Neonatal management and outcome in red cell alloimmunization

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Rhesus hemolytic disease of the newborn: postnatal management, associated morbidity and long-term outcome

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Abstract

Rhesus hemolytic disease of the newborn can lead to complications such as hyperbilirubinemia, kernicterus and anemia. Postnatal management consists mainly of intensive phototherapy, exchange transfusion and blood transfusion. During the last decades, significant progress in prenatal care strategies for patients with Rhesus hemolytic disease has occurred. New prenatal management options have led to a remarkable reduction in perinatal mortality. As a result of the increase in perinatal survival, attention is now shifting towards short-term and long-term morbidity. 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.

Introduction

Rhesus hemolytic disease of the newborn (RHDN) results from maternal red-cell alloimmunization. Production of maternal antibodies directed against the fetal red blood cells occurs when fetal red blood cells positive for a certain antigen, usually Rhesus D (Rh D), pass into the blood circulation of a mother negative for that particular antigen. Maternal immunoglobulin (IgG) antibodies might then cross the placenta into the fetal circulation and cause a wide variety of symptoms in the fetus, ranging from mild to severe hemolytic anemia and fetal hydrops. During the last few decades, a significant evolution in prenatal care strategies for patients with RHDN has occurred, including the introduction of Rh D prophylaxis, use of Doppler ultrasound to detect fetal anemia and in particular treatment with intrauterine blood transfusions (IUTs). These new management options have led to a dramatic decrease in perinatal mortality. Before the introduction of Rh D prophylaxis and IUTs, perinatal mortality was approximately 50% and the rate of perinatal morbidity was extremely high.[1,2] With the use of IUTs, overall perinatal mortality in severe RHDN has decreased to less than 10%.[3] As a result of the increase in perinatal survival, attention is now shifting towards short-term and long-term morbidity. Postnatal management of RHDN is based mainly on the treatment of hyperbilirubinemia and consists of intensive phototherapy (PT) and exchange transfusions (ETs) to prevent kernicterus. Various other postnatal complications in RHDN have been reported, including early and late anemia, thrombocytopenia, cholestasis and adverse long-term neurodevelopmental outcome. However, few studies have focused on postnatal management and outcome of RHDN.[2,4-7]

This chapter focuses on the management of neonatal and pediatric complications associated with RHDN, discusses the efficacy of various postnatal treatment options and summarizes the results of studies on short-term and long-term outcome in RHDN.

Management of hyperbilirubinemia and the prevention of kernicterus

RHDN can lead to severe hyperbilirubinemia, acute bilirubin encephalopathy and eventually chronic bilirubin encephalopathy, also known as kernicterus. Prevention of kernicterus is considered to be the primary goal of postnatal treatment of RHDN.[8]

The acute stage of bilirubin encephalopathy is divided into three phases. In the early phase, affected infants become lethargic, hypotonic and suck poorly; the intermediate phase is characterized by stupor, irritability, fever, high-pitched cry and alternating hypertonia

and hypotonia; the advanced phase is characterized by irreversible damage to the central nervous system (CNS) resulting in pronounced retrocollis and opisthotonus, shrill cry, no feeding, apnea, fever, deep stupor to coma, sometimes seizures and death.
The chronic stage of bilirubin encephalopathy, i.e. kernicterus, refers to the clinical CNS findings caused by bilirubin toxicity to the basal ganglia and various brain stem nuclei. In kernicterus, infants develop a severe form of athetoid cerebral palsy, hearing problems and psychomotor handicaps.[8-10]

Phototherapy

Treatment of neonatal hyperbilirubinemia with phototherapy (PT) was introduced in the early 1970s.[8,11] PT lowers serum bilirubin levels through photo-oxidation and converts bilirubin to a water-soluble substance. To deliver conventional PT, the infant is nursed under halogen or fluorescent lamps and the eyes are covered with a mask to prevent retinal damage. However, in the last 10 years new devices for delivering PT have been developed, these are the so-called fibreoptic PT devices. The infant is nursed on a blanket containing optical fibres that deliver light to the back. A recent Cochrane review suggests that even though fibreoptic PT has a place in the management of physiological neonatal hyperbilirubinemia, the use of fibreoptic PT in the treatment of pathological neonatal hyperbilirubinemia due to hemolysis should be investigated in a randomized controlled clinical trial.[11]
The efficacy of PT is dependent on a number of factors, including spectral qualities of the delivered light (optimal wavelength range 400-520 nm), irradiance (intensity of light), surface area receiving PT, distance from the light to the skin (the optimal distance is approximately 30 cm), skin pigmentation, total serum bilirubin concentration at the start of PT and duration of exposure.[4,12,13] PT is required when total serum bilirubin levels exceed the predefined bilirubin thresholds. Recently, new PT guidelines for bilirubin thresholds for children with RHDN have been published by the American Academy of Pediatrics (AAP).[8]

In RHDN, intensive PT should be started immediately after birth, as bilirubin levels may rise sharply after birth. Prompt and intensive PT treatment might prevent the need for ETs. Intensive PT implies the use of high levels of irradiance (430-490 nm, i.e. usually 30 μW/cm^2 per nm or higher) distributed to as much of the infant's surface as possible. In intensive PT the nappy (diaper) should be removed to achieve optimal surface area exposure. Additional surface area exposure can be achieved by lining the sides of the bassinet with aluminium foil or a white cloth. Intensive PT consists of (at least) two PT lamps above and a fibreoptic pad under the infant.[8]

Antenatal treatment with IUTs can reduce the need for PT. In a recent study performed at our center, we compared postnatal outcomes in 89 term and near-term infants with RHDN

treated with and without IUTs.[7] We found a significant reduction in duration of PT in the IUT group: the duration of PT in the IUT and no-IUT groups was 3.8 and 5.1 days, respectively ($p = 0.01$). Replacement of fetal red blood cells by donor adult red blood cells via IUT reduces hemolysis and hence also the need for PT. We found no correlation between the number of IUTs and the duration of PT.

In some forms of RHDN, in particular Kell alloimmunization, anemia is more prominent than hyperbilirubinemia. Kell alloimmunization is the second most common alloimmunization after anti-D and accounts for 10% of the cases of severe hemolytic disease of the neonate. In Kell alloimmunization, a trilineage pancytopenia due to suppressed hematopoiesis is seen. Therefore, antibodies against antigens of the Kell blood group system should be considered as a potential cause of unexplained inhibition of myelopoiesis[14]. Kell alloimmunization might therefore lead to severe fetal and neonatal anemia secondary to bone marrow depression rather than hemolysis. Consequently, only minimal PT might be necessary, despite severe anemia.[4,15,16]

Exchange transfusion

Treatment of neonatal hyperbilirubinemia with exchange transfusion (ET) was introduced in the early 1950s.[17] RHDN is one of the most common indications for ET. ET prevents kernicterus by removing bilirubin from the circulation. In infants with RHDN, ET has the additional benefits of removing maternal antibodies (thus limiting further hemolysis) and correcting the associated anemia. ETs are performed with double volume transfusion (160 mL/kg) using irradiated, leukocyte-depleted erythrocytes (cross-matched against the mother and compatible with the infant) via an intravenous catheter, usually an umbilical vein.

ET is required in RHDN when intensive PT management fails and serum bilirubin levels approach the threshold for ET. The percentage of children with RHDN requiring treatment with ET ranges from 20% to more than 70%.[7] This wide range is partly due to the use of different serum bilirubin thresholds for ET. Comparison of the incidence of ET in children with RHDN between the various studies is therefore difficult to accomplish. Several studies mandated the use of early ET, resulting in a higher rate of ET. Until 2005, management guidelines for RHDN at our center also mandated the use of early ET. The incidence of ET in term infants with RHDN delivered at our center before 2005 was 69%.[7] Most ETs (88%) were performed within the first 12 h of birth. In 2004, the AAP published new ET guidelines and serum bilirubin thresholds for children with RHDN.[8] These new guidelines do not recommend the use of early ET. Our center adopted these new guidelines in 2005 and the incidence of infants with RHDN requiring treatment with ET dropped significantly from 69% to less than 20% thereafter.

Whether treatment with IUT also reduces the need for ET in infants with RHDN is not clear. Neonates treated with IUT have a high percentage of adult (donor) red blood cells and a lower percentage of fetal red blood cells,[18] which should result in reduced hemolysis and less need for ET. In a recent retrospective study performed at our center, we compared the need for ET in infants with RHD treated with or without IUT.[7] We found that the median number of ETs was similar in the IUT and no-IUT groups. However, this paradoxical result might be related to the specific early ET criteria used in this study.[7,19,20]

Despite improvement in neonatal intensive care, ET still remains a high-risk invasive procedure associated with a significant rate of adverse reactions. Although the mortality rate associated with ET is nowadays less then 0.3% in term infants, morbidity rates may reach 24%.[21-25] Morbidity associated with ET includes, in particular, catheter-related complications. Umbilical venous catheterization is often required to perform an ET. Although umbilical venous catheterization is a common procedure in the management of sick neonates, it can lead to serious complications, including dislodgement, thrombosis, hemorrhage, arrhythmias, (pericardial) effusions, portal hypertension and infection.[25-30] The incidence of sepsis related to umbilical venous catheterization is reported to range between 6% and 24%.[31]

Intravenous Immunoglobulin

The new AAP guidelines recommend the use of 0.5–1.0 g/kg intravenous immunoglobulin (IVIg) in RHDN in case of failure of PT to reduce the need for ET.[8] The exact mechanism for IVIg in RHDN is yet incompletely unraveled and is the subject of ongoing research. IVIg might increase IgG catabolism, resulting in a shorter half-life of antibodies (including anti-Rh antibodies); IVIg might also block the IgG-receptor on macrophages, resulting in a decreased removal of anti-Rh-coated erythrocytes from the circulation. A third hypothesis is the presence of anti-idiotypic antibodies as a result of IVIg treatment neutralising anti-Rh antibodies.[32]

A few small, randomized controlled trials have suggested that IVIg combined with PT reduces serum bilirubin levels and the need for ET in neonates with RHDN compared with PT alone. In these studies, treatment with IVIg also reduced the duration of PT and length of hospitalization, but increased the need for late red blood cell transfusions. However, the number of patients included in these randomized controlled trials was small and the study-design and inclusion criteria varied considerably. One study included infants with ABO incompatibility;[33] an unexpected and large number of these children with ABO incompatibility and hemolytic disease required an ET. Finally, the criteria for ET were discordant between the various studies.[33-36] A recent Cochrane review suggested that the results of further trials of higher quality should be awaited and stated that: "further well designed studies are needed before

routine use of IVIg can be recommended for the treatment of isoimmune hemolytic jaundice".[37] In view of this dilemma, we recently started a prospective, randomized double-blind, placebo-controlled trial to assess the short- and long-term effects of the prophylactic use of IVIg in neonates with RHDN who were delivered at our center (the LIVIN study: http://www.controlledtrials.com/ISRCTN14013064/). A total of 40 patients is required in both arms of the study to detect a reduction in ETs from 30% in the placebo group to 6% in the IVIg group. To date, 38 patients have been enrolled, and final results will be awaited by the end of 2009.

Albumin

Bilirubin is transported in the plasma bound to albumin. The fraction of bilirubin that is not bound to albumin can more readily cross the blood-brain barrier and may cause bilirubin encephalopathy. The recent AAP guidelines suggest that serum albumin levels should be measured routinely, as an albumin level of less than 3 g/dL can be considered as a risk factor for lowering the threshold for PT.[8] The AAP also recommends that if an ET is being considered, the bilirubin/albumin ratio should be used to determine the need for an ET. Administration of albumin before ET may increase the efficacy of the ET, because more bilirubin will be mobilised from the tissues into the blood and excreted. However, evidence that albumin infusion increases the long-term outcome in infants with severe hyperbilirubinemia is not available and thus routine use of albumin is not recommended.[8]

Phenobarbital

Phenobarbital increases bilirubin uptake, conjugation and excretion. A few studies in the 1970s and 1980s suggested that administration of phenobarbital at birth to a child with hyperbilirubinemia might decrease the need for ET.[38-40] However, recent studies suggest that postnatal administration of phenobarbital does not offer additional advantage over routine use of intensive PT.[5,41]

A recent retrospective study by Trevett et al. showed that antenatal maternal administration of phenobarbital significantly reduces the need for ET in neonates affected with RHDN.[42] The incidence of ET in neonates with and without antenatal phenobarbital administration was 9% versus 52%, respectively ($p < 0.01$). As suggested by the authors, further study in a randomized controlled trial is necessary to confirm these results.[42]

Metalloporphyrins

In recent years, various metalloporphyrins (also known as heme oxygenase inhibitors) have been used to prevent and treat unconjugated hyperbilirubinemia. Metalloporphyrins act by inhibiting the enzyme heme oxygenase, the rate-limiting step in the catabolism of heme to bilirubin. Metalloporphyrins are natural or synthetic heme analogues, which reduce the

production of bilirubin. By preventing the formation of bilirubin, metalloporphyrins have the potential to reduce the level of unconjugated bilirubin and thus decrease the need for PT and hospitalization. However, routine treatment is not recommended at present. A recent Cochrane review suggests that randomized controlled trials are required to compare metalloporphyrin treatment with placebo and to report on important outcomes such as severe hyperbilirubinemia, neonatal kernicterus, ET and long-term neurodevelopmental impairment.[5,43,44]

Hydration

PT increases insensible water loss through the skin and raises the fluid requirements of infants undergoing PT.[45-47] In addition, by-products of PT are eliminated in the urine. If oral hydration is inadequate, intravenous hydration may be necessary.[48] However, there is no unequivocal evidence that increased fluid administration affects serum bilirubin concentration. An exception should be made for infants who are dehydrated, as they might need supplemental fluid intake to correct their dehydration. For breastfed infants with evidence of dehydration, supplementation with a milk-based formula inhibits the enterohepatic circulation of bilirubin and can improve the efficacy of PT.[13]

Management of anemia

Anemia may be present at birth (early anemia) or not until 1 - 3 weeks of age (late anemia). The degree of anemia varies in infants with RHDN. Late (hyporegenerative) anemia presenting 1 week - 3 months after birth is a common problem in neonates with RHDN. Late anemia in RHDN is characterised by a reduction in reticulocyte count and low serum erythropoietin (EPO) levels.[49] Other causal factors include reduction of the half-life of the transfused erythrocytes in infants who received IUTs and red blood cell transfusion or ET postnatally.[7,49-52]

The incidence of late anemia in neonates with RHDN ranges from 71 to 83%.[7,49] Late anemia in RHDN usually resolves by the third month of life.[5,7] In a recent study performed at our center we found that neonates with RHDN treated with IUTs required more top-up red cell transfusions during the first 6 months of life than neonates with RHDN not treated with IUTs (77% and 26.5% respectively; $p < 0.01$). Infants treated with IUTs had a significantly lower median reticulocyte count at birth than infants without IUT (7 ‰ versus 73 ‰, respectively; $p < 0.01$). The association between low reticulocyte count and increased need for top-up transfusions indicates that IUTs could result in suppression of erythropoiesis and in bone marrow hypoactivity.

Infants with RHDN treated with IUT must receive irradiated blood transfusions to prevent

the risk of transfusion associated graft-versus-host disease. Infants must be checked for the rate of hemoglobin fall once or twice a week (depending on the level of the hemoglobin concentration) until 3 months of age. However, international guidelines for red blood cell transfusion in infants during the first months after birth are not available and consensus on appropriate transfusion triggers and the volume of blood to be transfused is not available. Most countries use a transfusion protocol based on clinical condition, mechanical ventilation, gestational age, oxygen use and hematocrit or hemoglobin levels. In our center term neonates with RHDN are treated with transfusions of red blood cells when hemoglobin levels fall below 8.0 g/dL (5.0 mmol/L) or below 9.6 g/dL (6.0 mmol/L) when clinical symptoms of anemia are present (need of extra oxygen, poor feeding, tachycardia and/or tachypnoea).

Erythropoietin

Erythropoietin (EPO) can be used to prevent late anemia and reduce the need for top-up transfusions of red blood cells. Recently, several studies and meta-analyses of EPO administration showed insufficient evidence to comment on the possible advantages of EPO. Routine use of EPO in infants with late anemia due to RHDN is therefore not recommended.[53-56]

Folic acid

The administration of folic acid until 3 months of age might - hypothetically - decrease the need for top-up transfusions of red blood cells by stimulating erythropoiesis. Suggested dosages vary from 25 to 1000 µg daily. However, there are no available data in the literature to support or refute this hypothesis. Current studies do not provide any evidence that administration of folic acid reduces the need for top-up transfusions of red blood cells. The available data are therefore insufficient to directly guide routine clinical practice.[51]

Iron

As discussed above, neonates with RHDN often require IUTs and (multiple) transfusions of red blood cells. The risks and potential consequences of iron overload due to these multiple transfusions are poorly recognized. High levels of cord blood ferritine have been reported in infants with RHDN.[57] As infants with RHDN already have high iron storage, supplementation of iron is not recommended and should not be used.[57]

Management of other associated morbidity

Hydrops fetalis

Severe fetal anemia in RHDN can lead to hydrops fetalis. The immediate postnatal management of a newborn with hydrops fetalis constitutes one of the major challenges in neonatal medicine. Newborns with RHDN and hydrops fetalis have generalized subcutaneous edema and – often – fluid collections in pericardial, pleural or peritoneal spaces. Hydropic infants tolerate labour poorly and are usually depressed at birth. Intubation is often required and can be difficult because of edema. High pressures might be required during mechanical ventilation because of pulmonary edema and pulmonary hypoplasia (secondary to pleural effusions and ascites). Immediate drainage of ascites and pleural effusions in the delivery room might be life-saving procedures. If pulmonary hypertension induces severe hypoxemia, other treatment options should be envisaged, such as mechanical ventilation with high-frequency ventilation, inhaled nitric oxide or extra corporal membrane oxygenation. Circulatory insufficiency is often present and requires adequate inotropic support. As newborns with fetal hydrops frequently show signs of cardiac decompensation, correction of chronic anemia should preferably be performed with a partial ET rather than with a simple transfusion accompanied by administration of diuretics.[58]

Thrombocytopenia

Recent literature suggests an association between low fetal platelet counts and fetal hydrops in severe Rh D alloimmunized pregnancies.[59-61] Fetal thrombocytopenia may have grave consequences, such as intracranial hemorrhage and prolonged, possibly life-threatening bleeding from the puncture site of the IUT. In a recent study performed at our center, fetal platelet counts were measured prior to 914 IUTs in Rh D alloimmunized pregnancies. Severe fetal thrombocytopenia (platelet count < $50x10^9$/L) was found in 3% of all fetal blood samplings and in 23% of severely hydropic fetuses. Perinatal mortality in fetuses with severe thrombocytopenia was 36% (van den Akker, personal communication). The incidence and severity of thrombocytopenia during the neonatal period is not known.

Cholestasis

Several case reports describe elevated levels of conjugated bilirubin in neonates with RHDN.[8,62-65] The incidence and pathogenesis of cholestasis and bronze baby syndrome in newborns with RHDN is not known. Cholestatic liver disease in neonates with RHDN treated with multiple IUTs, red blood cell transfusions and/or ETs can result from hyperferritinemia and liver iron overload.[8,62-65] Accumulation of copper porphyrines in serum and tissues, found in bronze baby syndrome, can be responsible for a lower plasma albumin concentration and less binding of bilirubin, posing a greater risk for kernicterus in patients with bronze baby syndrome.[64]

The current AAP guidelines state that thresholds for the treatment of hyperbilirubinemia should be based on the total serum bilirubin levels, without subtracting the conjugated bilirubin fraction. Nevertheless, when conjugated bilirubin is significantly elevated (i.e. > 50%) there is no bilirubin threshold at which intervention is recommended. Bilirubin encephalopathy is due to unbound, unconjugated bilirubin. Whether neonates with elevated conjugated bilirubin are at increased risk for kernicterus is not known and management remains controversial. Treatment should ideally be based on the measurement of unbound, unconjugated bilirubin, but these measurements have not yet been adapted for clinical use.[8,62-65]

Long-term neurodevelopmental outcome and morbidity

Most study groups, including ours, nowadays report perinatal survival rates in red blood cell alloimmunization treated with IUTs above 90%.[3] As perinatal survival improves, attention is shifting towards long-term outcome in survivors. To date, only a few small studies have reported on the long-term neurodevelopmental outcome in RHDN. The main limitation of these studies is the small number of patients included (range 16-69). Moreover, although hydrops fetalis is associated with increased mortality, not much is known about the association between the severity of fetal anemia and long-term neurodevelopmental outcome.[66-70] Doyle et al. reported on the sensorineural outcome at 2 years of age in 38 survivors of fetal IUTs. The majority of these infants (92%) showed no sensorineural disability at 2 years of age.[66] In a follow-up study performed at our center, Janssens et al. found that the neurodevelopmental outcome for children with RHDN treated with IUTs compared favorably with a group of high-risk, very-low-birth- weight infants (10% versus 18%, respectively) and less favorably with a healthy control group (10% versus 6%, respectively).[70] Hudon et al. studied the neurodevelopmental outcome in 40 infants with RHDN treated with IUT. All infants showed normal developmental outcome at the age of 62 months.[69] Grab et al. described 35 infants treated with IUTs for severe erythroblastosis. At 6 years of age no moderate or severe neurologic impairment was observed.[68] Harper et al. evaluated long-term outcome in 18 hydropic fetuses treated with IUT. Death or major neurological morbidity occurred in 22% of the fetuses and 12% of the survivors had major neurologic sequele.[67]

In 2008, we will perform a follow-up study of all the children (n=350) with RHDN treated with IUTs at our center between 1992 and 2007. Our primary objective is to assess long-term neuromotor development, cognitive development and psychosocial well-being in the largest cohort reported so far. Our secondary objective is to investigate the association between adverse long-term outcome with risk factors, including gestational age at birth, cause and severity of fetal anemia, presence and severity of hydrops fetalis, and number of IUT procedures. Results of this study will be available by 2010.

Practice points

- New guidelines for PT and ET thresholds have been published recently by the AAP.
- The new AAP guidelines do not recommend the use of early ET.
- Supplementation of iron in infants with RHDN is not recommended in consideration of the high iron storage.

Research agenda

- Well-designed randomized controlled trials are necessary to address the efficacy and safety of IVIg use in newborns with RHDN.
- Randomized controlled studies in RHDN are required to evaluate the efficacy of various interventions, such as EPO and folic acid administration, to reduce the need of top-up red blood cell transfusions.
- Short-term outcome studies in infants with RHDN treated with IUTs are needed to investigate the incidence of associated morbidities, including cholestasis.
- Long-term follow-up studies in large cohorts of infants with RHDN treated with IUTs are required to determine their neurodevelopmental outcome and determine potential risk factors.

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