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Exploring Role of Intravenous Immunoglobulin in Management of Alloimmune Hemolysis Caused by Minor Blood Group Incompatibilities Leading to Severe Hyperbilirubinemia Requiring Exchange Transfusion

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Abstract

With better antenatal care and widespread use of Anti-D antibody in Rh negative pregnancies, hemolytic disease of fetus and newborn due to minor blood group antigens incompatibility has gradually increased in proportion in recent years. However most of them are mild to moderate. This series has two cases of minor blood group incompatibility in which IVIG was used as alternate therapy for exchange transfusion. In first case serum bilirubin was persistently rising high despite two exchange transfusions, so we used a single dose of IVIG @ 1 gm/kg iv over 6 h after which SB fell gradually to below phototherapy range. In second baby serum bilirubin was in exchange level at 8 h of life, DVET was contemplated but compatible blood was unavailable in blood bank. Based on first experience we started IVIG as alternative to exchange therapy while blood bank was arranging the blood. Serum bilirubin fell below exchange level after 6 h of IVIG infusion and phototherapy stopped after 72 h of IVIG.

Conclusion: Though it will be very early to say as there is limited data and still considered as an off label use in immune HDN but we may consider IVIG as an alternative for exchange transfusion.

Keywords: Rh antigen; Direct Coombs test; Fetomaternal bleed; Alloimmunization; Phototherapy; IVIG; Bilirubin; Pregnancy

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Introduction

Hemolytic Disease of the Fetus and Newborn (HDFN) due to Rh isoimmunization has long been associated with unconjugated hyperbilirubinemia and is an important cause of morbidity and hospitalization for phototherapy in newborns. Its incidence is approximately 276/100,000 live births per year [1]. Blood grouping apart from ABO system also includes Rh typing which are a complex system containing 49 Rh antigens and among them D is the most important one. However some minor blood group antigens C, E, c, e, Duffy, Kidd, MNS are also significant ones [2]. Over the years the frequency of indirect hyperbilirubinemia due to Rh sensitization in neonates has decreased significantly with better ante-natal care and widespread use of anti-D globulin, but at the same time the contribution for HDFN due to minor blood group antigens incompatibility such as Kell, c, C, E, e etc. has gradually increased [3,4] however most of them are mild to moderate. We are presenting two cases of minor blood group incompatibility in which we used IVIG as alternate therapy for double volume exchange transfusion. In first case serum bilirubin was persistently rising high despite one Double Volume Exchange Transfusion (DVET) and one Single Volume Exchange Transfusion (SVET) so we used a single dose of IVIG @ 1 gm/kg IV over 6 h after which it fell gradually to below phototherapy range. In second baby serum bilirubin was in exchange level at 8 h of life DVET was contemplated but compatible blood required was not available in blood bank. Based on first experience and unavailability of blood for DVET we started IVIG as alternative to exchange therapy while blood bank was arranging the blood. IVIG was given over 6 h after which serum bilirubin fell to phototherapy range so exchange transfusion deferred and serum bilirubin fell further to below phototherapy range in 72 h when phototherapy was no discontinued, thus the exchange transfusion was not needed.

Case Series

Case 1

A Term baby boy born to 2nd gravida (G2P1A0L1) mother by Elective LSCS, having uneventful course of pregnancy both in previous as well as current pregnancy, cried immediately after birth, received routine care and was shifted to mother side. At 20 h of life the baby was reported to be icteric up to palms and soles following which baby were started on Double Surface Phototherapy (DSPT) and Intravenous fluids and relevant investigations were sent. The investigations, interventions and other details are given in Table 1. TSB level was 25.44 mg/dl with Direct Bilirubin was 0.12 mg/dl, Direct Coombs Test (DCT) was positive (4+) , both mother's and Baby blood group were O positive, Indirect Coombs Test (ICT) of mother was also Positive. So Double Volume Exchange Transfusion (DVET) was done as the Bilirubin level was above exchange transfusion limit per AAP nomogram [5]. TSB at 4 h after DVET was 16.75 mg/dl and after 8 h rose to 19.55 mg/dl which was above exchange transfusion level, hence again one Single Volume Exchange Transfusion (SVET) done due to unavailability of required volume of blood for DVET. As evident in Table 1, the SB again kept on increasing and keeping that in mind IVIG [@ 1 gm/kg] was given due to persistent hyperbilirubinemia despite of exchange transfusions with ongoing DSPT and DCT 4 +ve signifying immune hemolysis. In view of severe immune hemolysis in absence of ABO/Rh incompatibility, minor blood group incompatibilities were suspected and investigated. In the mother's blood Anti-c, Anti-E allo-antibodies were detected in titers 1:512 and anti-s 1 in 256 and whereas in baby's blood Anti-c and Anti-E were detected in 1 in 256. Afterwards there was steady fall in bilirubin level and it came down below the phototherapy range after 48 h of phototherapy post IVIG, thus phototherapy was stopped on day 5 of life. Baby recovered well and post discharge ophthalmological and hearing evaluation was within normal.

Case 2

A late-preterm (36 wk + 6 D) baby girl born by Emergency LSCS (i/v/o non-reactive non stress test and thin Meconium stained liquor) to a 3rd gravida (G3P2A0L1D1) asymptomatic COVID-19 positive, hypothyroid mother. The mother had a bad obstetrics history in past as her 1st pregnancy was a monochorionic twin out of which one fetus had IUD and another died at 24 h of life however the 2nd pregnancy was uneventful. The baby cried immediately after birth, received routine care and shifted to NICU for isolation in view of COVID-19 and feeding stated with expressed breast milk and formula. At 8 h of life, baby found to be icteric up to thighs following which baby was started on Double Surface Phototherapy (DSPT) and intravenous fluids and relevant investigations were sent. TSB level was 12.66 mg/dl with Direct Bilirubin was 0.16 mg/dl, Direct Coombs Test (DCT) was positive (4+), both mother's and baby blood group were O positive and Indirect Coombs Test (ICT) of mother was negative. Bilirubin level was above exchange transfusion limit per AAP nomogram [5], but due to unavailability of compatible blood, exchange transfusion couldn't be done at that time hence IVIG (@ 1 gm/kg) was started at 16 h of life over a period of 6 h and double surface phototherapy continued while the compatible blood was to be arranged. Repeat TSB at 6 h after IVIG was 11.71 mg/dl which was below exchange transfusion limit but above phototherapy limit, thus dual surface phototherapy continued with IV fluid relaxation. Repeat TSB at 12 h, 24 h & 48 h after IVIG were 11.75 mg/dl, 14.09 mg/dl and 13.59 mg/dl respectively which were within phototherapy range thus dual surface phototherapy was continued with gradual introduction of oral feeding. In view of immune hemolysis in absence of ABO/Rh incompatibility, minor blood group incompatibilities were suspected and investigated, which revealed presence of anti-E antibody in baby's blood. The repeat TSB at 72 h after IV IG was 10.1 mg/dl which was below phototherapy range thus phototherapy was discontinued on day D 4 of life. The investigations and interventions with timelines are given in Table 2. Baby recovered well and post discharge ophthalmological and hearing evaluations were within normal limits.

Discussion

Immune hemolysis is an important cause of unconjugated hyperbilirubinemia in newborns requiring exchange transfusion and ABO and Rh incompatibility are the most common causes of severe immune hemolysis, but Minor Blood Incompatibilities (MBI) such as

Table 1: Investigations and Intervention details with timeline.

Post-natal age (in hours)	Investigation	Total Serum Bilirubin	4 hr	8 hr	16hr	24 hr	48 hr	DVET/SVET/INTERVENTION
20		**25.44**						**DSPT started**
24	HB: 14.6 gm/dl, CRC: 13%, CRP: <2.8 mg/L, PBS: macrocytic normochromic polychromasia noted (Normal for age) BBG: O positive, DCT: 4+ve AST: 47.1 U/L,ALT: <7.2 U/L Albumin: 3.59 gm/dl Urea: 26.6 mg/dl Creatinine: 0.80mg/dl Sodium:140.51 meq/L Potassium: 5.35 meq/L Uric acid: 7.66 mg/dl Blood C/S: Sterile (after 7 days of aerobic incubation)							DVET @ 30 hours of life
			16.75	19.55				SVET @ 44 hours of life
48	TSH: 3.20 IU/ml fT4: 29.02 pmol/L fT3: 4.39 pmol/L		19.78	21.70	21.44			IV IG (1 gm/kg) @ 64 hours of life
			14.27	13.09	13.29	10.5	8	DSPT stopped @ 118 hours (Day 5) of life
Day 9	BERA:WNL VEP: WNL							

Table 2: Showing investigations and intervention with timeline.

Post-natal age (in hours) 8 hours	Investigation	Total Serum Bilirubin (mg/dl) 12.66	POST INTERVENTION					DSPT/IVIG/DVET/ INTERENTION DSPT started
			6 hours	12 hours	24 hours	48 hours	72 hours	
16 hours	HB: 13.8 gm/dl 40 nRBCs /100 WBCs TLC:18400 N63L35 CRP: <2 mg/L, BBG: O positive MBG:O positive, DCT: positive ICT: negative Blood C/S: Sterile (after 7 days of aerobic incubation) RTPCR COVID-19: Negative TFT at 72 hours of life : TSH : 7.35 IU/ml fT4: 27.06 pmol/L							IVIG @ 16 hours of life And DSPT continued
88 hours (Day 4)			11.71	11.75	14.09	13.59	10.1	DSPT stopped
Day 6	BERA:WNL VEP:WNL							

anti-c, anti-Kell, anti-C, anti-E, anti-e can also causes severe neonatal jaundice [4,6-8] hence, must be kept in mind while dealing with cases of immune hemolysis. Minor blood group incompatibilities are responsible of 3% to 5% of the cases of neonatal hemolytic jaundice [9] however most of them remain mild. Clinical presentation for minor blood group erythrocyte alloimmunization depends on the type of antigen and degree of hemolysis. Although most of them are mild, severe hemolysis may be caused by Anti-c antibodies, second most common cause of severe HDFN after anti-D related HDFN [10]. With advancements and availability of investigations more and more cases of minor blood group incompatibilities are now being diagnosed which were missed previously. In fetomaternal bleed, the mixing occurs throughout the pregnancy and its chances increases by 3%, 12%, and 45% in the first, second, and third trimesters, respectively [11].

In our second case bilirubin level was above exchange cutoff but as the suitable blood was not available for Double Volume Exchange Transfusion (DVET) and serum bilirubin was rising real fast, the baby was under threat of developing bilirubin encephalopathy, instead of waiting for availability of blood for exchange transfusion IVIG was used based on our experience in managing MBI in case of first bay with the use of IVIG, where despite two exchange transfusions the serum bilirubin kept rising and IVIG had to be used to control the ongoing hemolysis, was satisfactory. IVIG blocks the Fc receptor and thus prevents antibodies from causing immune destruction of the red blood cells containing minor blood group antigens acquired due to genetic inheritance, from father. Thus it prevents requirement for multiple exchange transfusions. Though it will be very early to say as there is limited data and still considered as an off label use in immune HDN but we may consider IVIG as an alternative for exchange transfusion [12,13].

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