laboratory records, and to get biochemical and haematological blood results, maternal and infant blood groups and Coombs results from the laboratory and blood bank. Data collected from clinical records included demographic characteristics, anthropometric parameters, feeding, clinical signs at presentation, and outcome at time of discharge. Laboratory data were collected on maternal and infant blood groups, Coombs, haemoglobin, platelets, calcium and magnesium.

Data analysis: Data was entered into an Excel spreadsheet, and after cleaning it was imported into a statistical program, Statistica version 12.0 for analysis. Patients were divided into two groups, inpatients group, that is those who required EBT while still in hospital before discharge after delivery; and outpatients, that is those who had gone home after delivery. The means and standard deviations, medians and 25^{th} -75^{th} centile were used for summarized description of continuous variables. Categorical variables were described using frequencies and percentages. Comparison was performed between inpatient and outpatient group using a Chi-square or Fisher exact test for categorical variables, and Student t-test or Mann-Whitney U test for continuous variables. Differences were considered to be significant if the p-value was <0.05.

RESULTS

A total of 150 patients had EBT performed over the five year period, from January 2009 to December 2013, an average of 30 EBTs per year. A total of 101 patients' files were available for review. Among the 101 patients, 34 (33.6%) were inpatients (had not been discharged after birth), and 67 (66.4%) were outpatients, came in as self-referrals or referred by the local clinics.

Maternal and infants characteristics

The maternal and infant demographic, anthropometry, age at EBT, type of milk feeds and maternal blood groups are presented in Table 1. The majority of infants (92.1%) were born to African mothers. The average maternal age was 26.7±6.8 years and 28 (37.3%) mothers were primigravida. Overall, 93 (92.1%) delivered in a healthcare facility, 87 (86.1%) vaginally, 66 (65.4%) weighed ≥2500 grams and 83 (82.2%) were exclusively breastfed. Nine (10.5%) and 54 (66.7%) mothers were Rh negative and blood group O respectively. In comparing the inpatient and outpatient groups, the outpatient group had a higher proportion of patients born at the clinic (68.7% vs 5.9%, p<0.001), vaginally (92.5% vs 73.5%, p=0.009), were males (62.6% vs 38.3%, p=0.020), weighed ≥2500g (76.1% vs 44.1%, p=0.001), and were older (median age 6 vs 4 days, p=0.004) than inpatient group. Among the 101 infants who had blood transfusion, 23 (27%) had positive Coombs results. Five of these (22%) had positive Coombs due to Rh incompatibility and 18 (78%) were due to ABO incompatibility.

Clinical signs at presentation in patients who required exchange blood transfusion

Twenty five (24.8%) patients who needed an exchange blood transfusion had signs suggestive of acute bilirubin encephalopathy (ABE) (Table 2). The outpatient group accounted for most of the patients who presented with these signs at 88%. The clinical signs

noted and considered to suggest encephalopathy were abnormal tone (n=18, 17.8%), lethargy (n=17, 16.8%), apnoea (n=9, 8.9%), opisthotonus (n=4, 4.0%) and irritability (n=1, 1%). Infants with clinical signs had higher serum bilirubin levels than those without these signs (579±145 vs 483±128 mmols/l, p=0.002).

Table 1: Maternal and infant characteristics of patients who needed an exchange blood transfusion.

	All (n=101)	Inpatients (n=34)	Outpatient (n=67)	p-value
Race				
Black	93 (92.1%)	31 (91.2%)	62 (92.5%	0.819
Coloured	3 (7.9%)	3 (8.8%)	5 (7.5%)	
Maternal age (years) *	26.7 ± 6.8	26.9±6.9	27±6.7	0.496
Maternal gravidity				0.353
<2	28 (37.3%)	15 (44.1%)	13 (31.7%)	
2-4	41 (54.7%)	16 (47.1%)	25 (61.0%)	
>4	6 (8.0%)	3 (8.8%)	3 (7.3%)	
Place of birth				<0.001
Hospital	47 (46.5%)	30 (88.2%)	17 (25.3%)	
Clinic	48 (47.5%)	2 (5.9%)	46 (68.7%)	
Born before arrival	6 (5.9%)	2 (5.9%)	4 (6.0%)	
Mode of delivery				0.009
Caesarean section	14 (13.9%)	9 (26.5%)	5 (7.5%)	
Vaginal delivery	87 (86.1%)	25 (73.5%	62 (92.5%)	
Sex				0.020
Female	46 (45.5%)	21 (61.7%)	25 (37.3%)	
Male	55 (54.4%)	13 (38.3%)	42 (62.6%)	
Gestational age*	37.2 ± 2.4	36.4±3.4	37.5±1.6	0.441
≤37 weeks	51 (50.5%)	19 (55.9%)	32 (47.8%)	
>37 weeks	50 (49.5%)	15 (44.1%)	35 (52.2%)	
Birth weight*	2701 ± 614	2522± 850	2792 ±429	0.001
<2500 grams	35 (34.6%)	19 (55.9%)	16 (23.9%)	
≥2500 grams	66 (65.4%)	15 (44.1%)	51 (76.1%)	
Feeds				0.273
Breast feeding	83 (82.2%)	26 (76.5%)	57 (85.0%)	
Formula feeding	10 (9.9 %)	3 (8.8%)	7 (10.5%)	
Mixed feeding	8 (7.9 %)	5 (14.7%)	3 (4.5%)	
Median age at exchange in days†	5 (4-7)	4 (4-7)	6 (4-7)	0.004
Maternal Rh group				0.076
Rh Negative	9 (10.5%)	1 (3.0%)	8 (15.1%)	
Rh Positive	77 (89.5)	32 (97.0%)	45 (84.9%)	
Maternal ABO group				0.797
A	12 (14.8%)	5 (18.5%)	7 (13.0%)	

B O AB	14 (17.3%) 54 (66.7%) 1 (1.2%)	4 (14.8%) 18 (66.7%) 0	10 (18.5%) 36 (66.7%) 1 (1.8%)	

* = Mean ± SD; † = Median (25 – 75th centile)

Table 2 Clinical signs in patients receiving exchange blood transfusion

	Total (n=101)	Inpatients (n = 34)	Readmitted (n=67)
Asymptomatic, except jaundice	76 (75.2%)	31 (91.2%)	45 (67.2%)
Symptomatic with signs other than jaundice	25 (24.8%)	3 (8.8%)	22 (32.8%)
Abnormal tone	18 (72.0%)	2 (66.7%)	16 (72.7%)
Lethargy	17 (68.0%)	3 (100%)	14 (63.6%)
Apnoea	9 (36.0%)	1 (33.3%)	8 (63.6%)
Opisthotonus	4 (16.0%)	0	4 (18.2%)
Irritability	1 (4.0%)	1 (33.3%)	0

Maternal and infant Rhesus blood groups in those receiving exchange blood transfusions

Among the 86 mothers with known Rh blood group, nine (10.5%) were Rh negative, and eight of their infants were Rh positive, thus eight of the 86 (9.3%) mother infant pairs with known Rh results had Rh incompatibility. Five of the eight infants with Rh incompatibility had a positive Coomb results (62.5%) (Table 3). Eight of the infants born to mothers who were Rh negative were outpatients, and seven of these were born at the local clinic and one in hospital. Parity of mothers who were Rh negative was known for seven mothers and five of these seven (71%) had previous pregnancies. Among the 23 mother-infant pairs who were both Rh positive, nine (39%) were Coombs positive, and of these nine, two were ABO incompatible (mother O/ infant A and other mother O and infant B), suggesting that the other 7 were due to incompatibility from minor blood groups or another unknown diagnosis.

The ABO blood groups of mothers and infants requiring EBT

Table 4 illustrates maternal ABO blood groups against infant's ABO blood groups and possible incompatibilities as shown by the underlined numbers and those with positive Coombs test shown by numbers in parenthesis. Among the 81 mothers with known ABO blood group 54 (66.7%) were blood group O, 14 (17%) blood group B and 12 (15%) blood group A. Fifty seven (70%) of the 81 mother infant pairs with known results were ABO incompatible. The common ABO incompatible groups were mother O/ infant B, 30/57 (53%), mother O/ infant A, 17/57 (30%), and mother B/ infant A, 4/57 (7%). Eighteen of the 57 (32%) infants who had ABO incompatible were Coomb positive, with 37% of the mother O/ infant B and 23% of mother O/ infant A having positive Coombs.

Table 3: Rhesus blood group of mothers and infants receiving exchange blood transfusion

		Mothers			Total
		Rh positive	Rh negative	Rh unknown	
Infant	Rh positive	23 (9, 39%)*	8 (5, 62.5%)*	5	36
	Rh negative	0	1	0	1
	Rh not recorded	54	0	10	64
	Total	77	9	15	101

* = Positive coombs

Bilirubin results before EBT and calcium, magnesium, phosphate, haemoglobin and platelets after EBT

The majority of infants (65%) who required an EBT were infants with birthweight above 2500 gram, and had median serum bilirubin level of 544mmol/L before EBT (Table 5). Hypercalcaemia (total serum calcium >2.75 mmols/L) was noted in 55% and hypocalcaemia (total serum calcium <1.75) in 1% of all patients post-transfusion. Eighteen percent had hypomagnesaemia (serum magnesium <0.65 mmols/L). Only 7% had hypoglycaemia and

29% had hyperglycaemia amongst the whole group. Common haematological abnormalities post-transfusion were thrombocytopaenia (platelet count <150 x 10^9/L) (77%) and anaemia (haemoglobin <13 g/dL) (36%).

Mortality rate among the patients who received exchange blood transfusion

The median age at discharge or death was 7 days with 25^{th} and 75^{th} percentile at 6 and 11 days. Of 101 patients that had EBT, 6 patients died before hospital discharge giving a mortality rate of 6%. Infants who weighed >2000 grams, and were outpatients (Table 6). The age at exchange was 2-15 days, 3 were ABO incompatible, with serum bilirubin levels of 441-722 mmols/l. None of these infants died during the procedure of EBT. Three were assessed to have died from acute bilirubin encephalopathy, two of these were noted to have clinical signs of acute bilirubin encephalopathy on admission before EBT. Two were assessed to have died from sepsis post-exchange transfusion.

Table 5: Serum bilirubin before EBT and calcium, magnesium, glucose, haemoglobin and platelets at end of EBT.

	All	Birthweight			
		<1500 (n=4, 4%)	1500-1800 (n=5, 5%)	1801-2500 (n=26, 26%)	>2500 (n=66, 65%)
Median SB before EBT (25-75th centile)	508 (435-595)	249 (182-404)	398 (307-426)	482 (400-531)	544 (475-614)
Serum Calcium (mmol/L)					
- <1.75	1 (1%)	0	0	0	1 (2%)
- 2-2.75	33 (43%)	4 (100%)	1 (50%)	8 (35%)	20 (43%)
- >2.75	42 (55%)	0	1 (50%)	15 (65%)	26 (55%)
Serum Magnesium (mmol/L)					
- <0.65	14 (18%)	1 (25%)	2 (40%)	4 (17%)	7 (15%)
- ≥0.65	65 (82%)	3 (75%)	3 (60%)	19 (83%)	40 (85%)
Serum Glucose (mmol/L)					
- <2.6	7 (7%)	0	0	2 (8%)	5 (7%)
- 2.6-8	65 (64%)	2 (50%)	3 (60%)	20 (77%)	40 (61%)
- >8	29 (29%)	2 (50%)	2 (40%)	4 (15%)	21 (32%)
Haemoglobin (g/dL)					
- <13	29 (36%)	1 (25%)	1 (20%)	8 (33%)	19 (40%)
- 13-18	50 (63%)	3 (75%)	4 (80%)	15 (62%)	28 (60%)
- >18	1 (1%)	0	0	1 (4%)	0
Platelets (x10^9/L)					
- <150	62 (77%)	4 (100%)	3 (60%)	16 (67%)	39 (83%)
- 150-450	16 (20%)	0	2 (40%)	6 (25%)	8 (17%)
- >450	2 (3%)	0	0	2 (8%)	0

Table 6: The features of infants who died in hospital among the infants who had EBT

Birth weight	GA Sex	Age at EBT (days)	ABO Inc.	Serum bilirubin (mmol/l)	Rh Inc.	Relation to EBT	Cause of death	Days in relation to post-EBT
2540g	37, M	11	Yes	567	U	No	ABE	3
2470g	36, F	2	Yes	478	No	No	Nosoc. Sepsis	7
2550g	38, F	5	No	643	No	No	HCOM	1
2430g	37, M	6	Yes	441	No	No	ABE, Sepsis	5
2900g	40, M	4	No	722	No	No	DIC, Sepsis	1
2540g	37, M	15	U	620	U	No	ABE	2

GA – Gestational age, Inc. – Incompatibility, Nosoc.- Nosocomial, ABE – Acute bilirubin encephalopathy, HCOM- Hypertrophic cardiomyopathy, DIC- Disseminated intravascular coagulation, **U- presumed unknown**

DISCUSSION

Neonatal jaundice it is a benign condition in the majority of cases, when it is severe it can be fatal and among the survivors it can be associated with severe morbidity. With screening and close monitoring of those at risk, and implementing effective treatment modalities, namely phototherapy and EBT the morbidity and mortality associated with hyperbilirubinaemia has been significantly reduced [9]. Even though EBT reduces morbidity associated with severe hyperbilirubinaemia, if its performance is delayed these adverse outcomes may not be avoided. Therefore it is important that those who are at risk of severe hyperbilirubinaemia are identified and monitored closely, or are referred to a facility where they can be appropriately monitored and treated. The policy of early discharge often makes it difficult to closely monitor those at risk of hyperbilirubinaemia in hospital, thus the American Academy of Pediatrics, recommends that if infants are discharged early (less than 48 hours of life), they must have postnatal assessment at 48-72 hours after discharge and this should be conducted by a professional[10]. In developing countries, this postnatal assessment is not always possible for all babies because of limited resources, thus it is still important to identify those at risk of developing severe hyperbilirubinaemia so that the limited staff can focus in this group or an exception is made to keep them in hospital for longer period. To educate the mothers regarding SHB in the high risk population. Thus

in this study we aimed to identify features of infants with hyperbilirubinaemia requiring EBT in a setting where the policy of early discharge is followed.

The main findings in this study is that about two-thirds of patients with hyperbilirubinaemia requiring EBT were outpatients. Overall, most patients were in a health care facility

suggesting that there was an opportunity to identify those who were at risk of developing hyperbilirubinaemia. More than 90% of those who were outpatients were born vaginally suggesting that they were discharged early as the current policy in the setting where this study was done is that well vaginally delivered infants are discharged by 24 hours while those born by caesarean section are kept for at least 48 hours. More patients being born vaginally suggests that the outpatients were discharged early. Early discharge of newborn infants has been reported to contribute to an increase in the readmission rates of neonates, with jaundice contributing to 50% of the readmitted infants [2]. One study reported that 69% of severely jaundiced babies were readmissions, with 38% and 87% having been discharge within 24 hours and 72 hours post-delivery respectively[11].

Exclusive breastfeeding was noted in more than 80% of patients. Rhesus and ABO incompatibility was noted in 10% and 70% respectively among those with known blood groups which was at least 80% of all the patients who received EBT. About a quarter of patients presented with signs suggestive of acute bilirubin encephalopathy. The mortality rate was high at 6% and none of the deaths occurred during the time of the procedure of EBT.

The association between breastfeeding and jaundice has been well recognized, the breastfed infants are three times more likely to be jaundiced and six times more likely to develop severe jaundice as compared to formula fed counterparts[12]. This means even if screening is done before discharge, if patients are discharged early, those who are breastfed might still be missed as some of them might develop jaundice later.

Just over 70% of mothers who were Rh negative had previous pregnancy, this suggests failure in administering anti-D immunoglobulin with previous pregnancy or inadequate monitoring of Rh negative mothers during pregnancy. The incidence of ABO incompatibility of 70% in this study was high compared to that of 15.7% of those needing EBT and 44.4% of

all jaundiced patients in a study by Vos et al [6] while Rh incompatibility contributed only 3.2% of all the EBT [6]. The common ABO incompatibilities were the mother O/ infant B (52.6%), and mother O/ infant A (29.8%).

The high number of patients with signs of ABE is of major concern as many of these are most likely to develop neurologic deficit and also highlights the need for long-term follow up of patients with severe hyperbilirubinaemia. Common complications related to EBT were mainly biochemical and haematological. This finding is similar to those reported in other studies [13]. A recent study from an institution similar to where this study was conducted, using the similar protocols on EBT reported similar complications[14]. Hypercalcaemia was most likely iatrogenic as calcium gluconate was added to blood during the exchange as part of the local protocol of EBT. A total of six patients died within a week of EBT, giving a mortality rate of about 6%. Three of the deaths were assessed to be related to acute bilirubin encephalopathy, highlighting the dangers of severe hyperbilirubinaemia. Two died from sepsis again highlighting the importance of preventing severe hyperbilirubinaemia as hospitalization or performance of the procedure might have exposed these infant to sepsis. Severe hyperbilirubinaemia was associated with high mortality of 6%. This mortality is higher than that of 4% reported by Rugamba et al[14] and lower than that reported by Ibekwe et al who reported 17.5%; and both studies were from similar settings, developing countries[15].

A limitation of this study is that it was a retrospective study, therefore among the patients who received EBT about a third of their files were missing and we were unable to assess whether the infants were discharged early or not post-delivery. The conclusion from these findings is that severe hyperbilirubinaemia requiring EBT is most likely related to early discharge of newborn infants who have not yet establish breastfeeding; and that ABO

incompatibility plays a major role in development of severe jaundice. We recommend that all pregnant women should have ABO blood group typing in addition to Rh group typing during antenatal care. Infants at risk of blood group incompatibility, namely infants born to mothers who are Rh negative or blood group O, should not be discharged before 48 hours or until their blood groups are known. Newborn infants should not be discharged before 24 hours or at least until there is adequate flow of breast milk and/or that the infant is breastfeeding well. All newborn infants should be screened for hyperbilirubinaemia using transcutaneous bilirubinometer before discharge and those assessed to be at intermediate or high risk not to be discharged until serum bilirubin levels are known**.** To educate mothers about the SHB and to seek early medical assistance when babies are jaundiced. All clinics and hospital outpatient departments where neonates with jaundice might present should have transcutaneous bilirubinometers to assess levels of bilirubin so that all those with high levels can be started on phototherapy immediately while awaiting serum bilirubin results. In view of high number of patients with hypercalcaemia post EBT, addition of calcium in blood during the exchange should not be done, rather calcium levels should be monitored during EBT. Long term follow-up of all patients with severe hyperbilirubinaemia should be conducted, as a quarter of patients presented with signs of acute bilirubin encephalopathy are at risk of developing neurologic deficit.

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APPENDIX A: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Karabo Seake

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140482

NAME: (Principal Investigator)	Dr Karabo Seake
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Clinical Features, Laboratory Findings and Outcomes of Infants with Hyperbilirubinaemia requiring Blood Exchange Transfusion
DATE CONSIDERED:	25/04/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Sithembiso Velaphi
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/04/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 12/05/2014

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B: PROTOCOL

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

DEPARTMENT OF PAEDIATRICS

MMED PROTOCOL:

Clinical features, laboratory findings and outcomes of infants with hyperbilirubinaemia requiring exchange blood transfusion.

Student name: Dr Karabo Seake

Student number: 0102268N

Supervisor: Prof. S. Velaphi

CLINICAL AND LABORATORY FEATURES, COMPLICATIONS AND OUTCOMES OF INFANTS WITH HYPERBILIRUBINAEMIA REQUIRING EXCHANGE BLOOD TRANSFUSION

BACKGROUND

Neonatal jaundice is the commonest medical condition encountered by clinicians working in the neonatal wards. It affects 60-70% of term and up to 90% of preterm infants[1]. The unconjugated hyperbilirubinaemia is the commonest and it is a benign condition overall. In its severe form, it can be associated with morbidity and mortality. It is important to monitor patients for neonatal jaundice and to prevent the complications of severe form of the disease. Recommendations have been made to monitor every infant for the development of jaundice, importantly those high risk patients prior to discharge, to treat those who develop neonatal jaundice and to prevent complications[2].

In developing countries like South Africa, the health-care facilities are overwhelmed with a large number of deliveries, therefore patients are often discharged early before the conditions like jaundice develop. Thus they are at risk of not been screened for and more likely to subsequently present with severe neonatal jaundice.

There are certain infants that are at risk of developing severe neonatal jaundice with its complications. It is in these infants that a high vigilance strategy is needed to identify them. They include the following, older sibling with jaundice, large and small for gestational age, exclusive breastfeeding, delay passing meconium, sepsis, significant bruising and haematoma and haemolytic disease[3].

The haemolytic jaundice, most common being the ABO incompatibility and Rhesus incompatibility infants. Vos, et al reported that ABO incompatibility accounted for 41.7% of severely jaundiced and 44.4% of those requiring an exchange blood transfusion[4] . However they demonstrated that ABO incompatibility did not contribute significantly in the overall neonatal jaundice. Behjati et al, reported ABO incompatibility as the major cause of exchange blood transfusions and late presentation as the major contributing factor[5] .

Severe neonatal jaundice is associated with bilirubin encephalopathy which is the most important and devastating complication of severe neonatal jaundice. It is a worldwide phenomenon, despite comprehensive guidelines to identify and treat those who develop neonatal jaundice. The developing countries are faced with higher rates of exchange blood transfusion and complications of bilirubin encephalopathy[6].

It can present as a spectrum of clinical disorders ranging from acute to chronic bilirubin encephalopathy. Mortality being the most devastating complication. Hameed, in Iraq, the complications of neonatal hyperbilirubinaemia are still alarming in the developing countries[7]. In their study, they had a total of 162 infants admitted for severe hyperbilirubinaemia, 22% had advanced acute hyperbilirubinaemia, 12% died within 48 hours of admission and 21% had post icteric sequelae.

Acute bilirubin encephalopathy has been divided into a progression of three phases, as outlined in the 2004 American Academy of Paediatrics guidelines for the management of hyperbilirubinaemia[2]. Phase one, characterized by lethargy and poor feeding, these are most common nonspecific neonatal signs. They may lead to a delay in the diagnosis and initiation of treatment if the clinicians are not vigilant. Phase two of the disease, infants with abnormal tone, hypertonia of the extensor muscles is typical at this stage, high pitched cry, and drowsiness. It is at this second stage that irreversible brain damage may occur. In the advance phase, shrill cry, apnoea, fever, deep stupor to coma and death can occur. Chronic encephalopathy (kernicterus) is characterized by choreoathetoid cerebral palsy, hearing loss, intellectual impairment.

In order to prevent bilirubin encephalopathy, phototherapy and exchange blood transfusion are recommended in patients with severe hyperbilirubinaemia. Exchange blood transfusion is used in infants with imminent or acute bilirubin encephalopathy to prevent the long term complications of chronic bilirubin encephalopathy. It is used as the last treatment option in cases where the risk of bilirubin encephalopathy is high. It is an invasive procedure, requires close monitoring during and after the procedure and associated with complications.

The severity of complications are increased in patients with other comorbidities e.g. sepsis, very low birth weights. These complications include, electrolyte abnormality mostly calcium and magnesium, hypoglycaemia, hypothermia, apnoea and death[7].
The incidence of complications are higher in ill infants compared to healthy infants, with severe complications (death or permanent serious sequelae) being as high as 12%[8].

A significant number of patient born at CHBAH are discharged before 24 hours of life before jaundice can develop and be detected. This result in mothers being the ones who visually detect jaundice and bring back the babies for management of jaundice. Visual detection of jaundice is not accurate, it might result in these infants presenting late. Secondly, early discharge does not allow proper supervision of mothers who are breast feeding, especially those who are primigravida, and this may result in babies having severe hyperbilirubinaemia because of inadequate feeding.

In order to detect hyperbilirubinaemia in infants at risk of having blood group incompatibility infants born to mothers who are Rh negative are kept in hospital for screening for jaundice for the first 72 hours of life. In our region mothers and infants are not screened for ABO incompatibility unless the infant develops neonatal jaundice. Thus the contribution of blood incompatibility to the overall neonatal jaundice is unknown. Describing demographic, clinical and laboratory features and outcome of infants requiring exchange blood transfusion might assist in identifying factors that might be contributing to severe hyperbilirubinaemia. Identifying these will assist in reducing incidence of severe hyperbilirubinaemia requiring exchange transfusion.

AIM

To describe the clinical and laboratory features, complications and mortality rates in infants with neonatal jaundice requiring exchange blood transfusion

OBJECTIVES

1. To describe the demographic characteristics of infants requiring an exchange blood transfusion at CHBAH, over a 5 year period from 2009-2013.
2. To determine the blood group types of mothers and infants requiring an exchange blood transfusion

3. To describe the clinical signs and diagnosis in infants requiring exchange blood transfusion
4. To determine the serum bilirubin levels at the time of exchange blood transfusion
5. To determine complications and mortality rates associated with exchange blood transfusion.

METHODS

Study design: Retrospective descriptive study

Review of clinical records will be conducted

Study population

All infants admitted to CHBAH with neonatal jaundice requiring exchange blood transfusion in the past five years (2009 – 2013).

Inclusion criteria

- All infants admitted to CHBAH requiring an exchange blood transfusion will be included in the study. These include those admitted in both the neonatal unit and the general paediatrics wards.
- Infants with postnatal age <28 days.

Exclusion criteria

- Infants whose indication for exchange blood transfusion was not hyperbilirubinaemia.
- Both clinical information and laboratory information not available

Data collection

Data to be accessed, will include that retrieved from the admission books in paediatric admission ward and the record keeping books of all the exchange transfusions done at CHBAH, at both the neonatal and general paediatric wards. Access to the blood request register at the CHBAH blood bank will be requested. Names and hospital numbers of patients who had blood requested for exchange blood transfusion will be collected. Using the names and hospital numbers, hospital bed letters will be retrieved. From the blood bank records, the maternal and child blood group types will be recorded. Data on maternal and infant demographic features,

clinical signs, complications and outcomes of infants who were exchanged will be collected. The data to be collected will include the following variables:

- Maternal Rh group
- Age of infant at discharge
- Sex
- Gestational age
- Chronological age
- Birth weight
- Referred patients or in hospital delivery
- Clinical abnormalities on admission and time of exchange
- Serum bilirubin levels at the time of the exchange transfusion
- Maternal and infants blood types
- Coombs results
- Date of exchange
- Number of exchange blood transfusion
- Feeding choice
- Glucose level at exchange transfusion
- Electrolyte levels, calcium and magnesium
- Apnoea
- Ward of exchange blood transfusion
- Ward post exchange transfusion
- Outcome: died or survived
- Abnormalities before and at discharge, post exchange
    - Bilirubin encephalopathy or Kernicterus: This will be defined as any of the following abnormal neurological findings (posture abnormalities, tone abnormalities, and level of consciousness) or this diagnosis documented in the patient's chart by the attending physician.

Data analysis

Means and standard deviations will be used to summarize description of continuous variables with normal distribution, and medians and percentile ranges will be used to describe continuous variables that are not normally distributed. Continuous variables will include birth weight,

gestational age, age on admission and bilirubin levels. Frequencies and percentages will be used to describe categorical variables like blood groups, sex and race. Comparisons will be made between those who had kernicterus and those who did not, and survivors and non-survivors. In these comparisons chi-square will used for categorical variables and Student t-test for continuous variables. Differences will considered significant if p-values are <0.05. Statistical package that will be used for this analysis will be Statistica version 12.

Ethical consideration

Permission to use information from CHBAH blood bank will be requested from the blood bank manager. The ethics approval to conduct this study will be sought from the Wits Human Research Committee. Data collection will not commence until approval from ethics committee and hospital CEO has been granted. All the patients' information will be kept strictly confidential. Identifiers will not be used, rather codes will be used to identify patients once the clinical notes have been retrieved. The patient's clinical records will be strictly kept under lock and key under the care of the investigator. There will be no interaction with any of the patients or their parents and therefore it will not be possible to get informed consent as this will be a retrospective study.

Financial consideration

Financial consideration for the study are very negligible, the researcher will absorb all the expenses incurred during the study period**.**

Timelines

	April 2014	June 2014	July 2014	Aug-Sept 2014	Oct-Jan 2014-15	Feb-Mar 2015	Apr-May 2015
Writing the protocol							
Application for Ethics and Postgraduate Committees' Approval							
Response to comments from above committees							
Data collection							
Data analysis							
Writing up							

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APPENDIX C: Letter from a co-author

Department of Paediatrics
Metabolic Unit
Chris Hani Baragwanath Academic Hospital
P. O. Bertsham
2013

30 November 2015

The Chairperson
Postgraduate Committee
Faculty of Health Sciences
University of the Witwatersrand
Parktown
Johannesburg

Dear Madam/ Sir

Re: Submission of MMed Report through Publication Submissible Format

This is to confirm that Dr. Karabo Pertunia Seake was the main person involved with conception, design, analysis and interpretation of data. She developed the protocol, collected and analysed the data, wrote the results and discussion on her own. She drafted and revised the content of the paper, and was involved in the final approval of the version to be submitted for consideration for publication. I was her supervisor who guided her on how to develop the protocol, collect and analyze data, and with the writing up of the report/ manuscript. I was involved in the final approval of the version she is submitting to the University for MMed and to the South African Journal of Medicine for consideration for publication.

Yours Sincerely
Professor Sithembiso Velaphi (Supervisor)

APPENDIX D: Turnitin

turnitin **Turnitin Originality Report**

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by Karabo Seake

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CLINICAL FEATURES, LABORATORY FINDINGS AND OUTCOMES OF INFANTS WITH HYPERBILIRUBINAEMIA REQUIRING EXCHANGE BLOOD TRANSFUSION AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL Authors: Karabo P. Seake, MBChB; Sithembiso Velaphi MBChB, FC Paed, MMed

1**A research report submitted to the faculty of health Sciences, University of Witwatersrand,Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of paediatrics** and child health **Johannesburg,** 2015 **DECLARATION I** Karabo Pertunia Seake **declare that this research report is my own work. It** has been **submitted for the degree of Master of Medicine in the branch of Paediatrics** and Child Health **in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.** Signature_____ Signed **on** this _____**day of**_____,

2015 ACKNOWLEDGEMENT I would like to take this this opportunity to thank my supervisor Prof S Velaphi, for guiding me through this journey. For his patience and selflessness. My entire family for believing in my abilities. ABSTRACT: Background: Severe hyperbilirubinaemia (SHB) requiring exchange blood transfusion (EBT) continues to be a problem despite use of anti-D immunoglobulin and kinder-gentle approach in its management. Knowing features of infants with SBH might assist in its prevention. Objectives: To determine features, presentation and outcome of infants with SHB. Methods: We conducted review of records of infants admitted at Chris Hani Baragwanath Academic Hospital with SHB requiring EBT in 2009-2013. Descriptive analysis of characteristics, clinical presentation, laboratory findings, and outcome at discharge was performed. Results: Out of 150 patients who received EBT, 101 (67.3%) had records available for review. Majority were born vaginal (86.1%), weighed ≥2500g (65.4%), exclusively breastfed (82%) and were outpatients (66.3%). High proportion of outpatients were born at clinic (68.7% vs 5.9%, p<0.001), vaginally (92.5% vs 73.5%, p=0.009), male (62.6% vs 38.3%, p=0.020), weighing ≥2500g (76.1% vs 44.1%, p=0.001) than inpatients. Median postnatal age at EBT was 5days. Clinical presentation was suggestive of acute bilirubin encephalopathy (ABE) in 25%. Among mother-infant pairs with known blood groups 57% and 9% had ABO- and Rh-incompatibility respectively. Common abnormal laboratory findings post-EBT were thrombocytopaenia (77%), hypercalcaemia (55%) and anaemia (36%). A total of six patients (6%) died, all within 7days of EBT, but none during EBT. Deaths had a higher serum bilirubin than survivors (623±100 vs 498±136 mmols/l, p<0.001). Common causes of deaths were ABE (n=3) and sepsis (n=2). Conclusion Majority of patients with SHB were vaginal term births, exclusively breastfed from home or clinic-referrals, and had ABO incompatibility. SHB

14**is associated with significant morbidity and mortality.**

INTRODUCTION Neonatal jaundice due to unconjugated hyperbilirubinaemia remains one of the common clinical conditions that clinicians working with neonates encounter on a daily basis [1] . It is the leading cause of hospital readmissions during the neonatal period [2]. Severe hyperbilirubinaemia (SHB) at levels requiring

19**exchange blood transfusion (EBT) is associated with serious**

8**morbidity and mortality if left untreated**

or if treatment is delayed [3]. Unconjugated hyperbilirubinaemia is known to be a neurotoxin that can lead to significant neuronal damage [4]. Clinically it present acutely with signs of acute bilirubin encephalopathy (ABE) characterized by lethargy, abnormal tone, poor feeding, high pitched cry, seizures, opisthotonus and apnoeas, with mortality risk of 7%-10% [4]. Chronic hyperbilirubinaemia at the other end of the clinical spectrum ,clinically,

20athetoid cerebral palsy, sensorineural hearing loss, impaired upward gaze[

4]. Therefore it is important to characterize neonates who develop SHB so that it can be prevented, in order to avoid neuronal injury due to bilirubin. There are

8a number of factors that have been associated with development of

unconjugated hyperbilirubinaemia and these include early discharge, blood group incompatibilities, infections and cephalohaematoma[5]. Early postnatal discharge has become a common phenomenon in the world, with the escalation seen in the 1990's [2]. In the developing countries, where the health care facilities are overwhelmed, early postnatal discharge has also become a common practice, for example in our local setting the mothers and newborns are discharged as early as 6 hours post normal vaginal delivery if they are both well. Though there are many benefits for early discharged like early family bonding or attachment, reducing exposure to hospital-acquired infections and less financial cost associated with hospitalisation, the down side to it is that it is associated with an increase in neonatal readmissions with jaundice accounting for up to 50 % of readmissions [2]. Haemolytic disease secondary to ABO and Rh incompatibility is another major risk factor for development of SHB. In a study from South Africa in the early 1980's, it was found that ABO incompatibility lead to severe jaundice in 41.7% of cases and lead to EBT in 44.4% of infants [6]. Phototherapy is the treatment modality of choice for NNJ, it thought to

15reduce the serum bilirubin by 25%- 50% during its initial phase

and EBT reserved for those

15who fail to respond to the phototherapy,

at risk of bilirubin neurotoxity or those presenting with ABE [7]. EBT has decreased globally due to development of anti-D immunoglobulins, intensive phototherapy and use of guidelines for monitoring and managing infants at risk for jaundice [5]. The EBT can be associated with serious complication, such as apnoea, necrotizing enterocolitis, hypotension, seizures, arrhythmias, cardiac arrest and death [8]. In this study we sought to describe features and short-term outcomes of neonates with severe hyperbilirubinaemia requiring EBT during an era of early discharge. METHODS Study Design: It was a retrospective descriptive study. Study Population: All neonates (postnatal age <29 days) admitted at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2009 to December 2013 with hyperbilirubinaemia and received EBT were included in this study. Study Procedures: Names of infants who were issued with blood for EBT were requested from the local blood bank. In addition, patient registers in paediatric and neonatal wards were reviewed for names of patients who received EBT. The names and hospital numbers of patients who had EBT were used to retrieve the clinical and laboratory records. ; and to get biochemical and haematological blood results, maternal and infant blood groups and Coombs results from the laboratory and blood bank. Data collected from clinical records included demographic characteristics, anthropometric parameters, feeding, clinical signs

21at presentation, and outcome at time of discharge; and

from the laboratory we collected data on maternal and infant blood groups, Coombs, haemoglobin, platelets, calcium and magnesium. Data analysis: Data was entered into an Excel spreadsheet, and after cleaning it was imported into a statistical program, Statistica version 12.0 for analysis.

27Patients were divided into two groups, inpatients group,

that is those who required EBT while still in hospital before discharge after delivery; and outpatients, that is

those who had gone home after delivery. The means and standard deviations, medians and 25th -75th centile were used for summarized description of

24**continuous variables. Categorical variables** were described using **frequencies and percentages.** Comparison was **performed**

between inpatient and outpatient group using a

25**Chi-square or Fisher exact test**

11**for categorical variables, and Student t-test or Mann-Whitney U test for** continuous **variables. Differences were considered to be significant if** the **p-value**

was <0.05. RESULTS A total of 150 patients had EBT performed over the five year period, from January 2009 to December 2013, an average of 30 EBTs per year. A total of 101 patients' files were available for review. Among the 101 patients, 34 (33.6%) were inpatients (had not been discharged after birth), and 67 (66.4%) were outpatients, came in as self-referrals or referred by the local clinics. Maternal and infants characteristics The maternal and infant demographic, anthropometry, age at EBT, type of milk feeds and maternal blood groups are presented in Table 1. The majority of infants (92.1%) were born to African mothers. The average maternal age was 26.7±6.8 years and 28 (37.3%) mothers were primigravida. Overall, 93 (92.1%) delivered in a healthcare facility, 87 (86.1%) vaginally, 66 (65.4%) weighed ≥2500 grams and 83 (82.2%) were exclusively breastfed. Nine (10.5%) and 54 (66.7%) mothers were Rh negative and blood group O respectively. In comparing the inpatient and outpatient groups, the outpatient group had a higher proportion of patients born at the clinic (68.7% vs 5.9%, p<0.001), vaginally (92.5% vs 73.5%, p=0.009), were males (62.6% vs 38.3%, p=0.020), weighed ≥2500g (76.1% vs 44.1%, p=0.001), and were older (median age 6 vs 4 days, p=0.004) than inpatient group. Among the 101 infants who had blood transfusion, 23 (27%) had positive Coombs results. Five of these (22%) were due to Rh incompatibility and 18 (78%) were due to ABO incompatibility. Clinical signs at presentation in patients who required exchange blood transfusion Twenty five (24.8%) patients who needed an exchange blood transfusion had signs suggestive of acute bilirubin encephalopathy (ABE) (Table 2). Outpatient group accounted for most of the patients who presented with these signs at 88%. The clinical signs noted and 8 considered to suggest encephalopathy were abnormal tone (n=18, 17.8%), lethargy (n=17, 16.8%), apnoea (n=9, 8.9%), opisthotonus (n=4, 4.0%) and irritability (n=1, 1%). Infants with clinical signs had higher serum bilirubin levels than those without (579±145 vs 483±128 mmols/l, p=0.002). Maternal and infant Rhesus blood group in those receiving exchange blood transfusions Among the 86 mothers with known Rh blood group, nine (10.5%) were Rh negative, and eight of their infants were Rh positive, thus eight of the 86 (9.3%) mother infant pairs with known Rh results had Rh incompatibility. Five of the eight infants with Rh incompatibility had a positive Coomb results (62.5%) (Table 3). Eight of the infants born to mothers who were Rh negative were outpatients, and seven of these were born at the local clinic and one in hospital. Parity of mothers who were Rh negative was known for seven mothers and five of these seven (71%) had previous pregnancies. Among the 23 mother-infant pairs who were both Rh positive, nine (39%) were Coombs positive, and of these nine, two were ABO incompatible (mother O/ infant A and other mother O and infant B), suggesting that the other 7 were due to incompatibility from minor blood groups. The ABO blood groups of mothers and infants requiring EBT Table 4, illustrate maternal ABO blood groups against infant's ABO blood groups and possible incompatibilities as shown by the underlined numbers and those with positive Coombs test shown by numbers in parenthesis. Among the 81 mothers with known ABO blood group 54 (66.7%) were blood group O, 14 (17%) blood group B and 12 (15%) blood group A. Fifty seven (70%) of the 81 mother infant pairs with known results were ABO incompatible. The common ABO incompatible groups were mother O/ infant B, 30/57 (53%), mother O/ infant A, 17/57 (30%), and mother B/ infant A, 4/57 (7%). Eighteen of the 57 (32%) infants who had ABO incompatible were Coomb positive, with 37% of the mother O/ infant B and 23% of mother O/ infant A having positive Coombs. Bilirubin results before EBT and calcium, magnesium, phosphate, haemoglobin and platelets after EBT The majority of infants (65%) who required an EBT were infants with birthweight above 2500 gram, and had median serum bilirubin level of 544mmol/L before EBT

(Table 5). Hypercalcaemia (total serum calcium >2.75 mmols/L) was noted in 55% and hypocalcaemia (total serum calcium <1.75) in 1% of all patients post-transfusion. Eighteen percent had hypomagnesaemia (serum magnesium <0.65 mmols/L). Only 7% had hypoglycaemia and 29% had hyperglycaemia amongst the whole group. Common haematological abnormalities post-transfusion were thrombocytopaenia (platelet count <150 x 109/L) (77%) and anaemia (haemoglobin <13 g/dL) (36%). Mortality rate among the patients

26who received exchange blood transfusion The median

age at discharge or death was 7 days with 25th and 75th percentile at 6 and 11 days. Of 101 patients that had EBT, 6 patients died before hospital discharge giving a mortality rate of 6%. All deaths weighed >2000 grams, and were outpatients (Table 6). The age at exchange was 2-15 days, 3 were ABO incompatible, with serum bilirubin levels of 441-722 mmols/l. None of these infants died during the procedure of EBT. Three were assessed to have died from acute bilirubin encephalopathy, two of these were noted to have clinical signs of acute bilirubin encephalopathy on admission before EBT. Two were assessed to have died from sepsis post-exchange transfusion. DISCUSSION Neonatal jaundice it is a benign condition in majority of cases, when it is severe it can be fatal and among the survivors it can be associated with severe morbidity. With screening and close monitoring of those at risk, and implementing effective treatment modalities, namely phototherapy and EBT the morbidity and mortality associated with hyperbilirubinaemia has been significantly reduced [9]. Even though EBT reduces morbidity associated with severe hyperbilirubinaemia, if its performance is delayed these adverse outcomes may not be avoided. Therefore it is important that those who are at risk of severe hyperbilirubinaemia are identified and monitored closely, or are referred to the facility where they can be monitored if they cannot be monitored at the local facility. The policy of early discharge often makes it difficult to closely monitor those at risk of hyperbilirubinaemia in hospital, thus

22the American Academy of Pediatrics, recommends that if

infants are discharged early (less than 48 hours of life), they must have postnatal assessment at 48-72 hours after discharge and this should be conducted by a professional[10]. In developing countries, this postnatal assessment is not always possible for all babies because of limited resources, thus it is still important to identify those at risk of developing severe hyperbilirubinaemia so that the limited staff can focus in this group or an exception is made to keep them in hospital for longer period. Thus in this study we aimed to identify features of infants with hyperbilirubinaemia requiring EBT in a setting where the policy of early discharge is followed. The main findings in this study is that about two-thirds of patients with hyperbilirubinaemia requiring EBT were outpatients. Overall, most patients were either born in hospital or clinic for both inpatients and outpatients suggesting that there was an opportunity to identify those who were at risk of developing hyperbilirubinaemia. More than 90% of those who were 11 outpatients were born vaginally suggesting that they were discharged early as the current policy in the setting where this study was done is that well vaginally delivered infants are discharged by 24 hours while those born by caesarean section are kept for at least 48 hours. Exclusive breastfeeding was noted in more than 80% of patients. Rhesus and ABO incompatibility was noted in 10% and 70% respectively among those with known blood groups which was at least 80% of all the patients who received EBT. About a quarter of patients presented with signs suggestive of acute bilirubin encephalopathy. The mortality rate was high at 6% and none of the deaths occurred during the time of the procedure of EBT. More patients being born vaginally suggests that the outpatients were discharged early. Early discharge of newborn infants has been reported to contribute to an increase in the readmission rates of neonates, with jaundice contributing to 50% of the readmitted infants [2]. One study reported that 69% of severely jaundiced babies were readmissions, with 38% and 87% having been discharge within 24 hours and 72 hours post-delivery respectively[11]. Association between breastfeeding and jaundice has been well recognized, the breastfed

14infants are three times more likely to be

jaundiced and

17six times more likely to develop severe jaundice as compared to formula

fed

counterparts [12]. This means even if screening is done before discharged, if patients are discharged early, those who are breastfed might still be missed as some of them might develop jaundice later. Just over 70% of mothers who were Rh negative had previous pregnancy, this suggests failure in administering anti-D immunoglobulin with previous pregnancy or inadequate monitoring of Rh negative mothers during pregnancy. The incidence of ABO incompatibility of 70% in this study was high compared to that of 15.7% of those needing EBT and 44.4% of all jaundiced patients in the study of Vos et al [6] while Rh incompatibility contributed only 3.2% of all the EBT [6]. The common ABO incompatibilities were the mother O/ infant B (52.6%), and mother O/ infant A (29.8%). The high number of patients with signs of ABE is of major concern as many of these are most likely to develop neurologic deficit and also highlights the need for

8long-term follow up of patients with

severe hyperbilirubinaemia. Common complications related to EBT were mainly biochemical and haematological. This finding is similar to those reported in other studies [13]. Recent study from an institution similar to where this study was conducted, using the similar protocols on EBT reported similar complications [14]. Hypercalcaemia was most likely iatrogenic as calcium gluconate was added to blood during the exchange as part of the protocol of EBT. A total of six patients died within a week of EBT, giving a mortality rate of about 6%. Three of the deaths were assessed to be related to acute bilirubin encephalopathy, highlighting the dangers of severe hyperbilirubinaemia. Two died from sepsis again highlighting the importance of preventing severe hyperbilirubinaemia as hospitalization or performance of the procedure might have exposed these infant to sepsis. Severe hyperbilirubinaemia was associated with high mortality of 6%. This mortality is higher than that of 4% reported by Rugamba et al[14]and lower than that reported by Ibekwe et al who reported 17.5%; and both studies were from developing countries[15]. Limitation of this study is that it was a retrospective study, therefore among the patients who received EBT about a third of their files were missing and we were unable to assess whether the infants were discharged early or not post-delivery. Our conclusion is that severe hyperbilirubinaemia requiring EBT is most likely related to early discharge of newborn infants who have not yet establish breastfeeding; and that ABO incompatibility plays a major role in development of severe jaundice. We recommend that all pregnant women should have ABO blood group typing in addition to Rh group typing during antenatal care. Infants at risk of blood group incompatibility, namely infants

23born to mothers who are Rh negative or blood group O,

should not be discharged before 48 hours or until their blood groups are known. Newborn infants should not be discharged before 24 hours or at least until there is adequate flow of breast milk and/or that the infant is breastfeeding well.

8Long term follow-up of all patients with

severe hyperbilirubinaemia should be conducted, as a quarter of patients presented with signs of acute bilirubin encephalopathy therefore at risk of developing neurologic deficit. TABLES Table 1: Maternal and infant characteristics of patients who needed an exchange blood transfusion. All (n=101) Inpatients (n=34) Readmissions (n=67) p-value Race Black Coloured 93 (92.1%) 3 (7.9%) 31 (91.2%) 3 (8.8%) 62 (92.5% 5 (7.5%) 0.819 Maternal age (years) * 26.7 ± 6.8 26.9±6.9 27±6.7 0.496 Maternal gravidity <2 2-4 >4 28 (37.3%) 41 (54.7%) 6 (8.0%) 15 (44.1%) 16 (47.1%) 3 (8.8%) 13 (31.7%) 25 (61.0%) 3 (7.3%) 0.353 Place of birth Hospital Clinic Born before arrival 47 (46.5%) 48 (47.5%) 6 (5.9%) 30 (88.2%) 2 (5.9%) 2 (5.9%) 17 (25.3%) 46 (68.7%) 4 (6.0%) <0.001 Mode of delivery Caesarean section Vaginal delivery 14 (13.9%) 87 (86.1%) 9 (26.5%) 25 (73.5% 5 (7.5%) 62 (92.5%) 0.009 Sex Female Male 46 (45.5%) 55 (54.4%) 21 (61.7%) 13 (38.3%) 25 (37.3%) 42 (62.6%) 0.020 Gestational age* ≤37 weeks >37 weeks 37.2 ± 2.4 51 (50.5%) 50 (49.5%) 36.4±3.4 19 (55.9%) 15 (44.1%) 37.5±1.6 32 (47.8%) 35 (52.2%) 0.441 Birth weight* <2500 grams ≥2500 grams 2701 ± 614 35 (34.6%) 66 (65.4%) 2522± 850 19 (55.9%) 15 (44.1%) 2792 ±429 16 (23.9%) 51 (76.1%) 0.001 Feeds Breast feeding Formula feeding 83 (82.2%) 10 (9.9 %) 26 (76.5%) 3 (8.8%) 57 (85.0%) 7 (10.5%) 0.273 Mixed feeding 8 (7.9 %) 5 (14.7%) 3 (4.5%) Median age at exchange in

days† 5 (4-7) 4 (4-7) 6 (4-7) 0.004 Maternal Rh group Rh Negative Rh Positive 9 (10.5%) 77 (89.5) 1 (3.0%) 32 (97.0%) 8 (15.1%) 45 (84.9%) 0.076 Maternal ABO group A B O AB 12 (14.8%) 14 (17.3%) 54 (66.7%) 1 (1.2%) 5 (18.5%) 4 (14.8%) 18 (66.7%) 0 7 (13.0%) 10 (18.5%) 36 (66.7%) 1 (1.8%) 0.797 * = Mean ± SD; † = Median (25 – 75th centile) Table 2 Clinical signs in patients receiving exchange blood transfusion Total Inpatients Readmitted (n=101) (n = 34) (n=67) Asymptomatic, except jaundice 76 (75.2%) 31 (91.2%) 45 (67.2%) Symptomatic with signs other than jaundice Abnormal tone Lethargy Apnoea Opisthotonus Irritability 25 (24.8%) 18 (72.0%) 17 (68.0%) 9 (36.0%) 4 (16.0%) 1 (4.0%) 3 (8.8%) 2 (66.7%) 3 (100%) 1 (33.3%) 0 1 (33.3%) 22 (32.8%) 16 (72.7%) 14 (63.6%) 8 (63.6%) 4 (18.2%) 0 Table 3: Rhesus blood group of mothers and infants receiving exchange blood transfusion Mothers Total Rh positive Rh negative Rh unknown Infant Rh positive 23 (9, 39%)* 8 (5, 62.5%)* 5 36 Rh negative 0 1 0 1 Rh not recorded 54 0 10 64 Total 77 9 15 101 * = Positive coombs Table 4. ABO blood groups of mothers and infants who received exchange blood transfusion Maternal ABO Blood Groups A B O AB Total Infant's ABO Blood Group A 7 4$ 17$ 1 21$/ 29 (3, 75%)* (4, 23%)* (7/21, 33%) * B 1$ 4 30$ 0 31$/35 (2, 50%)? (11, 37%)* (11/31, 32%)* O 3 4 (1, 25%)* 5 0 0/12 AB 1$ 2$ 2$ 0 5$/5 Total 12 (15%) 14 (17%) 54 (67%) 1 (1%) 57$/81 (70%) (18/57, 32%)* $ - Underlined numbers are ABO incompatible pairs, * - Number in parenthesis represents number and percentage with positive Coomb results Table 5: Serum bilirubin before EBT and calcium, magnesium, glucose, haemoglobin and platelets at end of EBT. All <1500 (n=4, 4%) 1500-1800 (n=5, 5%) Birthweight 1801-2500 (n=26, 26%) >2500 (n=66, 65%) Median SB before EBT (25-75th centile) 508 (435-595) 249 (182-404) 398 (307-426) 482 (400-531) 544 (475-614) Serum Calcium (mmol/L) - <1.75 - 2-2.75 - >2.75 1 (1%) 33 (43%) 42 (55%) 0 4 (100%) 0 0 1 (50%) 1 (50%) 0 8 (35%) 15 (65%) 1 (2%) 20 (43%) 26 (55%) Serum Magnesium (mmol/L) - <0.65 - ≥0.65 14 (18%) 65 (82%) 1 (25%) 3 (75%) 2 (40%) 3 (60%) 4 (17%) 19 (83%) 7 (15%) 40 (85%) Serum Glucose (mmol/L) - <2.6 - 2.6-8 - >8 7 (7%) 65 (64%) 29 (29%) 0 2 (50%) 2 (50%) 0 3 (60%) 2 (40%) 2 (8%) 20 (77%) 4 (15%) 5 (7%) 40 (61%) 21 (32%) Haemoglobin (g/dL) - <13 - 13-18 - >18 Platelets (x109/L) 29 (36%) 50 (63%) 1 (1%) 1 (25%) 3 (75%) 0 1 (20%) 4 (80%) 0 8 (33%) 15 (62%) 1 (4%) 19 (40%) 28 (60%) 0 - <150 - 150-450 - >450 62 (77%) 16 (20%) 2 (3%) 4 (100%) 0 0 3 (60%) 2 (40%) 0 16 (67%) 6 (25%) 2 (8%) 39 (83%) 8 (17%) 0 Table 6: The features of infants who died in hospital among the infants who had EBT Birth weight GA Sex Age at EBT (days) ABO Inc. Serum bilirubin (mmol/l) Rh Inc. Relation to EBT Cause of death Days in relation to post-EBT 2540g 37, M 11 Yes 567 U No ABE 3 2470g 36, F 2 Yes 478 No No Nosoc. Sepsis 7 2550g 38, F 5 No 643 No No HCOM 1 2430g 37, M 6 Yes 441 No No ABE, Sepsis 5 2900g 40, M 4 No 722 No No DIC, Sepsis 1 2540g 37, M 15 U 620 U No ABE 2 GA – Gestational age, Inc. – Incompatibility, Nosoc.- Nosocomial, ABE – Acute bilirubin encephalopathy, HCOM- Hypertrophic cardiomyopathy, DIC- Disseminated intravascular coagulation REFERRENCES 1.

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