Rare problems with RhD immunoglobulin for postnatal prophylaxis after large fetomaternal haemorrhage

Amber Biscoe^{1,2} and Giselle Kidson-Gerber^{1,2,3}

Abstract

We report a case of unusually large fetomaternal haemorrhage in a RhD- patient; of symptomatic non-sustained haemolysis of fetal red cells in the maternal circulation with infusion of intravenous high-dose RhD immunoglobulin; and of a failure to prevent RhD alloimmunisation. The haemolytic reaction is not previously reported in this patient group and we suggest would be limited to patients where the number of fetal red cells in the circulation is high. We advocate caution in treatment and spaced dosing of RhD immunoglobulin where the required dose is high, and refer readers to the WinRhoSDFTM RhD immunoglobulin product information for their updated dosing recommendations. There is a need for better understanding of pathophysiology and RhD immunoglobulin effects, to further reduce alloimmunisation rates, and we support the reporting of prophylaxis failures to haemovigilance programmes as is in place in the United Kingdom.

Keywords

Haematology, haemorrhage, maternal–fetal medicine, perinatal medicine

Date received: 26 February 2015; accepted: 2 July 2015

We present a case of unusually large fetomaternal haemorrhage (FMH), with a rare side effect of haemolysis following RhD immunoglobulin ('anti-D') administration and failure to prevent RhD alloimmunisation.

A 30-year-old primiparous female with blood group O RhD- presented at 39 + 4/40 in labour. A lower section caesarean section was performed 24 h later for fetal distress; placental abruption was diagnosed by visual inspection of the uterus at delivery, and meconium stained liquor was noted to be present. The patient had no identifiable risk factors for abruption. Kleihauer acid elution test quantified the FMH at 174 ml (6.79% maternal cells). A retrospective positive Kleihauer (131 ml) on a leftover blood sample that had been obtained from the patient 24 h earlier for a routine admission full blood count indicated >24 h had elapsed from the onset of FMH.

A neonate with severe anaemia (Hb 84 g/l) and blood group A RhD+ was delivered. The neonate was stable and was urgently transfused packed red cells after delivery. The neonate suffered no clinical sequelae. Maternal serum contained no detectable antibodies to RhD (RhD immunoglobulin prophylaxis was given at 28 and 34 weeks gestation). Management with 29 vials of WinRho SDFTM RhD immunoglobulin was planned (120 mcg/600 IU per vial), due to it being the only product available for intravenous administration. Twenty-four vials (immediately available) were administered.

Thirty minutes later the patient developed fever, severe low back pain, nausea, tremulousness and red coloured urine. Pathology tests demonstrated haemolysis – LDH peaked at 1459 IU/l, decreasing to normal over days; mild bilirubin elevation to 30 µmol/l. Maternal Hb fell non-significantly to 102 g/l (122 g/l postdelivery, 4 h prior) without a reticulocytosis. There was no acute kidney injury (AKI) or disseminated intravascular coagulation (DIC). Serial Kleihauer tests documented complete clearance of fetal red cells after 48 h – we presume that haemolysis of fetal red cells occurred. Supportive care (fluids, oxygen, paracetamol) was administered and haemolysis resolved in 2 h. The outstanding dose of RhD immunoglobulin – 5x625 IU RhD immunoglobulin (CSL) – was administered intramuscularly the following day without reaction. The patient subsequently developed persistent anti-RhD alloantibodies.

We focus our discussion around maternal management in massive FMH; strategies to prevent alloimmunisation; and the risk of

haemolysis after RhD immunoglobulin, not previously reported in this patient group.

Prior to RhD prophylaxis, haemolytic disease of the fetus/newborn due to antibodies to the RhD antigen had a 50% death rate for affected infants. Postpartum prophylaxis with RhD immunoglobulin was introduced in the 1970s, but with persistent small rates of sensitisation, broadened to antenatal and postnatal prophylaxis in all RhD- women based on 2002 recommendations in the UK and 2003 NHMRC guidelines in Australia.^{1,2} Antenatal prophylaxis with 100 µg (500 IU) RhD immunoglobulin at 28 and 34 weeks of gestation has been shown to reduce rates of RhD alloimmunisation from 1 to 2% per pregnancy to 0.1–0.2%.^{3,4} An FMH >20 ml occurs in approximately 1:200 pregnancies, with haemorrhage >150 ml occurring in 1:2800.⁵ Thus, the incidence of large haemorrhages occurring in a RhD- women is an estimated 1:18,670 for Caucasian populations (based on a 15% rate of RhD negativity), and rarer for all other ethnicities; it confers a >20% risk of alloimmunisation.⁴

RhD immunoglobulin prophylaxis is given according to the calculated FMH volume. Choice of product depends on availability, dose and patient preference.⁶ Documented risks include fetal haemolysis and transmission of infections. Consensus in Australia is to prescribe IV therapy for large haemorrhages to avoid multiple IM injections. Alternative management includes divided IM dosing (e.g. 1200 mcg Q12H until full dose administered), with some advocating IM treatment to avoid potential adverse effects of IV formulations.⁴ This rationale, however, is based on case reports of AKI and DIC in RhD+ patients with immune thrombocytopenia, and a single report of AKI in a male RhD- patient who received RhD+ red cells erroneously.^{2,7,8} Mechanistically, haemolysis of RhD- red cells would seem implausible – rather, haemolysis of fetal

¹Department of Haematology, Prince of Wales Hospital, Sydney, Australia

²Department of Haematology, South Eastern Area Laboratory Services, Randwick, Australia

³Royal Hospital for Women, Sydney, Australia

Corresponding author:

Amber Biscoe, Department of Haematology, Prince of Wales Hospital, Randwick 2031, Australia.

Email: Amber.Biscoe@sswahs.nsw.gov.au

RhD+ cells may occur, which would suggest that these rare obstetric patients with large FMH are specifically at risk of haemolytic reactions. Whether the use of IM rather than IV RhD immunoglobulin lowers the risk is open for discussion, however we advocate slow administration, with concurrent intravenous fluids and clinical and laboratory monitoring for haemolysis. We support the revised product information to divide doses – maximum 600 mcg WinRho SDFTM every 8 h until the appropriate dose is reached.⁹

The mechanism of action of RhD immunoglobulin in preventing alloimmunisation in pregnancy is poorly understood. Theorised mechanisms include suppression of the maternal immune response to the RhD+ fetal red cells, rapid clearance of the RhD+ cells (supported by the rapid lysis of fetal cells in this case), and interference with presentation of the D-antigen by antigen-presenting cells.¹⁰ Risk factors for failure of prophylaxis include postmaturity (≥ 42 weeks), assisted delivery (including caesarean), twins and younger maternal age at first delivery. Receipt of red cell transfusion also increases risk, presumably through immunological priming.¹⁰ High body mass index and the specific risk factors for FMH are not identified as increasing the risk of prophylaxis failure.¹⁰

Failure of prophylaxis in this case may have been due to an underestimation of the FMH size and the timing of the FMH. Incorrect estimation of fetal red cell exposure by the Kleihauer test may be due to fetal blood entering the intraperitoneal space (the uterus contained blood at the time of caesarean section, presumably resulting in some intraperitoneal spillage), and the variable sensitivity and accuracy of the test.¹⁰ The rapid clearance of fetal cells from maternal circulation in our case favours adequate dosing albeit with potential ongoing immunogenic stimulus from fetal blood intraperitoneally. Administration of the RhD immunoglobulin later than the recommended 72 h period following the FMH may have occurred due to the silent nature of the placental abruption. There is a need to better understand and investigate failures of prophylaxis, with formal reporting now occurring in the UK through their haemovigilance programme, serious hazards of transfusion.^{11,12}

In summary, this case is a rare example of acute but not sustained haemolysis following a large dose of intravenous RhD immunoglobulin in a RhD- patient, due to haemolysis of fetal RhD+ red cells. The importance of data collection and investigation of failures of prophylaxis is made clear, and further research needed on pathophysiology and mechanisms of action of RhD immunoglobulin; ultimately to clarify management guidelines and further reduce these cases. We advocate caution with large doses of RhD immunoglobulin and reporting failures of prophylaxis through haemovigilance programmes.

Declaration of conflicting interest

The authors declare that this manuscript has not been previously published nor accepted for publication, in part or in full, nor is it under consideration for publication elsewhere.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Written consent from the patient was obtained for publication of this case report.

Guarantor

Dr Amber Biscoe

Contributorship

Dr Amber Biscoe is the primary author. She wrote the manuscript, conducted the literature review and approved the final text for publication. Dr Giselle Kidson-Gerber is the supervising author. She reviewed and edited the manuscript substantially and approved the final version for publication. Both authors meet authorship criteria as defined by the ICMJE.

References

1. Davies J, Chant R, Simpson S, et al. Routine antenatal anti-D prophylaxis – is the protection adequate? *Transfus Med* 2011; 21: 421–426.
2. Guidelines on the prophylactic use of Rh D immunoglobulin (anti-D) in obstetrics. National Blood Authority. 2003. Approved by the NHMRC.
3. Crowther CA, Middleton P and McBain RD. Anti-D administration in pregnancy for preventing Rhesus alloimmunisation (Review). *Cochrane Database Syst Rev* 2013; 2: CD000020.
4. Bowman J. Thirty-five years of Rh prophylaxis. Commentary. *Transfusion* 2003; 43: 1661–1666.
5. de Almeida V and Bowman JM. Massive fetomaternal hemorrhage: Manitoba experience. *J Obstet Gynecol* 1994; 83(3): 323–328.
6. Okwundu CI and Afolabi BB. Intramuscular versus intravenous anti-D for preventing Rhesus alloimmunisation during pregnancy. *Cochrane Database Syst Rev* 2013; 1: CD007885.
7. Sandler SG and Gottschall JL. Postpartum Rh Immunoprophylaxis. Clinical expert series. *Obstet Gynecol* 2012; 120: 1428–1438.
8. Garratty G. Editorial. What is the mechanism for acute hemolysis occurring in some patients after intravenous anti-D therapy for immune thrombocytopenic purpura? *Transfusion* 2009; 49: 1026–1031.
9. WinRho SDFTM Powder for injection. <http://www.mims.com.au> (2009, accessed 2 December 2014).
10. Koelewijn JM, de Haas M, Vrijkotte TG, et al. Risk factors for RhD immunisation despite antenatal and postnatal anti-D prophylaxis. *BJOG* 2009; 116: 1307–1314.
11. Keidan AJ. Routine antenatal anti-D prophylaxis. Letter to the editor. *Transfus Med* 2012; 22: 217.
12. Bolton-Maggs P. Commentary on Keidan 2012: routine antenatal anti-D prophylaxis – is the protection adequate? *Transfus Med* 2012; 22: 155.