Late anaemia in Rh haemolytic disease

As it is clearly stated in the review by Gottstein and Cooke, we consider it unethical to withhold or delay high dose intravenous immunoglobulin (IVIG) treatment in infants with haemolytic disease of the newborn. Since the study we did in 1995, we have treated 129 patients with Coomb’s positive haemolytic disease of the newborn, with the same method and had to resort to exchange transfusions only in three cases. On the other hand, late anaemia is a frequent problem in these cases, necessitating multiple blood transfusions, with well known complications. The authors suggest that multiple doses of IVIG may reduce late anaemia. However, our observation in a limited number of cases is that, even multiple doses of IVIG are ineffective in preventing late anaemia. In an earlier unpublished study, we had shown that the erythropoietin levels were low in these infants. Therefore, we had conducted a double blind, randomised pilot study to investigate the effects of recombinant erythropoietin (rHEPO) in these patients. In this study, rHEPO was administered at a dose of 200 units/kg, subcutaneously, three times a week, starting at the 14th day of life and lasting for six weeks. This protocol reduced the number of erythrocyte transfusions significantly. With the impetus of this pilot study, we have used the same protocol for the subsequent 103 patients and the mean number of transfusions in this group was 1.5, with the majority of patients (35%) not needing any transfusions at all. There were no complications, including changes in neutrophil or platelet counts, and haemorrhagic or infectious complications. The administration of rHEPO to patients with haemolytic disease of the newborn, who had received IVIG early in life, not only decreases the infants’ exposure to multiple blood donors, but also diminishes the need for hospitalisation and hence the cost that is involved. Therefore, rHEPO treatment is a suitable alternative to erythrocyte transfusions in these infants.

Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn

We read with interest the recent review of Gottstein and Cooke. Their systematic review of trials reporting treatment of infants with proven Rh and/or ABO haemolytic disease of the newborn (HDN) treated with high dose intravenous immunoglobulin (HDIVIG) and phototherapy, with phototherapy alone demonstrated that significantly fewer infants required exchange transfusion in the HDIVIG group. The authors point out that anti-D is the commonest red cell antibody responsible for HDN. We have recently treated two children both of whom developed evidence of immune haemolysis due to anti-D antibodies acquired from IVIG.

The first patient, a 4 month old infant with Kawasaki’s disease, was treated with intravenous immunoglobulin (2g/kg) with immediate control of fever and irritability. Ten days later her disease became clinically active again and she was therefore given a second dose of IVIG (2g/kg from a different batch), which is a recognised therapeutic option. Her clinical condition again improved rapidly. A blood count two days after the second dose of IVIG showed that her haemoglobin had fallen suddenly by 2g/dl to 6.4g/dl, the blood film showed spherocytes and the direct antiglobulin test was positive, evidence of immune haemolysis. Samples that were collected prior to the second dose of IVIG confirmed her blood group to be AB Rh D positive with a high titre anti-D. The manufacturer of the IVIG investigated the batch used and reported that the IVIG used for the second dose contained anti-D. The second patient, a 12 year old boy with systemic juvenile idiopathic arthritis received a fifth dose of IVIG from the same batch. He was screened for evidence of haemolysis and his antiglobulin test was positive 14 days after treatment. He remained asymptomatic with no fall in haemoglobin.

IVIG is a pooled blood product not a drug; each batch is made from a pool of plasma collected from several thousand donors. Passive transfer of potentially significant red cell antibodies is a recognised hazard, reported in the company literature but only as a serological phenomenon, not as a clinical warning.

The first case is a reminder that such complications may have serious clinical consequences. We would agree with the comment of Gottstein and Cooke that the use of IVIG is not without potential risks, including haemolysis. IVIG is not universally effective in autologous haemolysis in older children and adults where steroids are the first choice.

Indications for the use of IVIG must be clear and evidence based, and as with all pooled blood products, including albumin solutions, the individual batch numbers must be recorded in the case notes, so that adverse events can be appropriately and fully investigated.

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High dose intravenous immunoglobulin in haemolytic disease of neonates

It was encouraging to read article of Gottstein et al., on the use of high dose intravenous immunoglobulin (HDIVIG) in cases of haemolytic disease of newborns (HDN) with their conclusion showing the effectiveness of HDIVIG. I have the following observations to make with respect to its implications on practice and future research.

Firstly, all the references mentioned were between three and ten years old. These trials did not take into consideration the irradiance of the phototherapy used, although they did observe the number of exchange transfusions performed. Presently, a combination of blue and white fluorescent light double surface phototherapy, with effective higher irradiance of 20–40 uw/cm2/nm, can practically eliminate the need for exchange transfusion, even in severe cases of HDN. Irradiance of phototherapy can be increased further by decreasing the distance between the phototherapy unit and the patient, especially with an undersurface phototherapy unit, keeping thermal and nursing issues under consideration.

Secondly, the authors did not address enterohemorrhagic recirculation of bilirubin from the gut. Inexpensive measures can decrease the back entry of bilirubin from gut, like early enteral feeds, oral administration of agar agar, isabogol husk and so forth, and further reduce serum bilirubin levels. Further randomised controlled trials are required before administration of HDIVIG becomes routine in HDN. These trials should compare use of current effective phototherapy combinations with the...
highest possible irradiance, agents that de-
crease enterohpatic recirculation of bilirubin with or without HDIVIG, and the need for ex-
change transfusion in HDN. They should also address cost effectiveness and safety, con-
sidering the cost of HDIVIG in the developing
world.

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References

Authors’ reply
We are grateful to our colleagues for their interest and responses to our paper.1 In response to Dr Ovaly’s comments we agree that late anaemia can be a problem in babies who have received intravenous immunoglobulin (IVIG), as is also demonstrated in our systematic review. Even when infants have received exchange transfusions (XTs) top up red cell transfusions may be required. In a recent local audit of XT, 35% of babies received top up red cell transfusions after one or more exchange transfusions. During a five year period from 1998-2002, 27 babies with Rhesus, Kell, or ABO incompatibility had 28 XTs. Gestation ranged from 28 to 40 completed weeks. Of 26 infants for whom follow up data was avail-
able, nine (35%) had received top up red cell transfusions.

We read with interest Dr Ovaly and colleagues paper describing a double blind randomised controlled trial of subcutaneous recombinant human erythropoietin (rHEPO),1 this is a trial which is also demonstrated in our systematic review. We were interested to read Drs Cleary and colleagues case reports. We recognise that IVIG is not specific for a particular type of haemolysis and that it is a pooled blood product. We therefore agree that all the usual pro-
cedures regarding documentation of batch number and so on are followed as for any other blood product. IVIG has been used pre-
viously even in preterm and low birthweight infants2 and is currently being used in the INS Trial.3 As with any drug that is a blood product we will need to remain vigilant for the occur-
rence of any adverse events.

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References

Discharging twins separately from neonatal units
We recently had a debate in our unit about whether or not it was better for a well twin to remain with its sibling in hospital until the latter was fit to be discharged. Our current practice is to keep the well twin in the special care baby unit until its twin is fit for discharge. The group who favoured separate discharge cited reduced risk of nosocomial infection, decreased costs, cot availability, and the possibility of settling into a routine with one twin at home as supportive factors for their argument. Those against separate dis-
charge cited impaired bonding, breast feeding difficulties, and transport issues as their reasons.

We took the discussion to the RCPCH and colleagues case reports. We recognise that IVIG is not specific for a particular type of haemolysis and that it is a pooled blood product.1 As with any drug that is a blood product we will need to remain vigilant for the occur-
rence of any adverse events.

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Role of serum peak levels of vancomycin in neonatal intensive care units
We would like to comment on the article by Tan et al.1 The purpose of measuring serum levels of a drug is either to monitor the toxicit-
y of the drug or the therapeutic concentra-
tion for a particular condition. Emergence of infections with β-lactam-resistant Staphylococ-
cus epidermidis, Staphylococcus aureus, and Enter-
ococcus sp, has led to the frequent use of van-
comycin in neonates. Vancomycin has historically had a reputation for toxicity. Many of its original adverse reactions, includ-
ing otoxicity and nephrotoxicity, were prob-
able due to impurities in the formulation.1 Now that a more purified form is available, these adverse reactions are uncommon. However, concomitant administration with aminogly-
cosides or other nephrotoxins may increase the risk of toxicity.1 Effective drug therapy is measured by response, not by achievement of a particular circulating drug concentration. Because the association between vancomycin peak concentrations and toxicity is poor, some have recommended measuring trough con-
tent only2 as this study is clearly documenting, but others have suggested not measuring any concentrations in the majority of children with normal renal function.1 However, in critically ill premature neonates with poor glomerular filtration rate, prematu-
ry, and compromised cardiovascular func-
tion, it remains prudent to measure both peak and trough concentrations in those with poor or changing renal function. Caution must be exercised when other nephrotoxic or ototoxic drugs such as aminoglycosides are adminis-
tered concurrently.1 In this study, the authors did not mention the concomitant use of aminoglycoside.

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References

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Methaemoglobinaemia with concurrent blood isolation of Saccharomyces and Candida

Saccharomyces boulardii is closely related to Saccharomyces cerevisiae and is used as biotherapeutic agent, although some reports suggest pathogenicity. We present a case of neonatal fungaemia with concurrent methaemoglobinaemia, occurring after a brief period of treatment with S boulardii. A male infant was born at 30 weeks of gestational age by caesarean section because of intrauterine growth restriction and maternal hypertension. The baby was well apart from persistent gastrointestinal symptoms that hampered feeding and forced parenteral support. During the third week of life, administration of S boulardii (Codex DN8; half a capsule a day, equivalent to 2.5 x 10^8 organisms) was started in an attempt to prevent bacterial overgrowth. After four days of treatment, the baby developed symptoms suggesting sepsis and an unexplained methaemoglobinaemia (methaemoglobin concentration = 16%). Codex was stopped and empirical antibiotic coverage, including liposomal amphotericin B, was started. Blood cultures showed growth of Candida albicans, but the central venous catheter tip was negative. Methaemoglobin levels halved in two days (7%), but remained constant during the following two weeks of antifungal treatment. Blood cultures at that point showed growth of S cerevisiae, which is susceptible to amphotericin B, in the absence of any clinical finding; again, the catheter tip was sterile. Methaemoglobin concentration was still abnormal (6.2%). Liposomal amphotericin B treatment was prolonged for a further six days and then discontinued. At this time, methaemoglobin levels were near normal (3%), and blood cultures were negative. The gastrointestinal symptoms resolved with age and full gastrointestinal function was achieved.

Recovery of Saccharomyces two weeks after administration had been stopped suggests persistence in the gut. It is tempting to think that the methaemoglobinaemia was caused by the continued presence of the yeasts, perhaps through excessive host production of nitric oxide. Several studies have shown that nitric oxide plays a pivotal role in the interaction between yeasts and the phagocytic system, and it is well known that this radical readily oxidises haemoglobin. It is also reasonable to link late bloodstream invasion by Saccharomyces to previous enteric mucosal damage caused by a Candida infection, which was itself probably gut related. The recovery of S cerevisiae in place of S boulardii has been reported by others, and can be explained by the similarities between the two. It is ironic that the intervention used to prevent sepsis from enteric overgrowth not only did not succeed but was itself a cause of the problem that it was intended to prevent.

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References

Wafting does work

We were interested to see the article “Oxygen administration in infants”, and the letter responses. The original article and letters were unsure of the efficacy of “non-contact” oxygen delivery or “wafting” as it is more commonly known. Our study “The efficacy of noncontact oxygen delivery methods”, demonstrated how effective wafting oxygen can be. We found that an area of 34 cm by 37 cm obtained a concentration of >30% when oxygen is delivered by face mask at 10 l/min. Although this is not a substitution for the more reliable methods of administration as detailed by Drs Frey and Shann, in the short term it can be used with confidence.

We caution against holding a self inflating resuscitation bag over an infant’s airway (without manipulation of the bag itself), as it delivers a negligible amount of oxygen. It is much more efficient to use the oxygen tubing without any attachments.

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References

CORRECTION

We wish to apologise for an error that occurred in a letter by Daniels et al (Arch Dis Child Fetal Neonatal Ed 2003; 88:F257). The first line of the third paragraph should have read: The salient results were that two thirds of granulomas resolved over a three week period without cauterisation.

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