

EFFICACY OF INTRAVENOUS IMMUNOGLOBULIN AND PHOTOTHERAPY IN THE MANAGEMENT OF EXTREME-HYPERBILIRUBINAEMIA: A CASE REPORT

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ABSTRACT Background: Neonatal jaundice is one of the leading causes of neonatal morbidity and hospitalisations worldwide, and in the developing countries particularly, it still represents one of the main causes of neonatal mortality. While phototherapy is widely accepted as an effective treatment, adjunct modes of management such as the use of Intravenous Immunoglobulin (IVIG) are not so widely utilised in developing countries like Nigeria. This present case report is to show the usefulness of IVIG in the management of neonatal jaundice. **Case summary:** A case report of a 42-hour-old Caucasian term male neonate with extreme-hyperbilirubinaemia secondary to ABO incompatibility which was managed with a combination of guided phototherapy and Intravenous immunoglobulin (IVIG) is presented. The patient responded well to treatment with no apparent immediate adverse effects. **Conclusion:** The implications for clinical practice regarding reduction in the frequencies of Exchange Blood Transfusion (EBT) and the duration of phototherapy are at this moment presented.

KEYWORDS Extreme-hyperbilirubinaemia, Intravenous immunoglobulin (IVIG), Guided phototherapy

Introduction

Neonatal jaundice is one of the most common causes of morbidity in newborns globally, and severe neonatal jaundice is a frequent cause of hospitalisation or readmission for special care in the first week of life. [1] The approaches to management appear to differ considerably between developed and developing countries. [1,2] Exchange Blood Transfusion (EBT) and

phototherapy (PT) have traditionally been used to treat jaundice so as to avoid the associated neurological complications of severe hyperbilirubinaemia.[1] EBT is not without risk. Hence Intravenous Immunoglobulin (IVIG) has been suggested as an alternative therapy for isoimmunehaemolytic jaundice to reduce the need for exchange transfusion.[3] Some of the complications of exchange transfusion include haemodynamic instability, apnea, pulmonary haemorrhage, thrombocytopenia, coagulopathies, hypoglycaemia, hypocalcaemia, electrolyte imbalance, vasospasm, vascular thromboses, hypertension, arrhythmias, sepsis, necrotizing enterocolitis and bowel perforation with morbidity rates varying from 2.8-5.2% per procedure.[3-5]

While international guidelines for the management of neonatal jaundice are widely available and accessible globally; uniform practice guidelines are rare at all levels of healthcare delivery in Nigeria.[4] The threshold for EBT is often based on a TSB level of $\geq 20\text{mg/dL}$ and two-third of that level for commencing PT for term babies.[5]

Intravenous Immunoglobulin (IVIG) is an alternative therapy which may be effective in treating isoimmunehaemolytic jaundice. In isoimmunehaemolysis, red blood cells are proba-

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bly destroyed by an antibody-dependent cytotoxic mechanism mediated by Fc receptor bearing cells of the neonatal reticuloendothelial system. The putative mechanism of IVIG action is a nonspecific blockade of Fc receptors resulting in a decline in carboxyhaemoglobin levels. Carboxyhaemoglobin levels are a sensitive index of haemolysis and hence immunoglobulin could decrease haemolysis.[2]

The use of IVIG as an adjunct for the management of extreme and severe hyperbilirubinaemia in developing countries is uncommon due to non-availability of the drug and sometimes the limited knowledge of its use. EBT is, therefore, a common modality of treatment for severe neonatal jaundice in developing countries like Nigeria.[5,6] Literature and data are sparse from these regions in the use of standardised guidelines and IVIG in the management of NNJ. Therefore, the present case is presented to illustrate the use and response of IVIG in the management of extreme hyperbilirubinaemia.

Case report:

Complaint: A 42-hour-old Caucasian male neonate (gestational age 40 weeks, birth weight 3009g) presented at the neonatal unit of Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust, the UK with jaundice noticed on the 3rd day of life by the community midwife at 36 hours of life during the routine home visit.

Activity was good, and no other systemic symptoms were noticed. The patient was feeding well on exclusive breast milk. The patient was born by normal vaginal delivery to a 33-year-old mother. The mother's and baby's blood group were O positive and A positive respectively. He had been passing urine and opening bowels since birth. There were no risk factors for sepsis and no history of jaundice in the elder sibling. He had earlier been discharged from the postnatal ward at 24 hours of life. The total serum bilirubin (TSB) recorded by the midwife at home during the home visit with transcutaneous bilirubinometer was 421 micromol/L. By the published NICE guidelines for treatment threshold in neonatal jaundice, TSB value was on the exchange blood transfusion line. Hence, the baby was referred to the neonatal unit for possible exchange blood transfusion. At presentation, he was severely jaundiced, not pale, afebrile, not dehydrated, weight was 2800g, representing a 6% weight loss from birth weight. Systemic examination was normal, and there were no clinical signs of bilirubin encephalopathy.

Diagnosis: Severe neonatal jaundice (with TSB at exchange transfusion line) secondary to possible ABO incompatibility was made. Investigation results showed baby's blood group as A Rhesus positive. Direct Coombs Test was strongly positive. Total serum bilirubin (TSB) taken immediately on admission was 433 mmol/L; 4 hours after the referral value. Haemoglobin values were 15.5 g/dL and 14.9 g/dL on the 1st and 2nd day of admission respectively. Reticulocyte counts were initially 16.09%. Blood film on admission also showed numerous spherocytes with polychromasia. Blood glucose and gases were largely normal and infection screens were not suggestive of infection. Serum electrolytes and urea were also normal. Other liver function tests were normal with albumin 36 g/L, Alkaline Phosphatase 159 U/L and Alanine transferase (ALT) 12 U/L.

Interventions: The patient was admitted and started on quadruple phototherapy with three overhead phototherapy lamps and a Bilibed. Umbilical arterial and venous accesses were

Table 1 Timeline of care

Age	Level of jaundice (TSB mmol/L)	Treatment offered
42 hour	421	Referral to hospital by midwife
46 hour	433	Quadruple phototherapy IVIG 0.5mg/kg, IVF
52 hour	404	
58 hour	354	Phototherapy lamps reduced to 3
64 hour	222	
76 hour	211	Phototherapy
Day 4	169	Phototherapy discontinued
Day 5	150	Patient discharged
3 months		Follow up at clinic – Child was neurologically normal

obtained, and intravenous fluid was started at 120 ml/kg/day. The patient was placed on nil per by mouth. IVIG was given at 0.5g/kg at admission. By 6 hours into admission, which was after the administration of IVIG, TSB had reduced to 404 micromol/L, (conjugated fraction 43micromol/L). When plotted on the NICE guideline jaundice treatment graphs, this value was four boxes below the exchange transfusion line. 12 hours into admission showed a further reduction in the TSB to 354 micromol/L (conjugated fraction 38) which was eight boxes below exchange transfusion line. Phototherapy lamps were thus reduced to 3. TSB 6 hours later was 250 micromol/L which was on the phototherapy treatment line. On the second day of admission, haematocrit was 14.9 g/dL, and reticulocyte was 13.99%. Enteral feeds were restarted by the 2nd day of admission when the TSB had dropped significantly to 222 micromol/L, and this value was by now four boxes below phototherapy treatment line. The next TSB value by the end of the 2nd day of admission was 211 mmol/L, which was seven boxes below the phototherapy treatment line. Phototherapy was then reduced to 2 lamps. TSB was 169 mmol/L on the 4th day of life after which phototherapy was discontinued.

Outcome: The patient made a full recovery, as judged by the clinical appearance and the neurologic examination and the TSB values. He was subsequently discharged from the hospital on the 5th day of life. Neurodevelopmental follow-up in the outpatient clinic at three months of age was normal.

Discussion:

Extreme hyperbilirubinaemia is defined as a TSB greater than 428micromol/L (25mg/dL). [7] The patient's total serum bilirubin (TSB) taken immediately on admission was 433 micromol/L, and this was due to ABO blood group incompatibility as the mother's and baby's blood group were O positive and A positive respectively.

ABO hemolytic disease remains the most common cause of severe and early jaundice in the newborns. ABO blood group incompatibility is present in 15-25% of pregnancies.[8] ABO fetomaternal red blood cell incompatibility induces an immune hemolysis after fetal transfer of haemolysing maternal anti-A or anti-B. High levels of consequent unconjugated hyperbilirubinemia may induce both acute and chronic neurological complications.[8,9]

Although phototherapy (PT) and exchange transfusion (ET) are widely used in the management of severe jaundice, there is no standard or evidence basis for the thresholds for each intervention. It is also unclear what the safe upper limit of bilirubin level is or whether bilirubin level alone is a sufficient predictor of the need for exchange transfusion or as a determinant of neurodevelopmental outcome.[10] Many practitioners in developing countries use double set up or intensive phototherapy and defer EBT until the serum bilirubin has risen above high thresholds. Some paediatricians still use early rate of rising of bilirubin as an indicator for ET.[11]

Intravenous human polyclonal immunoglobulin (IVIG) has been proposed for concomitant use with PT to reduce the need for ET in ABO haemolytic disease with positive direct Coomb's test.[1]

The exact mechanism of action of IVIG in HDN is still unknown. IVIG is thought to decrease haemolysis by blocking Fc receptor sites of reticuloendothelial cells preventing lysis of neonatal erythrocytes. IVIG competes with sensitised neonatal erythrocytes for the Fc receptor sites of the reticuloendothelial system to prevent further haemolysis (competitive inhibition) thus suggesting that early administration of IVIG is necessary for efficacy in immune hemolytic diseases of the newborn. [12]

Recognising the potential benefits of IVIG over exchange transfusion is easy. The administration is less complicated and less labour intensive. As well as being a less invasive therapy, IVIG may also allow treatment of some infants in Level II centres or avoid delaying treatment while transferring infants to tertiary centres for exchange transfusion. Administration of IVIG has also been shown to reduce the duration of phototherapy. [13] This may particularly be helpful in developing countries where health care cost is related to duration of stay in the hospital and this cost is largely out of pocket expenditure.

Case reports and case series have reported the success of IVIG in the treatment of jaundice due to both Rhesus and ABO incompatibility. A systematic review of the use of IVIG in hemolytic disease of the newborn showed that significantly fewer infants required EBT when IVIG was administered in combination with PT compared to those who had PT alone. Also, hospital stay and duration of phototherapy were reduced. [14] However, there are still debates on the routine use of IVIG in ABO hemolytic disease of the newborn as some studies have failed to show the efficacy of IVIG in reducing the need for EBT. The reasons for this discrepancy have not been explained but it should be noted that in some of the studies that failed to show significant effects, IVIG was used more or less prophylactically for all apparently immunized infants, whereas in the studies that reported benefits, IVIG was used exclusively as a rescue therapy in infants headed for EBT.[15]

Numerous guidelines for the management of neonatal jaundice have been published, the NICE guideline being just one of them. The AAP and Norwegian guidelines all state explicitly the thresholds for commencing or stopping phototherapy as well as those for EBT. These guidelines also vary for both gestational

age and birth weight. In sharp contrast to the practice in most high-income nations, national or local guidelines for the effective management of severe hyperbilirubinaemia are rare in the developing countries even though the disease burden is high. [16] The absence of harmonised protocols either for classification or management in most low and middle-income countries renders it difficult if not impossible for comparisons between locations.

As regards the long/life term effect of our choice of management, the patient had no sign of bilirubin encephalopathy at admission nor at follow-up at three months. We, therefore, had no reason to fear that the prognosis will not remain excellent.

Implications for practice

Administration of IVIG to newborns with significant hyperbilirubinemia due to ABO haemolytic disease with positive direct Coomb's test combined with the use of PT reduces the need for EBT and the duration of PT. The efficacy and good tolerance prompt consideration of IVIG as a therapeutic adjuvant to PT in severe hemolytic hyperbilirubinemia due to ABO incompatibility. Since it appears safe, it may also have a role in special circumstances such as parental refusal for exchange transfusion, failed cannulation for EBT or where appropriate blood components for exchange transfusion are unavailable.

This case report also encourages the employment of standard protocols which are widely available in determining the need for phototherapy or exchange blood transfusion as well as the use of alternative treatments like IVIG in cases of extreme hyperbilirubinaemia with isoimmunization. This maximises the chances of a favourable outcome for patients with severe neonatal jaundice regarding reducing the need for EBT and the duration of accompanying phototherapy.

Authors' Statements

Competing Interests

The authors declare no conflict of interest.

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