Exchange blood transfusion for hyperbilirubinaemia: Neonatal characteristics and short-term outcomes

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Background. Factors that have been associated with severe hyperbilirubinaemia requiring exchange blood transfusion (EBT) are early discharge, late preterm birth and haemolytic disease. Early discharge is a common practice in neonatal care, so it is important to identify and audit neonates who received EBT, in order to identify modifiable factors.
Objectives. To describe the characteristics and outcomes of infants requiring EBT.
Methods. We reviewed records of infants admitted with severe jaundice requiring EBT from January 2009 to December 2013. Descriptive analysis of characteristics, clinical presentation, laboratory findings and outcome at discharge was performed.
Results. A total of 150 neonates received EBT (30 per year), and 101 were reviewed. Of these, 34 (33.7%) were inpatients and 67 (66.3%) were new admissions (2.34/1 000 new admissions). The majority of neonates requiring EBT were born vaginally (86.1%), were late preterm births (20.8%) and were exclusively breastfed (82.2%). The median postnatal age at presentation was 5 days. Clinical signs suggestive of acute bilirubin encephalopathy were present in 24.8% of cases. Among mother-infant pairs with known blood groups, 9.3% and 70.4% had rhesus (Rh) and ABO incompatibility, respectively. A Coombs test was positive in 62.5% of those with Rh incompatibility compared with 31.7% of those with ABO incompatibility. A total of 6 patients (5.9%) died, all within 7 days of EBT, but none during EBT.
Conclusion. The majority of neonates requiring EBT presented post discharge after birth and had been born vaginally at term, suggesting early discharge after delivery. More than two-thirds of cases were related to ABO incompatibility. Screening for jaundice before discharge must be prioritised, especially for infants born to mothers who are Rh negative or ABO blood group O.

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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] Hyperbilirubinaemia at levels requiring exchange blood transfusion (EBT), which is often called severe hyperbilirubinaemia (SHB), 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] Clinically it can present acutely with signs of acute bilirubin encephalopathy (ABE) characterised by lethargy, abnormal tone, poor feeding, a high-pitched cry, seizures, opisthotonus and apnoea, with a mortality risk of 7 - 10%.[4]

A number of factors have been associated with SHB, including early discharge, late preterm birth, blood group incompatibilities, and infections.[5] Early postnatal discharge has become common all over the world, with the escalation seen in the 1990s.[2] In South Africa (SA), where healthcare facilities are overwhelmed with high numbers of patients, early postnatal discharge has also become a common practice, with some hospitals discharging neonates as early as 6 hours after normal vaginal delivery. Early discharge is associated with an increase in neonatal readmissions, with jaundice accounting for up to 50% of these.[2] Late preterm infants have been reported to have an increased incidence of hyperbilirubinaemia, with odds three times higher than for term infants.[6-8] Hyperbilirubinaemia has been observed in 14 - 29% of late preterm infants in the first week of life.[9-11] Haemolytic disease of the newborn secondary to ABO and/or rhesus (Rh) incompatibility is another major risk factor for development of SHB. Some studies have reported that 14 - 44% of neonates requiring EBT had Rh and ABO incompatibility.[12,13]

EBT has been associated with serious complications such as apnoea, necrotising enterocolitis, hypotension, seizures, arrhythmias, cardiac arrest and death, so it should be reserved for neonates who fail to respond to phototherapy and those at risk of bilirubin neurotoxicity or presenting with ABE.[14,15] It is therefore important to characterise neonates who develop SHB so that it can be prevented, in order to avoid neuronal injury due to bilirubin and EBT-associated mortality. In this study we sought to measure the burden of this disease, and to describe characteristics and outcomes at hospital discharge of neonates with SHB requiring EBT.

Methods

Study design

This was a retrospective descriptive study. Registers of blood requests for EBT from the Department of Paediatrics over a 5-year period were requested from the South African National Blood Services (SANBS) based at Chris Hani Baragwanath Academic Hospital (CHBAH). A period of 5 years was estimated to be able to provide adequate numbers to achieve the objectives of the study. Registers from 2009 to 2013 were made available by SANBS.

Study population and setting

All neonates (postnatal age <29 days) admitted from 1 January 2009 to 31 December 2013 were eligible. We included all neonates who were born at and/or admitted to CHBAH during this time period who

developed or presented with SHB, defined as hyperbilirubinaemia requiring EBT as decided by the attending paediatrician.

Study setting

CHBAH is a tertiary public hospital in Johannesburg. It serves the community of Soweto and surrounding areas and is a referral centre for local Soweto clinics and hospitals in the southern part of Gauteng Province. The Department of Paediatrics is divided into two major clinical service areas, neonatology and general paediatrics. Neonates who have been discharged for more than 24 hours or were born at home or in a clinic and need admission after 24 hours are all admitted to and managed in the general paediatric wards.

The decision to manage hyperbilirubinaemia with EBT was based on the 2006 SA guidelines on the management of neonates with hyperbilirubinaemia.[16] Neonates who required EBT and presented with acute signs suggestive of encephalopathy, namely lethargy, apnoea, tone abnormalities and irritability, were classified as having ABE. EBT was performed through withdrawal and infusing aliquots of 5 - 20 mL of blood at a time, depending on the weight of the infant. Double the patient's blood volume was exchanged over a period of 1 - 2 hours. The procedure was performed either through the umbilical vein for both withdrawal of the patient's blood and infusion of donor blood, or using an arterial-venous approach with the patient's blood withdrawn from the radial artery and donor blood infused through the peripheral vein. Donor blood was warmed through a blood-warming coil before being infused. A registered nurse assisted during the procedure, monitoring the patient's condition and recording the volume of blood withdrawn and infused.

Study procedure

Names of infants who were issued with blood for EBT were retrieved from the registers requested from the local SANBS. In addition, patient registers in the 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. Data collected from clinical records included demographic characteristics, anthropometric parameters, clinical signs at presentation, and outcome at the time of hospital discharge. From the laboratory records we collected data on maternal and infant ABO and Rh blood groups, and infants' serum bilirubin level at presentation, Coombs test results, and full blood count and blood culture results. Neonates were grouped as either inpatients (were in hospital when the diagnosis of SHB was made) or outpatients or new admissions (not in hospital at the time of diagnosis, i.e. either from home or local clinics). The study was conducted after obtaining approval from the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. MP140482).

Statistical analysis

Data were entered into an Excel spreadsheet, Office 365 (Microsoft Corp., USA) and subsequently imported into a statistical programme, Statistica version 12.0 (Tibco Software Inc., USA) for analysis. Means and standard deviations (SDs) were used to summarise descriptions of continuous variables. Categorical variables were described using frequencies and percentages. Comparison was performed between the inpatient and outpatient groups using the χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test or the Mann-Whitney *U*-test for continuous variables. Differences were considered to be significant at $p<0.05$.

Results

A total of 150 neonates had EBT performed over the 5-year period 1 January 2009 - 31 December 2013, an average of 30 EBTs per year. A total of 101 patient files were available for review. Of the 101 patients, 34 (33.6%) were inpatients and 67 (66.4%) were outpatients and were therefore admitted to the general paediatric wards. All the inpatients were neonates who were in the neonatal unit and had not been discharged after birth. There were 28 664 new admissions in the general paediatric wards over the study period, giving an incidence of SHB of 2.34 cases/1 000 admissions.

Maternal and infant characteristics

The characteristics of the mothers and their infants are presented in Table 1. The majority of infants (92.1%) were born to black African mothers. The mean (SD) maternal age was 26.7 (6.8) years. Overall, 92.1% of mothers delivered in a healthcare facility, with the majority delivering vaginally and the majority of infants exclusively breastfed. Of the infants, 65.3% weighed ≥2 500 g and 72.3% were born at term (>36 weeks); 20.8% were late preterm births (34 - 36 weeks). All the 67 outpatients were referred from the local clinics for EBT, with none being referred from other hospitals. Of the neonates who needed EBT, 24.8% had clinical signs other than jaundice. Most of the patients with clinical signs other than jaundice were referred by local clinics. The clinical signs noted were abnormal tone, lethargy, apnoea, opisthotonus and irritability. Infants who had clinical signs had higher serum bilirubin levels than those without these signs (mean (SD) 579 (145) mmol/L v. 483 (128) mmol/L; $p=0.002$). The differential diagnosis in patients with these signs was sepsis, but none of them had positive cultures, and only 8% had an abnormality (thrombocytopenia, defined as a platelet count $<100 \times 10^9$/L) in the full blood count. The mean (SD) serum bilirubin level of patients who required EBT was 507 (138) mmol/L, and 73.3% presented with serum bilirubin levels >425 mmol/L.

Maternal and infant Rh and ABO blood groups

Maternal and infant blood groups are presented in Table 2. Of the 86 mothers with a known Rh blood group, 9 (10.5%) were Rh negative, and 8 of their infants were Rh positive, so 8 of the 86 mother-infant pairs with known Rh results (9.3%) had Rh incompatibility. Five of the 8 infants with Rh incompatibility (62.5%) had a positive Coombs test. Eight of the infants born to mothers who were Rh negative were outpatients, of whom 7 were born at the local clinic and 1 in hospital. Parity of mothers who were Rh negative was known for 7 mothers, of whom 5 (71.4%) had had previous pregnancies. Of the 81 mothers with a known ABO blood group, 54 (66.7%) were blood group O and 32.1% were group A or B. Fifty-seven (70.4%) of the 81 mother-infant pairs with known results were ABO incompatible. The common ABO-incompatible groups were mother O/infant B ($n=30/57$; 52.6%) and mother O/infant A ($n=17/57$; 29.8%). Eighteen of the 57 infants in the ABO-incompatible group (31.6%) were Coombs positive.

Comparing inpatients and outpatients (new admissions)

Characteristics of the inpatients and outpatients are compared in Table 3. The outpatient group had higher proportions of infants born at a clinic (68.7% v. 5.9%; $p<0.001$), vaginal deliveries (92.5% v. 73.5%; $p=0.009$), male infants (62.6% v. 38.3%; $p=0.020$), infants born at term (81.6% v. 55.1%; $p=0.004$), and older infants (median age at EBT 6 days v. 4 days; $p=0.004$) than the inpatient group.

Table 1. Maternal and infant characteristics of neonates who received EBT (*N*=101)

Characteristics	*n* (%)*
Black African	93 (92.1)
Maternal age (years), mean (SD)	26.9 (6.9)
Place of delivery	
Hospital	47 (46.5)
Clinic	48 (47.5)
Home	6 (5.9)
Delivery mode, sex and feeding	
Vaginal delivery	87 (86.1)
Sex male	55 (54.4)
Breastfeeding	83 (82.2)
Gestational age (weeks)	
<34	7 (6.9)
34 - 36	21 (20.8)
>36	73 (72.3)
Mean (SD)	37.2 (2.4)
Birthweight (g)	
<1 800	9 (8.9)
1 800 - 2 499	26 (25.7)
≥2 500	66 (65.3)
Mean (SD)	2 701 (614)
Postnatal age at EBT (days)	
<3	22 (21.6)
3 - 7	64 (62.8)
>7	16 (15.7)
Mean (SD)	5.8 (2.6)
Referral	
Not referred (inpatients)	34 (33.7)
Self-referrals	0
Referred from clinic	67 (66.3)
Referred from another hospital	0
Clinical signs	
Asymptomatic except jaundice	76 (5.2)
Symptomatic with signs other than jaundice	25 (24.8)
Abnormal tone	18 (72.0)
Lethargy	17 (68.0)
Apnoea	9 (36.0)
Opisthotonus	4 (16.0)
Irritability	1 (4.0)
Serum bilirubin levels (mmol/L)	
<255	1 (1.0)
255 - 340	4 (4.0)
340 - 425	22 (21.8)
>425	74 (73.3)
Mean (SD)	507 (138)

EBT = exchange blood transfusion; SD = standard deviation.
*Except where otherwise indicated.

Mortality rate among the patients who received EBT

Characteristics of the infants who died are presented in Table 4. The median age post admission at discharge or death was 7 days. Six infants died before hospital discharge, giving a mortality rate of 5.9%. All the infants who died weighed >2 000 g, and were outpatients. The age at EBT ranged from 2 to 15 days, 3 were ABO incompatible, and serum bilirubin levels ranged from 441 to 722 mmol/L. None of the infants died during the EBT procedure. All except 1 of those who died had signs of ABE on admission, so 5 (20.0%) of 25 who had ABE on admission died, compared with only 1 (1.3%) of the 76 who did not have signs of ABE ($p<0.001$).

Discussion

The main findings of this study were that about two-thirds of neonates with hyperbilirubinaemia requiring EBT were outpatients, giving an incidence of 2.34/1 000 admissions in general paediatric wards. Overall, of both inpatients and outpatients, most were born in hospital or a clinic. More than 90% of those who were outpatients were born vaginally. More than 80% of the infants were exclusively breastfed. Rhesus and ABO incompatibility was noted in 9.3% and 70.4%, respectively, among those with known blood groups, i.e. ~80% of all the patients who received EBT had blood group incompatibility. A quarter of the patients presented with signs suggestive of ABE. The mortality rate was high at nearly 6%, and none of the deaths occurred during the EBT procedure.

With most patients being born in hospital or a clinic, for both inpatients and outpatients, there was an opportunity to identify those who were at risk of developing hyperbilirubinaemia. 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 readmission rates, with jaundice contributing to 50% of the readmissions.[2] One study reported that 69% of severely jaundiced babies were readmissions, with 38% and 87% having been discharged within 24 hours and 72 hours after delivery, respectively.[17] The rate of readmission due to neonatal jaundice was noted to be significantly high if discharge was within 24 hours of delivery.[18] An association between breastfeeding and jaundice is well recognised, with breastfed infants three times more likely to be jaundiced and six times more likely to develop severe jaundice compared with their formula-fed counterparts.[19] This means that even if screening is done before discharge, if patients are discharged early, those who are breastfed may still be missed as some of them could develop jaundice later. Some of the patients who are discharged early may not have established adequate breastfeeding, therefore increasing the risk of jaundice.

Over two-thirds of the mothers who were Rh negative had had a previous pregnancy, suggesting failure in administering anti-D immunoglobulin with the previous pregnancy or inadequate monitoring of Rh-negative mothers during pregnancy. The 70% incidence of ABO incompatibility among neonates requiring exchange in this study is higher than the incidences of 12 - 28% reported from developed countries,[20,21] probably because of differences between screening ABO blood groups antenatally and monitoring patients for incompatibility post delivery. Contrary to our findings, other studies from low-resource countries have reported that Rh incompatibility contributes more highly than or equally to ABO incompatibility in neonates with SHB.[22-24] The high proportion of neonates requiring EBT who had ABO as opposed to Rh incompatibility in the present study is probably because the hospital protocol requires that all pregnant women are tested for Rh but not for ABO blood groups during antenatal care or at delivery, and that neonates born to Rh-negative mothers are kept in hospital for at least 48 - 72 hours and monitored for jaundice, irrespective of mode of delivery.

The cause of severe jaundice could be attributed to blood group incompatibility in 80% of our patients, and there was no identifiable cause in 20%. Other known causes of SHB include blood group incompatibility due to blood groups other than ABO or Rh, neonatal

Table 2. Proportion of neonates with Rh or ABO incompatibility

	Total, *N*	Incompatible, *n* (%)	
		Yes *n* (%)	No *n* (%)
Both mother and baby with known Rh results	86	8 (9.3)*	78 (90.7)
Both mother and baby with known ABO results	81	57 (70.4)†	24 (29.6)
Mother O	54	49 (90.7)	5 (9.3)
Mother B	14	6 (42.9)	8 (57.1)
Mother A	12	2 (16.7)	10 (83.3)

*Coombs test was positive in 62.5% of cases with Rh incompatibility.
†Coombs test was positive in 31.6% of cases with ABO incompatibility.

Table 3. Comparing inpatients and outpatients (new admissions) who received EBT (*N*=101)

Characteristics	Inpatients (*n*=34), *n* (%)*	Outpatients (*n*=67), *n* (%)*	*p*-value
Race			0.819
Black	31 (91.2)	62 (92.5)	
Coloured	3 (8.8)	5 (7.5)	
Maternal age (years), mean (SD)	26.9 (6.9)	27 (6.7)	0.496
Maternal gravidity			0.353
<2	15 (44.1)	13 (31.7)	
2 - 4	16 (47.1)	25 (61.0)	
>4	3 (8.8)	3 (7.3)	
Place of birth			<0.001
Hospital	30 (88.2)	17 (25.3)	
Clinic	2 (5.9)	46 (68.7)	
Born before arrival	2 (5.9)	4 (6.0)	
Mode of delivery			0.009
Caesarean section	9 (26.5)	5 (7.5)	
Vaginal delivery	25 (73.5)	62 (92.5)	
Sex			0.020
Female	21 (61.7)	25 (37.3)	
Male	13 (38.3)	42 (62.6)	
Gestational age (weeks), mean (SD)	36.4 (3.4)	37.5 (1.6)	0.004
<37	15 (44.1)	13 (19.4)	
≥37	19 (55.1)	54 (81.6)	
Birthweight (g)	2 522 (850)	2 792 (429)	0.001
<2 500	19 (55.9)	16 (23.9)	
≥2 500	15 (44.1)	51 (76.1)	
Feeds			0.273
Breastfeeding	26 (76.5)	57 (85.0)	
Formula feeding	3 (8.8)	7 (10.5)	
Mixed feeding	5 (14.7)	3 (4.5)	
Age at EBT (days), median (IQR)	4 (4 - 7)	6 (4 - 7)	0.004
Maternal Rh group			0.076
Rh negative	1 (3.0)	8 (15.1)	
Rh positive	32 (97.0)	45 (84.9)	
Maternal ABO group			0.797
A	5 (18.5)	7 (13.0)	
B	4 (14.8)	10 (18.5)	
O	18 (66.7)	36 (66.7)	
AB	0	1 (1.8)	

EBT = exchange blood transfusion; SD = standard deviation; IQR = interquartile range.
*Except where otherwise indicated.

sepsis, and red blood cell enzyme deficiencies. Except for sepsis, there was no record of minor blood group incompatibilities or other causes of jaundice having been investigated for in the cases reviewed in this study. Sepsis is common in the setting where this study was done, and although all the symptomatic patients had negative blood cultures, cultures have low sensitivity in diagnosing sepsis, so

Table 4. Features of infants who had EBT and died before discharge

Patient No.	Birth weight (g)	Gestational age (weeks)	Sex	Age at EBT (days)	ABO incom-patibility	Rh incom-patibility	Serum bilirubin at presentation (mmol/L)	Death related to EBT	Cause of death	Days post EBT (days)
1	2 540	37	Male	11	Yes	U	567	No	Encephalopathy	4
2	2 470	36	Male	2	Yes	No	478	No	Nosocomial sepsis	7
3	2 550	38	Female	5	No	No	643	No	Cardiomyopathy	1
4	2 430	37	Male	6	Yes	No	441	No	Encephalopathy, nosocomial sepsis	5
5	2 900	40	Male	4	No	No	722	No	Sepsis	1
6	2 540	37	Male	15	U	U	620	No	Encephalopathy	2

EBT = exchange blood transfusion; U = unknown.

sepsis cannot be excluded as a possible cause of SHB in this study. Prematurity is another possible cause, as 27% of patients in this study were born preterm, and prematurity has been associated with SHB.[9]

The high proportion of 25% of neonates presenting with signs of ABE is of major concern, as many of these are likely to develop neurological deficit, and this finding highlights the need for long-term follow-up of patients with SHB. This 25% incidence of ABE in neonates presenting with SHB is similar to the 22% reported by Hameed *et al*.,[25] but lower than the 49.3% reported by Ogunlesi *et al*.[26] Severe hyperbilirubinaemia was associated with high mortality of 6%. Our mortality rate is similar to studies at facilities where resources for offering advanced life support are available,[13,20] but lower than the rate of 17.5% reported from a setting in which facilities for advanced life support are limited.[27] Mortality in neonates requiring EBT may therefore be related to availability of facilities to monitor and manage them, and the severity of ABE at presentation, as most of deaths in the present study and that of Ibekwe *et al*.[27] were assessed as being due to ABE.

Study limitations

A limitation of this study is that it was a retrospective study. About a third of the files for patients who received EBT were missing, so we were unable to assess whether or not the infants were discharged early after delivery. It is therefore possible that the morbidity and mortality noted in the study could be an under- or an overestimate. The study also did not collect information on the duration of SHB or hospital stay. These could be used as a proxy in assessing the effect of SHB on neurological outcomes, as patients with severe ABE are likely to have difficulties with feeding and therefore to have a prolonged duration of hospital stay. The other limitation is that there was no follow-up information to assess long-term neurodevelopmental outcome.

Conclusion

Early discharge, being born vaginally and breastfed, and blood group incompatibility were frequent findings in neonates who required EBT. ABO incompatibility was a common blood group incompatibility. Screening of neonates for jaundice at the time of discharge, and ensuring that breastfeeding is fully established before discharge, may therefore prevent SHB.

We recommend that all pregnant women should have ABO blood group typing in addition to Rh group typing during antenatal care. Routine screening for hyperbilirubinaemia in the first 48 hours of life should be performed in high-risk infants, especially in those born to mothers whose ABO blood group is O or who are Rh negative. Newborn infants should not be discharged until they are feeding well and there is good flow of breastmilk, and if keeping the mother in hospital is not possible, mothers must be educated about the signs of babies not getting enough milk or any other abnormal signs. All mothers should be educated about the importance of taking their babies to the local healthcare facility at day 3 - 6 for follow-up after discharge. Neonates with SHB should be followed up for neurodevelopmental assessment, as they are at risk of developing neurological impairment.

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