

Intravenous Immunoglobulin in Neonatal Rhesus Hemolytic Disease

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Rhesus (Rh) isoimmunisation by alloantibodies (anti D, anti C and anti E) can cause severe hemolytic disease of the newborn (HDN). HDN results from maternal sensitization following fetomaternal hemorrhage when there is a Rh positive fetus and a Rh negative mother. Maternal immunoglobulin antibodies produced against a paternally derived fetal blood group antigen cross the placenta and the anti-D fetal coated red blood cells are eliminated in the reticuloendothelial system. The outcome for the fetus depends on the balance between the antibody-mediated hemolysis and the erythropoietic capability. In severely affected cases, the anemia results in fetal hydrops. Affected individuals may die in utero or in the immediate postnatal period because of pulmonary hypoplasia due to lung compression from ascites and pleural effusions. Lung growth may also be affected by a direct immune mediated injury and/or that an invasive antenatal procedure [diagnostic or therapy (intrauterine transfusion)] was performed at a critical stage of lung growth(1). The introduction of prophylaxis with anti-DRh0 immunoglobulin (anti-D) has resulted in a marked reduction in the sensitisation of Rh-negative women and deaths attributable to Rh HDN. Nevertheless, HDN remains an important problem and optimising postnatal management is essential.

Standard postnatal management of HDN due to Rh isoimmunisation includes phototherapy and exchange transfusions for infants with severe anemia and/or severe or rapidly increasing hyperbilirubinemia, but this is not always successful. It has been hypothesised that elimination of the anti-D coated red blood cells with Rh antigens is mainly mediated by antibody-dependent cellular cytotoxicity via Fc receptors on the cells of the reticuloendothelial system in the neonate(2). In addition, that immunoglobulin administered intra-

venously in high dose could occupy the Fc receptors and compete with the anti-D sensitised neonatal erythrocytes(2), thus preventing further hemolysis and improving outcome. A systematic review(3) has been reported of randomized and quasi-randomized controlled trials comparing high dose intravenous immunoglobulin (HDIVIG) and phototherapy to phototherapy alone in infants with HDN due to Rh and/or ABO incompatibility. Six randomized trials were identified, but only four were included in the review (total 226 infants). Three studies reported the number of exchange transfusions and the fourth exchange and red cell transfusions together. Meta-analysis of the results of the four trials demonstrated a significant reduction in the need for exchange transfusion (relative risk (RR) 0.28, 95% confidence intervals (CI) 0.17 to 0.47). The number needed to treat was 2.7 (95% CI 2.0 to 3.8)(3). Analysing the results of neonates with Rh HDN alone ($n=73$) also demonstrated a reduction in the need for exchange transfusion (RR 0.21, 95% CI 0.10 to 0.45); number needed to treat 1.7 (95% CI 1.3 to 2.5)(3). Two studies reported on the length of hospital stay and, although overall there was a significant reduction, one study reported a longer stay. The duration of phototherapy was significantly reduced in the infants who received HDIVIG in the studies that reported that outcome. There was, however, a significant increase in the number of red cell transfusions required for late anemia in those who received HDIVIG, although the confidence intervals were large (RR 8.0, 95% CI 1.03 to 62.2)(3). No other adverse events were reported with the use of HDIVIG in the four trials(3), although potential risks include allergy and transmission of disease(4).

The American Academy of Pediatrics recommends the use of HDIVIG in neonates with isoimmune hemolytic anaemia in a dose of 0.5 to

1.0 g/kg(5). Given the possible side-effects it is important to identify the lowest possible efficacious dose. In this issue of the journal, Girish and colleagues(6) have compared the outcome of Rh isoimmunized infants (>31 weeks of gestational age) given 0.5 g/kg or 1.0 g/kg HDIVIG. They conclude that the two regimes of HDIVIG had comparable effects on the duration of phototherapy, duration of hospital stay and need for exchange transfusion. The study, however, was powered only to detect a difference in the duration of phototherapy between the two groups of 24 hours and not to confidently assess differences in other outcomes reported. The authors found the mean duration of phototherapy was 77.3 hours in the low dose group and 55.4 hours in the high dose group (mean difference 21.9, 95% CI-13.1 to 56.9), even though the high dose group was disadvantaged by containing more infants who were hydropic at birth (1/19 versus 6/19) and had required intrauterine transfusions (2/19 versus 8/19, $P=0.06$). The results of this study(6), should encourage further randomized trials to identify the optimum dose of HDIVIG, but such trials should have sample size sufficiently large enough to detect clinically important long term outcomes.

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Single versus Multiple Courses of Antenatal Corticosteroids

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Antenatal steroids for preterm labor, a revolutionary low cost intervention in perinatology, is responsible for improving the neonatal survival and reducing severity of respiratory distress syndrome (RDS) in preterm babies(1). The current recommendations originate from the 1994 National Institute of Health (NIH) Consensus Conference and reinforced by a second NIH Consensus Conference in 2000(2). One

of the key points from the guidelines mention repeated courses of corticosteroids may not be safe and should not be administered outside of clinical trials.

After one course (total of 24 mg of Betamethasone or Dexamethasone, given over 24 or 48 hours respectively) of antenatal steroid, the