Original Article

Postnatal outcomes of infants affected by rhesus hemolytic disease in a tertiary care center in Northern India

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ABSTRACT

Background: Advances in prenatal and postnatal care of neonates with rhesus hemolytic disease of the newborn (RHDN) have led to improved outcomes. Studies evaluating the postnatal outcomes in rhesus (Rh) isoimmunized infants from developing countries are limited. **Objective:** The objective of this study was to evaluate the postnatal outcomes of neonates ≥32 weeks gestation with RHDN. **Methods:** A prospective observational study was conducted from July 2014 to June 2016 in a tertiary care neonatal unit in North India. Neonates affected by RHDN were managed as per the standard protocol and were followed up for the first 6 months of life. Primary outcomes were the duration of phototherapy (PT), need for exchange transfusion (ET), occurrence of late-onset anemia, and need for top-up transfusions. **Results:** A total of 33 newborns with RHDN were included in the study. Median duration of PT was 138 h (interquartile range 64–188) and was inversely correlated with intrauterine transfusion number (Spearman correlation coefficient −0.46; p=0.02). Of 33 neonates with RHDN, 14 (42.4%) neonates required ET. Late-onset anemia was seen in 25 (75.7%) neonates and 17 (51.5%) required at least one top-up transfusion. Cholestasis was seen in 5 (15.1%) neonates. **Conclusions:** Despite advances in care, short-term morbidities in neonates affected by RHDN are common and require intensive management.

Key words: *Exchange transfusion, Newborn, Rhesus hemolytic disease*

Rhesus hemolytic disease of the newborn (RHDN) occurs due to red cell alloimmunization, leading to the production of maternal antibodies which cross the placenta and affect the fetus. The most common alloimmunization is of rhesus (Rh) type D followed by other non-Rh blood group antigens. With the introduction of anti-D immunoprophylaxis in the late 1960s, the incidence of RHDN has decreased dramatically [1]. Improved prenatal treatment with intrauterine transfusions (IUT) has further decreased the associated mortality and morbidity [2]. Despite these advances, fetal anemia, hydrops, and neonatal hyperbilirubinemia are still seen; more so in developing nations, where resources and expertise are limited [3,4].

Early postnatal complications include hyperbilirubinemia, anemia, cholestasis, and acute bilirubin encephalopathy while long-term complications include anemia and adverse neurodevelopmental outcome. Management primarily comprises intensive phototherapy (PT), exchange transfusion (ET), and top-up transfusions for late-onset anemia. Besides these, the use of immunoglobulins has altered the clinical course of RHDN. Studies evaluating postnatal outcomes in Rh-negative isoimmunized infants from developing countries are limited [5-7]. This study was conducted with the aim to describe the outcomes of newborns affected by RHDN at a tertiary care center in North India.

MATERIALS AND METHODS

This was a prospective observational study, conducted in a 20 bedded neonatology unit of a tertiary care teaching hospital in North India from July 2014 to June 2016. All neonates, admitted during the study period with RHDN and gestational age at birth ≥32 weeks, were included in the study. Neonates with maternal red cell isoimmunization other than Rh D, presence of other comorbidities such as perinatal asphyxia, severe sepsis (based on clinical symptoms of infection or positive blood culture) or necrotizing enterocolitis, and neonates with gross congenital anomalies or syndromic disorders were excluded from the study.

The study was approved by the institute's ethics committee. Written informed consent was obtained from all the participating families. Primary outcomes were the duration of PT, need for ET, occurrence of late-onset anemia, and need for top-up transfusions. Secondary outcomes were conjugated hyperbilirubinemia, neurological examination at discharge, and duration of hospital stay.

Relevant data were collected in a pre-structured pro forma. Neonates were managed for jaundice, anemia, or any other acute problem as per standard protocol. The American Academy of Pediatrics (AAP) charts for neonates ≥35 weeks gestation and weight-based PT charts for preterm babies <35 weeks were used

for guiding the management of hyperbilirubinemia [8,9]. Intensive PT was administered through blue light-emitting diode (LED) PT devices (Make – Phoenix LED PT) at a distance of 30–45 cm from the bed surface with irradiance of at least 30 μW/cm^2/nm.

Indications for ET were cord hematocrit (Hct) <30% or cord total serum bilirubin (TSB) >5 mg/dl; rate of rise of TSB>1 mg/dl/h despite intensive PT; any TSB >12 mg/dl in the first 24 h and TSB >20 mg/dl in the neonatal period and TSB in double volume exchange transfusion zone as per AAP charts for ≥35 weeks or weight based charts for 32–35 weeks gestation; presence of hydrops at birth or history of previous sibling requiring exchange because of Rh isoimmunisation and index patient is born with pallor, hepatosplenomegaly and positive DCT. ET was performed using freshly collected (<7 days) compatible packed red blood cells and plasma that was reconstituted in the blood bank and irradiated and leukoreduced before the procedure. Intravenous immunoglobulin (IvIg) was given to patients with severe hemolysis when TSB approached exchange zone as per AAP.

Following discharge from NICU, neonates received folic acid supplementation and were followed up for late-onset anemia and conjugated hyperbilirubinemia. Late-onset anemia was defined as anemia (Hct <30%) occurring after the 1st week of life. Hct was monitored weekly after discharge until 1 month, fortnightly until 3 months of age, and then monthly for the first 6 months of life. Top-up transfusions were given when the Hct was <20% with reticulocyte count <2% in an asymptomatic neonate or at higher levels if clinical symptoms of anemia (congestive cardiac failure, lethargy, feeding problems, or failure to thrive) were present. For conjugated hyperbilirubinemia, total and direct bilirubin fractions were monitored fortnightly after discharge until 3 months of age and a direct fraction >20% of total was considered as conjugated jaundice (cholestasis).

Data were analyzed using SPSS statistics version 17.0. Descriptive data were expressed as median with interquartile range (IQR) for continuous data or as frequency (percentage) for categorical data. Association between variables was tested using Spearman correlation coefficient.

RESULTS

A total of 683 neonates were admitted during the study period; 44 Rh-positive neonates born to Rh-negative mothers were admitted during the study period. Of these, eight were non-isoimmunized, one was isoimmunized due to anti-M antibody, and two were lost to follow-up. Thus, 33 neonates were included for analysis. Baseline characteristics and laboratory parameters are shown in Tables 1 and 2. Outcomes are shown in Table 3.

Overall, the median duration of PT was 138 h (IQR 64–188) with the median maximum bilirubin on PT of 13.7 mg/dl (IQR 10.8–14.8). As the number of IUTs increased, the duration of PT decreased (Spearman correlation coefficient −0.46; p=0.02). A total of 14 (42.4%) neonates required at least one ET; only one required two ETs. Most (12 [85.7%]) ETs were performed within the first 12 h of life with median age at the first ET of 10 h (IQR 9–12). No correlation was found between the number of IUTs and ET use (Spearman correlation coefficient 0.22; p=0.28).

Late-onset anemia was seen in 25 (75.7%) newborns; 17 (51.5%) required at least one top-up transfusion. The median number of top-up transfusions was 1 (IQR 0–1) and most (13 [76.4%]) of them were done within the first 6 weeks of life. No correlation was seen between reticulocyte count at birth and top-up transfusions

Table 1: Baseline characteristics of the study population (*n*=33)

Variables	Median (interquartile range)/N (%)
Gestational age at birth (weeks)	36 (35^{+4}–36^{+5})
Birth weight (g)	2670 (2380–2865)
Male gender	16 (51.5)
Antenatal indirect Coombs test titer	1:64 (1:16–1:112)
Fetal intrauterine transfusion	25 (75.8)
Number of intrauterine transfusions	2 (3–4)
Mode of delivery	
Cesarean section	21 (63.6)
Vaginal	12 (36.3)
Intravenous immunoglobulin use	17 (51.5)

Table 2: Laboratory parameters in the study population (*n*=33)

Variables	Median (interquartile range)/N (%)
Cord blood hematocrit at birth (%)	40 (37.2–46.2)
Cord blood total bilirubin (mg/dl)	3.9 (3.2–5.4)
Cord blood reticulocyte count (%)	2.9 (0.2–5.2)
Cord blood positive direct antiglobulin test	18 (54.5)
Maximum total bilirubin on phototherapy (mg/dl)	13.7 (10.8–14.8)

Table 3: Clinical outcomes in the study population (*n*=33)

Outcome	Median (interquartile range)/N (%)
Duration of phototherapy	138 (64–188)
Neonates requiring exchange transfusion	14 (42.4)
Presence of late-onset anemia	25 (75.7)
Need for top-up transfusion	17 (51.5)
Number of top-up transfusions (*n*)	1 (0–2)
Development of conjugated hyperbilirubinemia	5 (15.1)
Neurological examination at discharge	
Normal	31 (93.9)
Tone abnormalities	2 (6.1)
Duration of hospital stay (days)	14 (11–16)

(Spearman correlation coefficient −0.20; p=0.26). Similarly, no association was seen between the use of either IUT or ET and top-up transfusions. Trend of Hct within the first 6 months of life showed nadir around 6 weeks of age as shown in Fig. 1.

Conjugated hyperbilirubinemia was seen in 5 (15.1%) neonates and was unrelated to IUT number. Cholestasis was mild and transient in three neonates while two required choleretics. The median duration of hospital stay was 14 days (IQR 11–16). There was no mortality until discharge. Neurological examination at discharge was normal in 31 neonates; two had tone abnormalities.

DISCUSSION

As mortality due to RHDN is declining with the advent of Rh immunoprophylaxis, attention is shifting toward morbidities associated with it. Neonates still require intensive care admissions for the management of complications. This study showed that hyperbilirubinemia in neonatal period requires intensive PT and was related to IUT number. Fetal transfusions are indicated in affected fetuses with severe hemolysis which leads to anemia. IUTs result in replacement of fetal red blood cells by donor Rh-negative red cells which may result in less active hemolysis and thus less severe hyperbilirubinemia. The finding of decreased PT duration with an increased number of IUTs supports this hypothesis and is similar to other studies [10,11].

ET was performed in 42.4% of neonates and was unrelated to the number of IUT; results are similar to that described in other studies [10-16]. The possible reasons for significant rate of ET in our study can be explained by the persistence of hemolysis despite IUT and the use of strict early criteria of ET in Rh isoimmunization. Most of the ETs were performed within the first 12 h of life which is similar to reports by De Boer *et al*. [11] and signifies aggressive approach used in our unit for management, as well as early criteria for ET.

Three-fourth of the neonates developed late-onset anemia and more than half required at least one top-up transfusion. The possible reasons could be low-grade ongoing hemolysis, erythropoiesis suppression due to IUT or IvIg use, shortened life span of donor adult red cells, and persistence of anti-D antibodies in the bone marrow which destroy erythroid precursors [17-20]. The study did not find any correlation of the use of IUT, ET, or reticulocyte count with top-up transfusions. Published literature is inconsistent with some studies favoring association of IUT, ET, or reticulocyte count with more top-up transfusions [11,16,19,21] while others show no association [7,22].

The occurrence of cholestatic jaundice in our study cohort was 15% which is comparable to the published studies [7,23]. The likely mechanisms include inspissation of bile pigment causing stasis and blocking of bile canaliculi, liver damage due to iron overload, and hypoxic injury due to anemia.

This prospective study is one of the few studies [5,7,16] describing postnatal outcomes in RHDN from a developing country. The study also describes the trends of Hct in the first 6 months of life which has not been reported previously. With

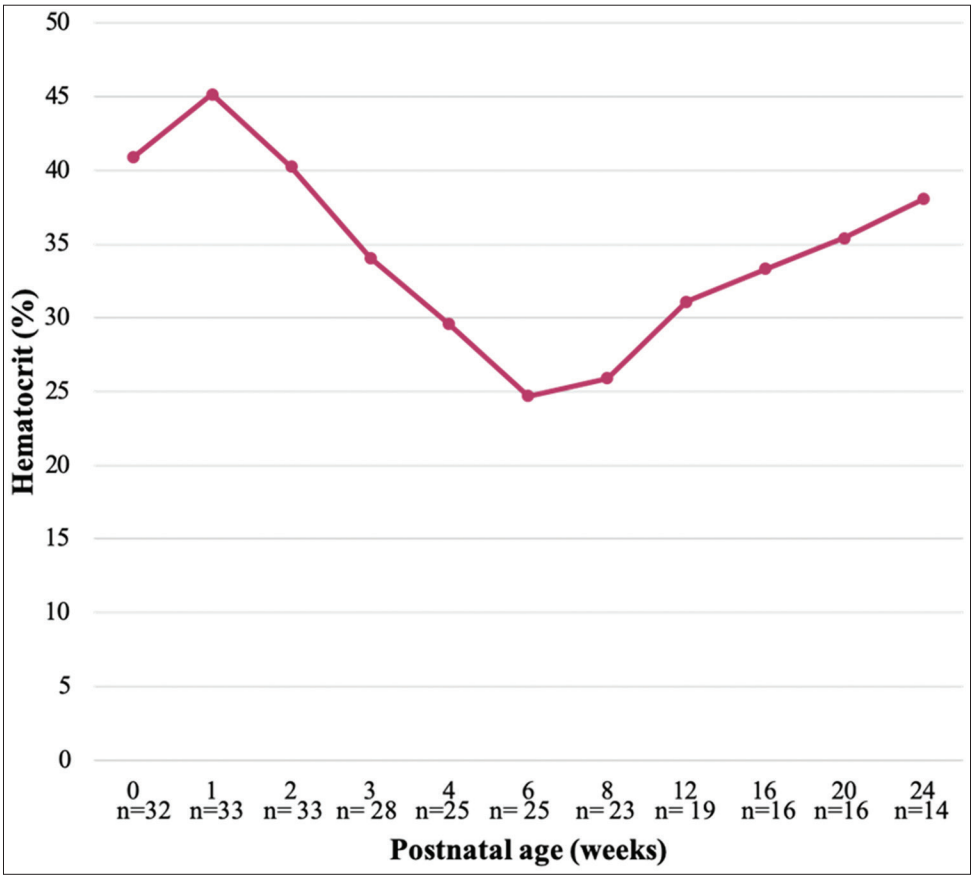

Figure 1: Trend of median hematocrit levels in the study population

RHDN still persisting in many countries, it is important to know about current outcomes so as to plan optimal management and follow-up. Our study provides recent data from India to assist further research on this topic. There are a few limitations of this study. The study has small sample size which could be due to overall decreased incidence of RHDN. Further, we have not studied the long-term morbidities including neurodevelopmental outcomes.

CONCLUSIONS

Short-term morbidities requiring intensive care in neonates affected by RHDN are common. They include hyperbilirubinemia needing PT and ET, late-onset anemia necessitating top-up transfusions, cholestasis, and considerable hospital stay. There is a need for further research in this disease which is cause of significant morbidities in affected neonates. Future research areas include indications for ET, optimal PT, role of IvIg, cost of care, and long-term morbidities in RHDN.

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