Neonatal management and outcome in red cell alloimmunization

Smits-Wintjens, V.E.H.J.

12

Summary

Rhesus hemolytic disease of the neonate (RHDN) results from alloimmunization to red cell antigens, for which mother and fetus are incompatible. In RHDN, maternal immunoglobulin (IgG) antibodies cross the placenta and cause destruction of fetal red blood cells. RHDN may lead to excessive hyperbilirubinemia and prolonged fetal and neonatal anemia. Unconjugated bilirubin may pass through the blood-brain-barrier and lead to permanent brain damage due to kernicterus. Traditional neonatal treatment of RHDN consists of intensive phototherapy and exchange transfusion (ET).

In this thesis, several studies on neonatal red cell alloimmune hemolytic disease are presented, including various management options, associated complications and co-morbidities and the short-term and long-term outcome of children with RHDN.

In **Chapter 2** an overview of the literature is presented. This review focuses on the management of neonatal and pediatric complications associated with Rhesus hemolytic disease, discusses postnatal treatment options and summarizes the results of studies on short-term and long-term outcome.

In **Chapter 3** we present the results of a randomized double-blind, placebo-controlled trial, to test whether the prophylactic use of IVIg reduces the need for ETs in neonates with Rhesus hemolytic disease (HDN): the LIVIN study. ET is an invasive, high-risk procedure associated with a significant rate of adverse effects. To avoid ET, international guidelines recommend the use of intravenous immunoglobulin (IVIg) in neonates with Rhesus hemolytic disease in case of failure of phototherapy. However, recommendations for the routine use of IVIg are controversial because of the small number of RCTs reported on this topic and the methodological limitations of these studies. In the LIVIN study we found no difference in the rate of ETs between the IVIg and placebo groups (17% versus 15%), nor in duration of phototherapy (4.7 versus 5.1 days), maximum bilirubin levels (14.8 versus 14.1 mg/dL) and proportion of neonates requiring top-up red cell transfusions in the first three months of life (83% versus 87%). Our findings do not support the use of IVIg in neonates with Rhesus hemolytic disease. In view of the absence of beneficial effects, the use of IVIg for this indication should be discouraged.

In **Chapter 4** we report a term neonate with RHDN treated with an ET through an umbilical venous catheter who developed brain abscesses due to a Bacillus cereus sepsis. This severe complication has not previously been reported. We discuss possible causes for this severe infection, discuss the possible association with ET treatment and provide suggestions for prevention.

In **Chapter 5** we present the results of a study on complications related to ET. As previously stated, ET is a high-risk invasive procedure requiring the use of central lines. Reported ET-related adverse events include mainly catheter-related complications, metabolic derangements, hematologic complications and cardio-respiratory reactions. To investigate morbidity and mortality rates associated with ET in our unit, we studied a large series of neonates with RHDN admitted to our center. We recorded the number and rate of complications during admission in the group of neonates treated with and without ET. A total of 347 infants with red cell alloimmune hemolytic disease were included, 39% was treated with at least one ET during admission (ET-group) and 61% did not require ET (no-ET-group). Comparison between the ET-group and no-ET-group showed that ET treatment was independently associated with: proven sepsis (8% versus 1% respectively), leukocytopenia (88% versus 23%), severe thrombocytopenia (platelet count < 50 x 10^9/L) (63% versus 8%), hypocalcemia (22% versus 1%) and hypernatremia (8% versus 0%). Neonatal death did not occur in the group treated with ET. We conclude that in experienced hands severe permanent morbidity and mortality rates due to ET-procedures can be reduced to a minimum.

Chapter 6 focuses on cholestasis, a frequently observed neonatal disorder associated with red cell alloimmunization. Etiology of cholestatic liver disease in neonates with RHDN has been associated with iron overload due to (multiple) IUT(s). Data on the incidence and severity of cholestasis in neonates with HDN due to red cell alloimmunization is scarce, and little is known about pathogenesis, risk factors, neonatal management and outcome. We retrospectively studied a large group of 313 infants with red cell alloimmune hemolytic disease treated with or without IUT, admitted to our center. We found that cholestasis occurred in 13% of these infants and was indepently associated with IUT treatment and Rhesus D type of alloimmunization. Although cholestasis is mild and transient in most cases, a few neonates have severe cholestatic liver disease with protracted course and require intensive treatment and in one case chelation therapy was needed. We therefore conclude that larger follow-up studies are required to determine the exact course and etiology of cholestasis in infants with red cell alloimmune hemolytic disease.

In **Chapter 7** we describe the occurrence of thrombocytopenia at birth, another frequently noticed disorder associated with RHDN. Limited studies have shown that fetuses with red cell alloimmunization are at increased risk of thrombocytopenia. However, incidence and severity of and risk factors for thrombocytopenia at birth in neonates with red cell alloimmunization is unclear. Therefore we retrospectively investigated the platelet count at birth in 362 neonates with red cell alloimmunization admitted to our center. We determined the incidence of thrombocytopenia (platelet count < 150x10^9/L) and severe thrombocytopenia (platelet count < 50x10^9/L) and evaluated risk factors for thrombocytopenia. We found that

thrombocytopenia was present in 26% of included neonates at birth. Severe thrombocytopenia was found in 6% of neonates. Only one neonate with thrombocytopenia had clinical sings of bleeding at birth (intraventricular hemorrhage grade 2). Although this neonate was thrombocytopenic at birth, other factors such as prematurity and hydrops could have contributed to this bleeding complication. We found that three risk factors were independently associated with thrombocytopenia at birth: treatment with IUT, small for gestational age (SGA) and lower gestational age at birth.

In **Chapter 8** we studied the effect of a restrictive guideline for ET on the number of top-up transfusions (red blood cell transfusions) in neonates with RHDN in the first three months of life. In December 2005 we changed our ET policy (according to the recommendations of the American Academy of Pediatrics) from using liberal ET criteria to more restrictive ET criteria. In this study we included 183 (near)-term neonates with RHDN admitted to our center. We recorded the number of ETs and the number of top-up transfusions in the group of neonates before (group I, n = 156) and after (group II, n = 27) the guideline change. The percentage of neonates requiring an ET decreased significantly from 66% in group I to 26% in group II. The percentage of neonates receiving a top-up transfusion increased from 68% in group I to 81% in group II. We conclude that restrictive ET criteria in neonates with RHDN lead to a reduction of the rate of ET but an increase in the number of top-up transfusions for neonatal anemia.

The aim of the study described in **Chapter 9** was to evaluate neonatal and hematological outcome in a large series of neonates with Kell HDN compared to neonates with Rhesus D HDN. Kell type of red cell alloimmunization is second only to Rhesus D in causing antibody-mediated fetal anemia and accounts for 10% of all antibody-mediated fetal anemias. In contrast to Rhesus D HDN, fetal anemia in Kell HDN is primarily due to concomitant suppression of erythropoiesis rather than hemolysis of erythrocytes and is thus associated with milder hyperbilirubinemia. Consequently, the immediate neonatal management in Kell HDN is different from Rhesus D HDN and is mainly based on top-up transfusions rather than phototherapy or ET. In this study, we included 191 neonates and found that fetuses with severe Kell HDN were more often treated with IUT than fetuses with Rhesus D HDN (82% versus 66% respectively). Infants with HDN due to Kell-antibodies needed less phototherapy (2.4 versus 4.1 days) and ETs (6% versus 62%) in the neonatal period than neonates with Rh D hemolytic disease. However, the need for top-up transfusions was similar in both groups (62% versus 72%), justifying similar follow-up management as in Rhesus D hemolytic disease.

The long-term neurodevelopmental outcome in children with alloimmune hemolytic disease of the fetus/newborn treated with IUT is presented in **Chapter 10**. Nowadays, treat-

ment with IUT is the most successful procedure in fetal therapy, with perinatal survival rates exceeding 95% in experienced centers. However, one of the concerns of the more widespread and successful use of fetal therapy is that a decrease in perinatal mortality may lead to an increase of children with long-term handicaps. Only a few studies with small patient numbers have reported on long-term neurodevelopmental outcome after IUT. Therefore the LOTUS study was designed. The aim of this study was to determine the incidence and risk factors for adverse neurodevelopmental outcome after IUT treatment in the largest cohort of children worldwide. Neurodevelopmental outcome in children at least 2 years of age was assessed using standardized tests, including the Bayley Scales of Infant Development, the Wechsler Preschool and Primary Scale of Intelligence and the Wechsler Intelligence Scale for Children, according to the children's age. Primary outcome was the incidence of neurodevelopmental impairment (NDI) defined as at least one of the following: cerebral palsy, severe developmental delay, bilateral deafness and/or blindness. A total of 291 children were evaluated at a median age of 8.2 years (range 2 to 17 years). Cerebral palsy was detected in 2.1% of children, severe developmental delay in 3.1% of children and bilateral deafness in 1.0% of children. The overall incidence of NDI was 4.8%. We also found that severe hydrops was independently associated with NDI. We concluded that prevention of fetal hydrops by timely detection, referral and treatment may further improve long-term outcome.

In conclusion, perinatal morbidity and mortality rates in red cell alloimmunization decreased remarkably during the last 50 years due to the significant evolution in prenatal and postnatal care strategies. However, several questions still remain unanswered and provide a basis for future research.