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Exchange Blood Transfusion in a Nigerian Teaching Hospital

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Abstract: Exchange Blood Transfusion (EBT) is the commonest mode of management of severe hyperbilirubinaemia in newborns, occasionally resulting in severe complications. To determine the frequency of EBT and the epidemiological characteristics of the newborns that underwent the procedure. The case notes of all newborns that underwent EBT at Abia State University Teaching Hospital from January 1st, 2005 to December 31st, 2009 were reviewed. The EBT rate among newborns that had jaundice was 27.9%. This was more common in males than females. Babies without antenatal care who were delivered outside the hospital had more EBT than the inborn ($p = 0.001$). The identified causes of the severe jaundice that lead to the EBT in the subjects in order of frequency were ABO incompatibility, sepsis, G6PD deficiency, prematurity and Rhesus isoimmunisation. The frequency of EBT is high in the centre. Lack of antenatal care by mothers contributed significantly to the development of severe NNJ necessitating EBT. It therefore becomes mandatory that expectant mothers should be educated on the need for antenatal visits in pregnancy and delivery in appropriate health facility.

Key words: Exchange blood transfusion, severe jaundice, NNJ, center, Nigeria

INTRODUCTION

Neonatal jaundice is a common occurrence worldwide occurring in up to 60% of healthy term neonates and 80% of preterms (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004; Mazzi, 2005).

Hyperbilirubinaemia which is a common consequence of neonatal jaundice may result in kernicterus or even death or permanent neurological damage such as cerebral palsy or sensorineural deafness in survivors usually from unbound unconjugated bilirubin (Calligaris *et al*., 2007; Ahlfors *et al*., 2009; Shapiro, 2005; Ip *et al*., 2004). Kernicterus is the most easily preventable form of brain damage in term and near term neonates (Smitherman *et al*., 2006). Hyperbilirubinaemia is commonly managed by phototherapy and more drastically with Exchange Blood Transfusion (EBT) (Bhutani *et al*., 2004; Ariel and Mazzi, 2008). When it is severe or the level of serum bilirubin rising rapidly. Though, EBT is increasingly de-emphasized in developed countries (Maisels and McDonagh, 2008) in favour of effective phototherapy and more recently use of prophylactic measures such as metalloporphyrins and casein containing formula (Gourley *et al*., 1997), it is still the procedure of choice in rapidly bringing down the level of Serum Bilirubin (SB) in severe hyperbilirubnaemia often encountered in developing countries (Ibekwe *et al*., 2012; Owa and Ogunlesi, 2009). Hyperbilirubinaemia necessitating the use of EBT has varied aetiologies from locality to locality some of which may be easily preventable. Whereas, Rhesus isoimmunsation is a common aetiology of hyperbilirubinaemia in some developed countries, the cause is mostly ABO incompatibility, sepsis or G6PD deficiency in developing countries, Nigeria inclusive (Ariel and Mazzi, 2008; Ibekwe *et al*., 2012; Owa and Ogunlesi, 2009; Kapplan and Hammerman, 2004; Ebbesen *et al*., 2005).

EBT is an invasive procedure and may be associated with complications such as those related to umbilical catheterisation such as arrhythmia, catheter breakage, necrotizing enterocolitis, lower limb gangrene, thrombosis, embolism, metabolic complications such as hypoglycaemia, hypocalcaemia, hyponatraemia, hyperkalaemia, thrombocytopaenia and infections including hepatitis, malaria, HIV/AIDS and syphilis (Bulbul *et al*., 2011; Olusanya *et al*., 2009; Badie, 2007).

This study is aimed at determining the frequency of EBT and epidemiological characteristics of the neonates requiring it in the management of their hyperbilirubinaemia. Analysis of the results obtained therefore is likely to provide a greater insight into the factors necessitating its use and possibly other ways the severity of jaundice requiring the use of EBT can be prevented thereby helping to limit its application in future to the management of hyperbilirubinaemia that cannot be prevented or managed otherwise.

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MATERIALS AND METHODS

This study is a retrospective survey of neonates (aged 28 days or less) admitted into the Newborn Intensive Care Unit (NICU) of Abia State University Teaching Hospital (ABSUTH), Aba, Nigeria who had severe Neonatal Jaundice (NNJ) and were managed by Exchange Blood Transfusion (EBT) over a 5 years period, January 1st, 2005 to December 31st, 2009. The Ethics Committee of the Teaching Hospital approved the study before commencement.

The hospital was formerly a state government general hospital and was converted to the Teaching Hospital of the newly established Abia State University in 1994. It became baby friendly in 1999. It is located in Aba, the densely populated commercial nerve centre of Abia State about 45 km south of Umuahia, the state capital. It serves both as a secondary health care centre and a referral centre for peripheral hospitals and maternities in Aba and neighbouring states of Akwaibom, Rivers, in the Niger Delta (South South) and Imo (South East) of Nigeria. It has an annual delivery rate of ~1,100.

In ABSUTH, phototherapy and EBT are the usual methods of managing NNJ. EBT is done when the unconjugated component of serum biliruhin approaches the level which is considered to be neurotoxic to cerebral neurons. For otherwise healthy full term neonates, it is 20 mg dL^{-1} or 340 μmol L^{-1} while for ill term babies or babies of low birth weight, it is lower (Owa and Ogunlesi, 2009). Prophylactic phototherapy is administered to very low birth weight babies (weighing <1.5 kg) and EBT done at much lower SB levels between 10 and 15 mg dL^{-1} depending also on the presence of additional complications such as birth asphyxia, acidosis, hypoglycaemia, serious infections including meningitis, hypoalbuminaemia (Owa and Ogunlesi, 2009). Sepsis ordinarily is managed with antibiotics but when the unconjugated component of serum bilirubin in NNJ accompanying or arising from sepsis approaches the cerebral neurotoxic level, EBT is indicated (Owa and Ogunlesi, 2009).

In ABSUTH, EBT is usually conducted by the resident doctor on call assisted by an attendant nurse. Fresh whole blood (<72 h) is used and double volume exchange procedure completed over about 60-90 min by repeatedly withdrawing and replacing small aliquots of blood 5-7 mL kg^{-1} according to standard published protocol (Bulbul *et al*., 2011). Smaller aliquots are exchanged in ill babies or babies of lower birth weight. The 1 mL of 10% calcium gluconate is given for every 100 mL of blood exchanged.

As part of work up for NNJ the following investigations are requested for and done on all patients who can afford them, SB total and conjugated, blood group (ABO, Rh), complete blood count with differentials. Direct coomb's test is also done in suspected case of Rhesus isoimmunisation. ABO incompatibility is defined as jaundice in a new born with A or B antigen born to type O mother while Rhesus disease was defined as jaundice in a Rh-positive newborn delivered to Rh-negative mother. A positive coomb's test against these antigens is supportive but not always done. Sepsis was diagnosed clinically and supported by laboratory evidence with or without positive blood culture result. Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency was diagnosed in a neonate with NNJ in whom G6PD assay result was deficient.

All newborns admitted in the NICU with the diagnosis of NNJ were identified in the admission register and their case notes retrieved from the medical records department. Those managed with EBT were selected out and constituted the subjects of the study. Data were extracted from their records and included the patients' gestational age, sex, birth weight, age at onset of NNJ, age at EBT, place of delivery, mode of delivery, maximum serum bilirubin level attained, probable cause of neonatal jaundice, duration of admission, outcome of admission. Newborns delivered outside the Teaching Hospital are classified as outborn.

Data were arranged in frequency tables and results analysed using Statistical Software EPI Info Version 6.04. The $p<0.05$ were considered as significant.

RESULTS AND DISCUSSION

There were a total of 1196 admissions of which 172 (14.5%) newborns had neonatal jaundice. The 80 (46.5%) of the newborns with NNJ were inborn while 92 (53.5%) were outborn giving an inborn:outborn ratio of 1:1.2. Forty eight babies (27.9%) had EBT as the mode of management of their NNJ. Of this, 6 were excluded for inadequacy of data and hence 42 were used for further analysis. They comprised 28 males and 14 females giving male:female ratio of 2:1.

The 7 (16.7%) of the newborns with NNJ managed with EBT were inborn; 20 (47.6%) were delivered in other health facilities; 10 (23.8%) in churches; 3 (7.1%) in traditional birth attendants' place and 2 (4.8%) at home. The 35 (38.04%) of the outborns with NNJ had EBT and these were significantly >7 (8.75%) of the inborns with NNJ that were managed with EBT ($p = 0.001$). Some of the demographic and clinical characteristics of the newborns with NNJ managed with EBT are shown in Table 1.

Table 1: Descriptive data of neonates that had EBT

Variables	Number	Percentage
Birth weight (g)		
<2500	10	23.8
2500-4000	30	71.4
>4000	2	4.8
Gestational age (weeks)		
<37	8	19.0
37-41	32	76.2
>41	2	4.8
Age at onset of jaundice (days)		
<1	12	28.6
1-3	7	16.7
4-7	22	52.3
8-28	1	2.4
Age at presentation (days)		
<1	2	4.8
1-3	3	7.1
4-7	32	76.2
8-28	5	11.9

EBT: Exchange Blood Transfusion

The mean weight of the babies that had EBT was 2.94±0.54 kg with a range of 2.2-4.2 kg. The mean gestational age was 36.6±2.6 weeks, range 30-42 weeks (Table 1).

The 8 (19%) of newborns with NNJ managed with EBT were preterm. The range of age at onset of jaundice was <1-8 days with a mean of 2.3±1.24 days. The 39 (92.9%) developed jaundice within 5 days of life (Table 1). The mean age at presentation of the newborns with NNJ managed with EBT was 4.2±1.7 days, range <1-21 days; for the inborn the mean age at presentation was 1.3 days, range <1-4 days while for the outborns the mean age at presentation was 5.6 days, range 3-21 days with a significant difference between them ($p = 0.03$).

The maximum level of serum bilirubin in the subjects ranged from 158-668 μmol L^{-1}, median 366 μmol L^{-1}. For the outborns the range was 158-668 μmol L^{-1}, median 460 μmol L^{-1}. For the inborns the range was 256-398 μmol L^{-1} and median 356 μmol L^{-1}. The maximum SB level of the outborns was significantly higher than that of the inborns ($p = 0.036$).

Majority, 35 (83.3%) of the subjects were products of Spontaneous Vertex Delivery (SVD), 30 (85.7%) being outborn and 5 (14.3%) inborn while 7 (16.7%) were delivered by Emergency Caesarian Section (EMCS), 5 (71.4%) being outborn and 2 (28.6%) inborn. There is no significant difference in the mode of delivery of the inborn and outborn subjects ($p = 0.64$).

Most of the mothers of the subjects, 36 (85.7%) were booked while 6 (14.3%) were not. All the 7 (100%) of mothers of the inborn that had EBT were booked while 29 (82.9%) of the 35 mothers of the outborn who had EBT were booked. Mothers of the inborn subjects who were booked were significantly more than those of the outborns that were booked ($p = 0.046$).

Table 2: Probable causes of severe NNJ in patients who had EBT

Probable cause of NNJ	Number	Percentage
ABO incompatibility	10	23.8
Sepsis	9	21.5
G6PD deficiency	9	21.5
Prematurity	8	19.0
Rhesus isoimmunization	3	7.1
Unknown	3	7.1

G6PD deficiency: Glucose 6 Phosphate Dehydrogenase deficiency

The 38 (90.5%) of the mothers were married while 4 (9.5%) were unmarried. All 7 (100%) of mothers of the inborn were married while 31 (88%) of mothers of the outborn were married with no significant difference in marital status between them ($p = 0.07$).

ABO incompatibility was the leading probable aetiology of NNJ in this study closely followed by sepsis and G6PD deficiency and Rhesus isoimmunisation the least (Table 2).

The outcome of EBT in the 42 newborns was as follows: 35 (83.3%) of newborns who had EBT were discharged home, 5 (11.9%) developed kernicterus while 2 (4.8%) died.

Sepsis was diagnosed significantly more in outborn newborns managed with EBT than in the inborns ($p = 0.045$) (Table 3). Prematurity, G6PD deficiency and kernicterus occurred significantly more in the outborns than in the inborn ($p = 0.048$, 0.047, 0.046, respectively). Significantly more inborns than outborns were discharged home well ($p = 0.020$) (Table 3).

Three of the newborns with kernicterus were G6PD deficient exposed indirectly to naphthalene balls used in storing the wrappers used in carrying them.

The EBT rate of 27.9% in the management of severe neonatal jaundice in this survey is quite high. However, this is similar to what obtains in other parts of this country and other developing countries (Ariel and Mazzi, 2008; Ibekwe *et al*., 2012; Owa and Ogunlesi, 2009). This is attributable to the majority of the newborns being outborn and presenting late to the hospital for management. Additionally, G6PD deficiency which was reported among the leading causes of severe NNJ in this study can rapidly result in high levels of serum bilirubin following inadvertent exposure of the affected newborn either directly or indirectly to oxidant materials (such as naphthalene balls often used in storing babies' clothes), the consequence of which the child care givers are often ignorant by Olusanya *et al*. (2009). Other areas of the world where high EBT rates have been reported include the Middle East and Asian countries due to racial disposition of the newborns to the development of neonatal jaundice (Ariel and Mazzi, 2008; Bulbul *et al*., 2011; Badie, 2007) as well as Canada (Sagro *et al*., 2006) due to early discharge of preterm babies from nurseries

Table 3: Differences in some clinical parameters between inborn and outborn with NNJ managed with EBT

Clinical variables	Number in inborn who had EBT	Total in born who had EBT	Percentage	Number in outborn who had EBT	Total outborn who had EBT	Percentage	p-values
ABO	2	7	28.6	8	35	22.9	0.760
Incompatibility							
Sepsis	1	7	14.3	9	35	25.7	0.045
G6 PD deficiency	1	7	14.3	8	35	22.9	0.046
Prematurity	1	7	14.3	7	35	20.0	0.048
Rhesus isoimmunization	1	7	14.3	2	35	5.7	
Outcome of EBT							
Discharged well	7	7	100.0	28	35	80.0	0.030
Kernicterus	0	7	0.0	5	35	14.3	0.046
Died	0	7	0.0	2	35	5.7	0.740

NNJ: Neonatal Jaundice; EBT: Exchange Blood Transfusion; G6PD: Glucose-6-Phosphate Dehydrogenase

and the re-emergence of NNJ with SB level rising very highly in them later. However, screening of babies to detect those likely to develop severe NNJ using methods including the SB level within the first 24 h is now undertaken prior to discharge (Randev and Grover, 2010).

In contrast, the EBT rate in most developed countries of the world is quite low due to the use of very effective phototherapy to bring down the serum bilirubin levels usually detected early in newborns with NNJ (Steiner *et al*., 2007; Olusanya *et al*., 2009). Also, other available effective methods of managing NNJ when noticed include use of supplementary fiberoptic phototherapy blankets and prophylaxis with casein containing formula and metallo-porphyrins (Gourley *et al*., 1997). These facilities are not usually available in the developing coutries for now.

Preterm (19%), though fourth amongst the probable causes of the NNJ in this study still competes strongly in frequency with the 3 leading causes with ABO incompatibility, the most frequent of them all being 23.8% (Table 2). Preterm also occurred more significantly in the outborn in this study (Table 3). Preterm and low birth weight were the predominant aetiologies of NNJ in newborns managed with EBT in Ilesha (Owa and Ogunlesi, 2009), South Western Nigeria and Abakaliki (Ibekwe *et al*., 2012), South Eastern Nigeria probably because overwhelming majority (76% in Ilesha for instance) of the newborns subjected to EBT were outborn with a large proportion being preterm compared with 53% that were outborn in this study. NNJ in preterms can progress rapidly resulting in excessive SB levels when jaundice is not managed promptly (Ebbesen *et al*., 2005) as it is apt to occur in outborn cases.

There was on the average a delay of nearly 2 days between the age at onset of jaundice and presentation to the hospital of the newborns whose NNJ was managed with EBT in this study. This is similar to the finding in the study conducted at Abakaliki, South East Nigeria (Ibekwe *et al*., 2012) while there was a delay on the average of up to 5 days from the time of onset of jaundice to the presentation of the newborn to the hospital in Bolivia (Mazzi, 2005). Such delays contribute to the severity of neonatal jaundice and high rate of EBT (17% in Abakaliki, 21% in Bolivia) (Mazzi, 2005; Ibekwe *et al*., 2012).

Significantly, more mothers of the outborn babies than those of the inborn were not booked. This is understandable as unbooked mothers are not as likely to receive antenatal health education including signs signifying NNJ and the essence of prompt presentation of the newborn to appropriate health facility for management. Newborns of such mothers present late to healthcare facilities and often with kernicterus.

As commonly reported previously, the predominant causes of severe NNJ in Nigeria played themselves out in this study (Ibekwe *et al*., 2012; Owa and Ogunlesi, 2009; Olusanya *et al*., 2009) but with ABO incompatibility being the leading cause followed closely by sepsis, G6PD deficiency and prematurity. Again, Rhesus isoimmunization being a relatively rare aetiology of NNJ in Nigeria (Ibekwe *et al*., 2012) is confirmed by this study accounting for only 7.1% of the probable causes of NNJ requiring EBT.

The outborn babies had significantly higher levels of maximum serum bilirubin and frequencies of EBT in this study. Significantly, more outborns than inborns among the neonates that had EBT had sepsis and were also G6PD deficient (Table 3). On the other hand, significantly more inborn than outborn babies were discharged home well. Outborn situation is more likely to expose the newborn to unhygienic conditions during delivery and after birth than the inborn baby predisposing it to the development of sepsis (possibly associated with NNJ) (Adimora and Odetunde, 2007). Neonatal jaundice in the inborn patients generally is not likely to be associated with as much complications such as infections, consequences of inadequate obstetric care and lack of health education on the side of the mother as with the

outborn babies whose mothers are often unbooked and hence, the inborns are generally less severely ill and likely to respond to management better than the outborn neonates. For instance, 55.6% of all the G6 PD cases who happened to be outborn were exposed to wrappers previously stored with an oxidizing agent, naphthalene balls also because significantly their mothers were not booked and lacked relevant antenatal health education. Sepsis and the possibly resultant NNJ are more likely to occur and be made worse in outborn situation (Adimora and Odetunde, 2007).

CONCLUSION

The EBT rate in this study is quite high. The outborn status of the majority of the newborns who had EBT and lack of booking on the part of their mothers contributed strongly to their development of severe NNJ. Exposure of the neonates who had G6PD deficiency to naphthalene ball which is an oxidant agent consistently resulted in severe hyperbilirubinaemia and often kernicterus. Also, the outborns responded less favourably to management than the inborn newborns most probably because they presented late to the hospital. It therefore becomes mandatory that the general populace, particularly pregnant women should be educated on the need for regular antenatal visit for antenatal care in pregnancy and delivery in appropriate health care facility.

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